CCDR | CANADA COMMUNICABLE DISEASE REPORT

canada.ca/ccdr

June 2026 - Volume 52-6

OPTIMAL TIMING OF SEASONAL VACCINATION

Public Health Agency of Canada | Agence de la santé publique du Canada

Canada

CCDR
CANADA COMMUNICABLE DISEASE REPORT

The *Canada Communicable Disease Report* (CCDR) is a bilingual, peer-reviewed, open-access, online scientific journal published by the Public Health Agency of Canada (PHAC). It provides timely, authoritative and practical information on infectious diseases to clinicians, public health professionals, and policy-makers to inform policy, program development and practice.

The CCDR Editorial Board is composed of members based in Canada, United States of America, European Union and Australia. Board members are internationally renowned and active experts in the fields of infectious disease, public health and clinical research. They meet four times a year, and provide advice and guidance to the Editor-in-Chief.

Editorial Team

Indexed
in PubMed, Directory of Open Access (DOAJ)/Medicus

Available
in PubMed Central (full text)

Contact the Editorial Office

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

Photo credit

The cover photo represents a flu shot isolated concept vector illustration highlighting virus infection vaccine and flu season vaccination programs. The image was taken from Adobe Stock #615291807.

CCDR Editorial Board Members

ISSN 1481-8531/Cat. HP3-1E-PDF/Pub. 260002

CCDR
CANADA COMMUNICABLE DISEASE REPORT

OPTIMAL TIMING OF SEASONAL VACCINATION

TABLE OF CONTENTS

Summary of the National Advisory Committee on Immunization (NACI) Statement: Updated guidance to protect infants and children from respiratory syncytial virus disease

April Killikelly[1]*, Winnie Siu[1,2], Nicholas Brousseau[3] on behalf of the National Advisory Committee on Immunization (NACI)

Abstract

Background: Respiratory syncytial virus (RSV) is a leading cause of hospitalization among Canadian infants. In March 2026, the National Advisory Committee on Immunization (NACI) released updated guidance reflecting new evidence on the monoclonal antibodies (mAbs) nirsevimab (Beyfortus®) and clesrovimab (Enflosia) and the RSVpreF pregnancy vaccine (Abrysvo). This article summarizes NACI's updated guidance on protecting infants and children from severe RSV disease.

Methods: To develop the statement, NACI used its standard evidence-based process, reviewing clinical trial data, real world effectiveness studies, RSV epidemiology, and Canadian cost utility modelling, as well as ethics, equity, feasibility and acceptability considerations, to inform program recommendations.

Results: Both mAbs and the RSVpreF vaccine demonstrated strong protection against RSV related hospitalization, intensive care unit (ICU) admission, and medically attended illness in infants. All products showed favourable safety profiles. The RSVpreF vaccine was effective when administered ≥14 days prior to delivery. Economic modelling indicated that a combined program of RSVpreF vaccination during pregnancy and targeted infant mAb administration offers the best value for money at current product prices. NACI strongly recommends universal seasonal RSV immunization for infants. Jurisdictions may choose either 1) a universal infant mAb program or 2) a combined pregnancy RSVpreF vaccination plus targeted infant mAb administration program. Infants at increased risk of severe RSV disease should receive mAbs regardless of gestational RSVpreF vaccination status.

Conclusion: Universal seasonal RSV immunization will substantially reduce RSV associated morbidity in infants and could likely be achieved through both program approaches. At current product list prices, the combined pregnancy-infant program offers better value than a universal mAb program. Jurisdictions should consider local epidemiology, feasibility, cost-effectiveness considerations and equity when selecting a program model.

Suggested citation: Killikelly A, Siu W, Brousseau N on behalf of the National Advisory Committee on Immunization (NACI). Summary of the National Advisory Committee on Immunization (NACI) Statement: Updated guidance to protect infants and children from respiratory syncytial virus disease. Can Commun Dis Rep 2026;52(6):223–6. https://doi.org/10.14745/ccdr.v52i06a01

Keywords: immunization, vaccination, monoclonal antibodies, respiratory syncytial virus, infants, pregnancy

Affiliations

[1] Centre for Immunization Surveillance and Programs, Public Health Agency of Canada, Ottawa, ON

[2] School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON

[3] Département de médecine sociale et préventive, Faculté de médecine, Université Laval, Québec, QC

***Correspondence:**

april.killikelly@phac-aspc.gc.ca

Introduction

Respiratory syncytial virus (RSV) is one of the most common respiratory pathogens affecting infants and young children. Nearly all children acquire RSV by two years of age, with the highest risk of severe disease—including hospitalization and intensive care unit (ICU) admission—occurring during the first months of life. While chronic lung disease, congenital heart disease, prematurity, immunodeficiency, and certain genetic conditions increase risk, most infants hospitalized with RSV each year are otherwise healthy.

In 2026, the authorization of clesrovimab in Canada, alongside expanding real-world evidence for the previously authorized products nirsevimab and RSVpreF, prompted the National Advisory Committee on Immunization (NACI) to review and update its previous guidance to support national program planning (1).

Methods

NACI followed its established evidence-based process, which included:

- Reviewing randomized controlled trial data for monoclonal antibodies (mAbs) and RSVpreF.
- Examining real-world vaccine and mAb effectiveness from multiple countries, including new Canadian evidence.
- Assessing RSV epidemiology in infants and in pregnancy.
- Applying the Ethics, Equity, Feasibility, and Acceptability (EEFA) framework.
- Evaluating cost-effectiveness using an updated Canadian cost-utility model incorporating product effectiveness, protection duration, hospitalization rates, and current product list prices (2).

Recommendations were formulated through consensus of the RSV Working Group and approved by the full NACI committee.

Results

Clinical trials and real-world evaluations consistently demonstrate that the long-acting mAbs, nirsevimab and clesrovimab, and the RSVpreF pregnancy vaccine, significantly reduce medically attended RSV illness, hospitalization, and ICU admission in infants (1). Clesrovimab showed 84% efficacy against RSV hospitalization with no ICU admissions in the pivotal trial. Nirsevimab demonstrated strong real-world effectiveness, lowering hospitalization and ICU admission rates across multiple jurisdictions. The RSVpreF vaccination in pregnancy reduced RSV-associated hospitalization and severe disease in infants when administered at least 14 days prior to delivery, with the highest protective effects observed during the first three months of life.

All products demonstrated favourable safety profiles. Clinical trials found no meaningful differences in severe adverse events compared with placebo or the previously used short-acting mAb palivizumab. Surveillance data did not identify significant safety concerns with nirsevimab. For RSVpreF, an imbalance in preterm births was observed in a clinical trial between individuals who received RSVpreF during pregnancy and those who did not (3). Recent real-world evidence from high-income settings did not show an increased risk of preterm birth. Monitoring for preterm birth and for other obstetric outcomes such as hypertensive disorders continues.

Economic analyses showed that universal programs are not cost-effective at current list prices. Among broader programs, the most economically favourable strategy is a combined program of RSVpreF vaccination during pregnancy for infants expected to be born during the RSV season, plus targeted mAb administration for infants at high risk. For healthy infants born before the RSV season, cost-effectiveness declines with increasing age at season start, and jurisdictions may consider prioritizing the youngest of these infants.

Discussion

Key messages

Several key messages emerge from the review of evidence:

- Respiratory syncytial virus remains a leading cause of hospitalization in Canadian infants, particularly in those younger than six months of age.
- New evidence on long-acting mAbs (nirsevimab, clesrovimab) and the RSVpreF pregnancy vaccine supports new protection strategies for infants.
- Either an infant mAb program or a combined pregnancy vaccine with a targeted infant mAb program could be used for universal seasonal RSV immunization programs. Infants at increased risk for severe RSV disease should receive mAbs regardless of gestational vaccination status.
- Economic modelling indicates that a combined pregnancy RSVpreF and targeted infant mAb program is the most economically favourable option at current list prices.

Summary of recommendations

NACI strongly recommends that provinces and territories implement universal seasonal RSV immunization for infants, delivered through one of two approaches, with an additional recommendation for infants at increased risk of RSV disease:

Recommendation 1: NACI recommends to implement universal seasonal RSV immunization for infants. **(*Strong NACI recommendation*)**

Recommendation 2: NACI recommends that jurisdictions implement a seasonal RSV immunization program, based on local context, feasibility and program priorities:

- Universal Infant Monoclonal Antibody Program
  - Administer nirsevimab or clesrovimab to all infants entering their first RSV season, with second-season doses for children at continued increased risk.

OR

- Combined Pregnancy + Targeted Infant Program
  - Offer RSVpreF vaccination during pregnancy (28–36 weeks gestation) for infants expected to be born during RSV season.

    Note: NACI recommends RSVpreF vaccine can be given during pregnancy from 28–36 weeks gestation. The RSVpreF vaccine is authorized in Canada at 32–36 weeks gestation. The off-label recommendation from NACI is supported by safety and efficacy data, supports broader access and opportunities for immunization, and aligns with recommendations by the World Health Organization.

  - Offer mAbs to:
    - Infants at increased risk of severe RSV disease
    - Infants born <14 days after maternal vaccination
    - Infants born to unvaccinated individuals

(***Strong NACI recommendation***)

Recommendation 3: Infants at increased risk of severe RSV disease

- Infants at increased medical risk of severe RSV disease (**List 1**) should receive mAbs in both their first and second RSV seasons. Infants for whom transportation for severe RSV disease treatment is complex, and/or whose risk of severe RSV disease intersects with established social and structural health determinants (such as those experienced by some individuals in or from First Nations, Inuit and Métis communities) are also at increased risk and should receive a mAb in their first RSV season.

  Note: Clesrovimab is not authorized for infants and children at ongoing risk in their second RSV season but could be considered off-label based on evidence of immunogenicity and safety.

(***Strong NACI recommendation***)

Limitations

These recommendations do not include individual-level recommendations as it is anticipated that immunizations will be primarily offered through public programs.

List 1: Infants and children at increased medical risk of severe respiratory syncytial virus disease

Infants and children at increased medical risk of severe RSV disease are those with:

- Chronic lung disease, including bronchopulmonary dysplasia, requiring ongoing assisted ventilation, oxygen therapy or chronic medical therapy in the six months prior to the start of the RSV season
- Cystic fibrosis with respiratory involvement and/or growth delay
- Haemodynamically significant chronic cardiac disease
- Severe immunodeficiency
- Severe congenital airway anomalies impairing clearing of respiratory secretions
- Neuromuscular disease impairing clearing of respiratory secretions
- Down syndrome

Premature infants less than 32 weeks gestational age are also at increased medical risk of severe RSV disease.

Abbreviation: RSV, respiratory syncytial virus

Conclusion

NACI recommends that universal seasonal RSV immunization programs be implemented, and that either a program of mAbs for all infants, or the pregnancy vaccination combined with targeted mAb administration, can be used. At present, the combined approach of RSVpreF vaccination during pregnancy and targeted mAbs for infants at high risk offers the best value for money among universal program options while ensuring that infants at increased risk receive optimal protection.

Jurisdictions are encouraged to apply local epidemiology, feasibility, cost considerations, and equity principles when implementing RSV prevention programs to protect infants across Canada.

Authors' statement

AK — Writing–original draft, writing–review & editing
WS — Writing–original draft, writing–review & editing
NB — Writing–review & editing

The *Summary of NACI statement of April 10, 2026: Updated guidance to protect infants and children from respiratory syncytial virus (RSV) disease: Use of monoclonal antibodies (nirsevimab and clesrovimab) and the RSVpreF vaccine* was prepared A Killikelly, E Abrams, W Siu, A Tuite, G Gebretekle, N Brousseau, and V Dubey, on behalf of the NACI RSV Working Group and approved by NACI.

Competing interests

None.

Disclaimer

This article summarizes NACI recommendations based on the best available evidence at publication. It does not replace product monographs. Recommendations may differ from

monographs; refer to NACI/Public Health Agency of Canada guidance for program decisions.

ORCID numbers

Nicholas Brousseau — 0000-0001-6042-3177

Acknowledgements

The authors acknowledge the contributions of the NACI RSV Working Group, the CCDR editorial team, and partners consulted by NACI.

Funding

The work of NACI is supported by the Public Health Agency of Canada.

References

1. Public Health Agency of Canada. Statement on the prevention of respiratory syncytial virus disease in infants. Ottawa, ON: PHAC; 2024. [Accessed 2025 Aug 4]. https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-statement-prevention-respiratory-syncytial-virus-disease-infants.html

2. Gebretekle GB, Lan M, Xi M, Ximenes R, Buchan SA, Abrams EM, Andrew MK, Brousseau N, Killikelly A, Money D, Papenburg J, Rafferty E, Robinson JL, Siu W, Tunis M, Tuite AR. Evaluating respiratory syncytial virus immunization strategies for infants in Canada: a cost-utility analysis. medRxiv2026. DOI

3. Madhi SA, Kampmann B, Simões EA, Zachariah P, Pahud BA, Radley D, Sarwar UN, Shittu E, Llapur C, Pérez Marc G, Maldonado Y, Kachikis A, Zar HJ, Swanson KA, Lino MM, Anderson AS, Gurtman A, Munjal I. Preterm Birth Frequency and Associated Outcomes From the MATISSE (Maternal Immunization Study for Safety and Efficacy) Maternal Trial of the Bivalent Respiratory Syncytial Virus Prefusion F Protein Vaccine. Obstet Gynecol 2025;145(2):147–56. DOI PubMed

Summary of the National Advisory Committee on Immunization (NACI) Statement: Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults and for adults at high risk of severe RSV disease

Joseline Zafack[1], Elissa M Abrams[1,2,3], Nicholas Brousseau[4] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Respiratory syncytial virus (RSV) is a common respiratory virus that can have serious complications, for older adults and adults with certain medical conditions. Since July 2024, the National Advisory Committee on Immunization (NACI) has provided immunization guidance for the protection of older adults against RSV. In April 2026, NACI updated its guidance to reflect emerging epidemiological data identifying younger adults at high risk of severe RSV and evidence on the benefits of RSV vaccines in older adults and adults at high risk.

Methods: NACI reviewed available evidence on the benefits and risks of RSV vaccination in older adults and individuals at higher risk, as well as additional factors, including ethics, equity, feasibility, acceptability and cost-effectiveness.

Results: The RSV disease burden in younger adults with certain underlying conditions is comparable to that in older adults. Among older adults, RSV infection may increase the risk of cardiovascular events and Guillain-Barré syndrome (GBS). The RSV vaccines demonstrate strong protection against RSV-associated lower respiratory tract disease and severe outcomes, with favourable safety profiles. Monitoring for rare adverse events following immunization, total duration of protection, and need for boosters is ongoing.

Conclusion: NACI expanded the use of RSV vaccines to some adults at high risk for whom the balance of clinical benefits, safety and feasibility is favourable. NACI strongly recommends RSV immunization programs for all adults aged 75 years and older; adults aged 65–74 who are at increased risk of severe RSV disease; and adults aged 18 years and older who reside in chronic care facilities, have received a lung or hematopoietic stem cell transplant, are receiving home or chronic oxygen therapy, or are receiving dialysis. For other adults, vaccination may be considered on an individual basis.

Suggested citation: Zafack J, Abrams EM, Brousseau N on behalf of the National Advisory Committee on Immunization (NACI). Summary of the National Advisory Committee on Immunization (NACI) Statement: Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults and for adults at high risk of severe RSV disease. Can Commun Dis Rep 2026;52(6):227–30. https://doi.org/10.14745/ccdr.v52i06a02

Keywords: National Advisory Committee on Immunization, respiratory syncytial virus, RSV, adults, RSVPreF3/Arexvy, RSVpreF/Abrysvo, mRNA-1345/mRESVIA, vaccine

Affiliations

[1] Centre for Immunization Surveillance and Programs, Public Health Agency of Canada, Ottawa, ON

[2] Department of Pediatrics and Child Health, Section of Allergy and Immunology, University of Manitoba, Winnipeg, MB

[3] Department of Pediatrics, Division of Allergy, University of British Columbia, Vancouver, BC

[4] Département de médecine sociale et préventive, Faculté de médecine, Université Laval, Québec, QC

***Correspondence:**
naci-ccni@phac-aspc.gc.ca

Introduction

Respiratory syncytial virus (RSV) is a common respiratory virus that can be associated with serious complications, including hospitalization, intensive care unit admission, and death, among older adults and adults with certain medical conditions (1–3). Risk for severe outcomes increases with age, residence in chronic care or long-term facilities, presence of comorbidities (e.g., cardiorespiratory disease, metabolic disease, immunocompromise, chronic liver or kidney disease, neurologic disease, or class 3 obesity), or due to factors related to the social determinants of health (1). Recent data suggest a higher burden of RSV-associated hospitalization than previously reported (2,3). Among older adults, RSV infection may increase the risk of Guillain-Barré syndrome (GBS) and cardiovascular events, such as ischemic heart disease, stroke, or heart failure (3,4).

There are three vaccines available to protect older adults and adults at high risk of severe disease from RSV in Canada: RSVPreF3 (AREXVY, GSK), which is authorized to protect individuals 60 years of age and older, and individuals 50–59 years of age at increased risk of RSV disease; and RSVpreF (ABRYSVO®, Pfizer) and mRNA-1345 (mRESVIA®, Moderna), which are authorized to protect individuals 60 years of age and older, and individuals 18–59 years at increased risk of lower respiratory tract disease caused by RSV.

Methods

Evidence synthesis was performed by the National Advisory Committee on Immunization (NACI) Secretariat and reviewed by the NACI RSV Working Group. This included such considerations as the burden of RSV disease in target populations; safety, immunogenicity, efficacy, and effectiveness of the vaccines; and other aspects of the overall immunization strategy (ethics, equity, feasibility, acceptability and cost-effectiveness) (3,5). The evidence and programmatic considerations were organized by the NACI Secretariat using a process informed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) framework and all of the information was used to facilitate development of NACI guidance. Further information on NACI's evidence-based methods is available in *Evidence-based recommendations for immunization–Methods of the National Advisory Committee on Immunization* (6).

Recommendations were developed through discussion of the RSV Working Group, then reviewed and approved by the full NACI committee.

Results

Clinical trials and observational studies demonstrate that RSV vaccines provide meaningful protection against RSV-associated lower respiratory tract disease. NACI judged that all three vaccines work well from a clinical perspective, though there are currently less data available for the safety and efficacy/effectiveness of mRNA-1345 compared to the protein subunit vaccines (3).

All three vaccines have demonstrated favourable safety profiles. An increased risk of GBS has been identified in individuals aged 65 years and older following receipt of the RSVpreF and RSVPreF3 vaccines (3). At this time, it is unclear whether this increased risk will also be seen following mRNA-1345 or among adults aged less than 65 years (3). NACI will continue to monitor safety data on all RSV vaccines (RSVpreF, RSVPreF3, and mRNA-1345) as they become available.

Available evidence demonstrates that a single dose of RSV vaccine provides protection from RSV disease for at least three years (3). It is not yet known if the immune responses to these vaccines can be boosted with further vaccine doses. As a result, younger adults at low or moderate risk may wish to defer vaccination until a time when they are at greater risk.

Economic evidence was derived from an environmental scan of recently published economic evaluations of RSV vaccination in adult populations at increased risk of RSV and an updated Canadian cost-utility model for individuals 50 years and older. Together, these findings indicate that extending immunization programs to include some younger adults at increased risk of severe RSV disease may provide good value for money (3).

Discussion

NACI recommendations on respiratory syncytial virus (RSV) vaccines for public health program-level decision making

The following are recommendations for provinces/territories making decisions for publicly funded immunization programs (3):

Recommendation 1: NACI continues to recommend that RSV immunization programs should include all adults 75 years of age and older **(*Strong NACI recommendation*)**.

Recommendation 2: NACI recommends that RSV immunization programs should include adults 65–74 years of age who are at increased risk of severe RSV disease **(List 1; *Strong NACI recommendation*)**.

Recommendation 3: NACI recommends that RSV immunization programs should include adults 18 years of age and older, who:

- Are residents of nursing homes and other chronic care facilities.
- Have had a lung transplant.

- Have had a hematopoietic stem cell transplant (in the previous two years or who remain on immunosuppression).
- Are on home oxygen or require chronic oxygen therapy regardless of living at home or elsewhere.
- Are receiving dialysis (***Strong NACI recommendation***).

List 1: Clinically significant chronic health conditions for which respiratory syncytial virus (RSV) vaccination is particularly important

- Cardiac or pulmonary disorders (includes chronic obstructive pulmonary disease, asthma, cystic fibrosis, and conditions affecting ability to clear airway secretions)
- Diabetes mellitus and other metabolic diseases
- Moderate and severe immunodeficiency (refer to the list of immunocompromising conditions developed for COVID-19)
- Chronic renal disease
- Chronic liver disease
- Neurologic or neurodevelopmental conditions (includes neuromuscular, neurovascular, neurodegenerative [e.g., dementia], neurodevelopmental conditions, and seizure disorders, but excludes migraines and psychiatric conditions without neurological conditions)
- Class 3 obesity (defined as BMI of 40 kg/m^2 and over)

Abbreviation: BMI, body mass index

Recommendations for individual-level decision making

The following recommendation is for healthcare providers advising individual clients:

Recommendation 1: NACI recommends that RSV vaccines may be considered for adults 18–64 years of age who are at increased risk of severe RSV disease, based on an individual decision informed by discussion with their healthcare provider (***Discretionary NACI recommendation***).

Conclusion

Respiratory syncytial virus represents a substantial source of morbidity in older adults and adults at increased risk. In this update, NACI has recommended a small expansion of the adult RSV vaccine program to also include some groups of adults with medical conditions that place them at higher risk of severe RSV disease. This update reflects recent expanded age indications authorized by Health Canada and new national and international data identifying certain medical conditions as being at higher risk of severe RSV disease.

Successful RSV programs will depend not only on efficacy, but also on feasibility, access, and equity. Jurisdictions should consider local epidemiology, resource allocation, and population needs when considering RSV vaccination strategies.

Authors' statement

JZ — Writing–original draft, writing–review & editing
EA — Writing–original draft, writing–review & editing
NB — Writing–review & editing

Competing interests

None.

Disclaimer

This article summarizes NACI recommendations based on the best available evidence at publication. It does not replace product monographs. Recommendations may differ from monographs; refer to NACI/Public Health Agency of Canada guidance for program decisions.

ORCID numbers

Joseline Zafack — 0000-0001-5261-3333
Elissa M Abrams — 0000-0003-3433-1986
Nicholas Brousseau — 0000-0001-6042-3177

Acknowledgements

The authors acknowledge the contributions of NACI and the NACI RSV Working Group.

Funding

The work of NACI is supported by the Public Health Agency of Canada.

References

1. Abrams EM, Doyon-Plourde P, Davis P, Lee L, Rahal A, Brousseau N, Siu W, Killikelly A. Burden of disease of respiratory syncytial virus in older adults and adults considered at high risk of severe infection. Can Commun Dis Rep 2025;51(1):26–34. DOI PubMed

2. Rahal A, Nwosu A, Schanzer DL, Bancej C, Shane A, Lee L. Hospital burden of influenza, respiratory syncytial virus, and other respiratory viruses in Canada, seasons 2010/2011 to 2018/2019. Can J Public Health 2026;117(1):93–103. DOI PubMed

3. Public Health Agency of Canada. An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI). Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults and for adults at high risk of severe RSV disease. Ottawa, ON: PHAC; 2026. https://publications.gc.ca/collections/collection_2026/aspc-phac/HP40-401-2026-eng.pdf

4. Public Health Agency of Canada. Updated guidance on respiratory syncytial virus (RSV) vaccines for older adults including the expanded use of RSVPreF3 for individuals 50-59 years of age and use of the new mRNA-1345 vaccine. Ottawa, ON: PHAC; 2025. https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-statement-updated-guidance-rsv-vaccines-older-adults-including-expanded-use-rsvpref3-individuals-50-59-years-age-use-new-mrna-1345-vaccine.html

5. Ismail SJ, Hardy K, Tunis MC, Young K, Sicard N, Quach C. A framework for the systematic consideration of ethics, equity, feasibility, and acceptability in vaccine program recommendations. Vaccine 2020;38(36):5861–76. DOI

6. National Advisory Committee on Immunization (NACI). Advisory Committee Statement (ACS). Evidence-based recommendations for immunization--methods of the National Advisory Committee on Immunization. Can Commun Dis Rep 2009;35(ACS-1):1–10. https://epe.lac-bac.gc.ca/100/202/301/chronic_diseases_canada/html/2010/v31n01/publicat/ccdr-rmtc/09vol35/acs-1/index-eng.php?nodisclaimer=1

SCOPING REVIEW

Intraseasonal waning of influenza vaccine effectiveness and implications for the optimal timing of seasonal vaccination programs: A scoping review

Pamela Doyon-Plourde[1]*, Fazia Tadount[1,2]*, Anabel Gil[1], Calin Lazarescu[1], Marie-Michelle Ursu[1,2], Nadine Sicard[1], Winnie Siu[1,3], Angela Sinilaité[1]

Abstract

Background: Seasonal influenza vaccination programs aim to provide protection before the virus circulation begins. However, vaccine effectiveness (VE) may decline within a single influenza season due to waning immunity, antigenic drift, and season-specific factors, raising questions about optimal vaccination timing. The purpose of this review was to synthesize evidence on intraseasonal waning of seasonal influenza VE and examine the implications and key considerations for optimizing the timing of seasonal vaccination in Canada.

Methods: A scoping review was conducted, with searches of MEDLINE, Embase, Scopus, Cochrane Library, and ProQuest Public Health Database that identified studies published from 2010 to June 2024, with an update in July 2025. Eligible studies included clinical trials, observational studies, systematic reviews, and modelling studies reporting at least two VE estimates by time since vaccination within a season or assessing vaccination timing and its impact on influenza outcomes.

Results: Forty-nine studies met inclusion criteria, including 37 assessing intraseasonal waning and 12 examining vaccination timing. Overall, VE was generally highest within one to three months post-vaccination and declined over the season (e.g., three to six months post-vaccination). Waning was more consistently observed for influenza A, particularly A(H3N2), and among adults aged 60 years and older. Modelling studies suggested that delaying vaccination could reduce influenza burden under select late-peaking or fast-waning scenarios; however, estimated benefits were generally small and highly sensitive to assumptions.

Conclusion: Intraseasonal waning of influenza VE is consistently observed, particularly for influenza A and in older adults, but represents a gradual decline that does not typically undermine season-long effectiveness. Evidence does not support substantial or consistent population-level benefits from delaying vaccination.

Suggested citation: Doyon-Plourde P, Tadount T, Gil A, Lazarescu C, Ursu MM, Sicard N, Siu W, Sinilaité A. Intraseasonal waning of influenza vaccine effectiveness and implications for the optimal timing of seasonal vaccination programs: A scoping review. Can Commun Dis Rep 2026;52(6):231–45. https://doi.org/10.14745/ccdr.v52i06a03

Keywords: influenza vaccine, duration of protection, vaccine effectiveness, waning, optimal timing

Affiliations

[1] Centre for Immunization Surveillance and Programs, Public Health Agency of Canada, Ottawa, ON

[2] Département de microbiologie, infectiologie et immunologie, Université de Montréal, Montréal, QC

[3] School of Epidemiology and Public Health, Faculty of Medicine, University of Ottawa, Ottawa, ON

***Correspondence:**

naci-ccni@phac-aspc.gc.ca

Introduction

Seasonal influenza in Canada follows a predictable annual pattern, typically beginning in December and lasting 12–16 weeks, although seasons may start as early as October or as late as February and can extend up to 20 weeks (1). Influenza activity generally progresses from west to east across the country (1). Annual vaccination is the primary strategy for preventing influenza and its complications, and in Canada and other northern hemisphere countries, immunization programs typically begin in October to ensure protection before virus circulation increases (1–3).

While fall vaccination is well established as the recommended timing for seasonal influenza immunization, research continues to examine how vaccination timing may influence effectiveness across the influenza season. Emerging evidence indicates that vaccine effectiveness (VE) may decline within a season due to waning immunity, prior immunity, underlying health conditions, and changes in circulating strains (4–6). Observational studies have reported increasing odds of laboratory-confirmed influenza (LCI) with longer time since vaccination, particularly for A(H3N2), raising concerns that early vaccination could result in reduced protection later in the season, especially among populations at higher risk of severe outcomes (7).

Beyond waning immunity, VE and vaccination impact are influenced by season-to-season variability in influenza circulation, antigenic drift, vaccine-strain match, and programmatic factors, such as supply and uptake (8).

While prior reviews have examined intraseasonal waning, an integrated assessment that jointly considers waning and evidence informing vaccination timing has been lacking. This scoping review addresses this gap by mapping the available evidence and synthesizing insights to support evidence-based public health decision-making and ongoing national work to optimize influenza vaccination strategies in Canada. The objectives were to: i) summarize recent evidence on intraseasonal waning of protection conferred by seasonal influenza vaccines; and ii) identify key considerations related to the optimal timing of seasonal influenza vaccination.

Methods

This scoping review followed the Joanna Briggs Institute methodological framework and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for scoping reviews (PRISMA-ScR) (9,10). The protocol was registered on the Open Science Framework (OSF ID: Rkzc9) (11).

Search strategy

A comprehensive search strategy was developed with a research librarian and applied to MEDLINE, Embase, Scopus, Cochrane Library, and the ProQuest Public Health Database (**Appendix**, Supplemental material, Tables S1–S8). Searches included English and French language publications from January 1, 2010 (post-2009 H1N1 strain introduction) to June 17, 2024, and were updated on July 15, 2025.

Eligibility criteria

Studies included individuals six months of age and older in temperate regions of the northern or southern hemisphere, as well as Australia and New Zealand, due to their research quality and mostly having a temperate climate. Eligible study designs included primary studies (i.e., clinical trials and observational studies), systematic reviews, and meta-analyses.

For evidence on waning protection conferred by seasonal influenza vaccination, studies were required to report two VE estimates by time since vaccination within a single influenza season, using LCI or influenza-related hospitalization outcomes. For evidence related to optimal timing of influenza vaccination, eligible studies assessed vaccination timing through comparisons of earlier versus later vaccine administration in relation to influenza outcomes or modelled the impact of vaccination timing on influenza-related outcomes.

Studies of pandemic monovalent or investigational vaccines, immunogenicity-only outcomes, relative VE without absolute estimates, non-human studies, and studies focused solely on vaccination coverage or uptake were excluded.

Study selection and data extraction

Citations were imported into Zotero for deduplication and uploaded to DistillerSR (Evidence Partners Inc, Ottawa, Canada) for screening. Titles and abstracts were screened by three independent reviewers. A record was included if at least one reviewer deemed it potentially eligible; exclusion required agreement by two reviewers. The DistillerSR artificial intelligence (AI) review tool was used to support exclusion at title and abstract level using a conservative relevance threshold of 0.2 (scores near 0 indicating high-confidence exclusion). All AI-flagged exclusions were manually reviewed. A record was excluded only when at least one reviewer agreed with the AI's recommendation. Disagreements were resolved through discussion. Records not flagged by AI underwent standard dual human screening. Full-text screening was conducted by two independent reviewers, with discrepancies resolved through discussion.

Data extraction was completed by one reviewer and validated by a second, capturing study characteristics (e.g., population, setting, design), interventions, outcomes, and findings relevant to each objective.

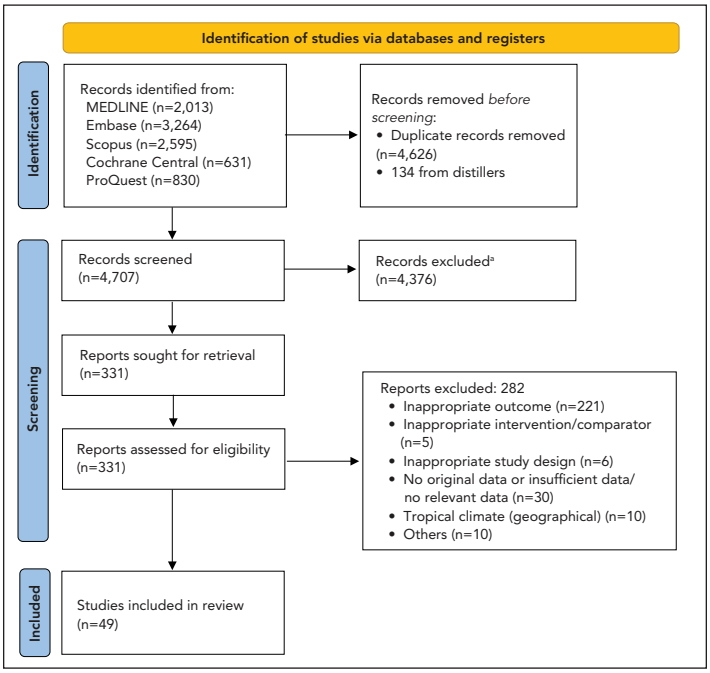
Risk of bias assessment

Risk of bias was assessed to provide context for policy interpretation. Critical appraisal was conducted by one reviewer and validated by a second reviewer. Tools included the revised Cochrane Risk of Bias Tool for randomized trials (12), the Risk of Bias in Non-randomized Studies of Interventions (13,14) and A MeaSurement Tool to Assess Systematic Reviews (AMSTAR 2) (15). Modelling studies were not assessed for risk of bias.

Evidence synthesis

Findings were summarized narratively and VE estimates stratified by time since vaccination were presented graphically in a forest plot. Findings related to optimal timing of influenza vaccination were synthesized separately, highlighting key assumptions and factors influencing timing decisions.

Figure 1: PRISMA diagram[a]



[a] Level 1 (title/abstract) screening in DistillerSR used a dual configuration (human reviewer + AI reviewer). The AI was restricted to suggesting potential exclusions only. All AI-suggested exclusions (n=3,242) were reviewed and confirmed by a human reviewer

Results

Overall, 49 studies met inclusion criteria (**Figure 1**), covering influenza seasons from 2005–2006 to 2023–2024 across multiple countries (**Table 1** and **Table 2**). Most studies used a test-negative design (TND) and assessed intraseasonal waning of VE against LCI.

Intraseasonal waning of seasonal influenza vaccine protection

Thirty-seven studies assessed intraseasonal waning, including 34 TND studies, one cohort study, one randomized controlled trial (RCT), and one systematic review and meta-analysis (Table 1).

The RCT was assessed as low risk of bias (Table 1). Most non-randomized studies were rated low (n=27) to moderate (n=7) risk of bias, with one at serious risk. The systematic review received a moderate confidence rating. Common limitations included residual confounding (e.g., health status) and missing data.

Overall population-level estimates

Across 28 studies reporting population-level estimates without age stratification, VE was highest shortly after vaccination and generally declined over the course of the influenza season (**Figure 2**) (4,7,16–41). Waning was more consistently observed for influenza A than for influenza B, particularly A(H3N2) (Supplemental material, Table S9). For LCI, most studies reported waning within three to six months post-vaccination, although magnitude varied; one study reported no evidence of decline (Figure 2) (30).

Three studies evaluated VE against influenza-related hospitalization (25,26,36). Two reported declining VE with increasing time since vaccination, with reductions of approximately 20%–35% beyond 120 days (26,36), while one observed relatively stable VE (~39%) with wider confidence intervals (CIs) later in the season (25). Strain-specific estimates from Lewis *et al.* showed greater stability for influenza B than influenza A, with VE declining from 72% to 62% for influenza B and from 42% to 16% for influenza A across comparable time intervals (26).

A meta-analysis by Young *et al.*, which included studies also captured in this review, reported significant pooled declines in VE between early (15–90 days) and later (91–180 days) intervals for influenza A(H3N2) (ΔVE=−33%, 95% CI: −57%–−12%, n=11 studies) and influenza B (ΔVE=−19%, 95% CI: −33%–−6%, n=6 studies), but not for A(H1N1) (ΔVE=−8%, 95% CI: −27%–21%, n=5 studies) (7). These results aligned with patterns observed in individual studies.

Analyses modelling time since vaccination as a continuous variable further supported waning. Ray *et al.* reported a 16% increase in the odds of influenza infection per 28 days post-vaccination (odds ratio [OR]: 1.16, 95% CI: 1.13%–1.20%) (33). Ferdinands *et al.* estimated average VE declines per 30 days of 7.5% (95% CI: 0.3%–16.3%) for A(H3N2), 8.5% (95% CI: 3.0%–17.0%) for A(H1N1), and 8.0% (95% CI: 1.4%–21.9%) for influenza B/Yamagata among hospitalized adults, with similar findings for infection outcomes reported by Ferdinands *et al.* (40,41).

Table 1: Characteristics of primary research studies (observational studies and clinical trials)

Author, year	Country, season	Study design	Study population (n) setting	Intervention (n)	Control (n)	Outcome	RoB
Intraseasonal waning of seasonal influenza vaccine protection							
Castilla *et al.*, 2013	Spain 2011–2012	TND	Individuals (≥6 months), excluding HCWs, and nursing home residents (n=757) Hospitals-regional influenza surveillance	IIV3-SD (n=193)	Unvaccinated (n=564)	LCI hospitalization (PCR)	Low[a]
Jimenez-Jorge *et al.*, 2013	Spain 2011–2012	TND	Older adults (≥65 years old) and individuals <65 years old at high risks with ILI (n=378) Primary care	IV (n=134)	Unvaccinated (n=208)	LCI (PCR and/or culture)	Low[a]
Kissling *et al.*, 2013	France, Hungary, Ireland, Italy, Poland, Portugal, Romania and Spain 2011–2012	TND	Non-institutionalized adults (≥18 years old) with ILI or ARI (n=1,016) Primary care and hospitals part of the sentinel networks	IV (n=367)	Unvaccinated (n=649)	LCI (PCR or culture)	Low[a]
Pebody *et al.*, 2013	United Kingdom 2011–2012	TND	Individuals with ILI (n=3,869) Primary care	IIV3 (n=745)	Unvaccinated (n=2,954)	LCI (PCR)	Low[a]
Andrews *et al.*, 2014	United Kingdom 2012–2013	TND	Individuals (≥6 months) with ILI (n=3,286) Primary care	LAIV3 (n=534)	Unvaccinated (n=2,752)	LCI (PCR)	Low[a]
Sullivan *et al.*, 2014	Australia 2012	TND	Individuals with ILI (n=600) Primary care	IIV3 (n=134)	Unvaccinated (n=466)	LCI (PCR)	Low[a]
Pebody *et al.*, 2015	United Kingdom 2014–2015	TND	Individuals (≥6 months) with ILI (n=2,931) Primary care	LAIV (children) or IIV (n=732)	Unvaccinated (n=2,199)	LCI (PCR)	Low[a]
Gherasim *et al.*, 2016	Spain 2014–2015	TND	Individuals with ILI (n=5,044) Primary care and hospitals part of the sentinel networks	IIV3 (n=520)	Unvaccinated (n=4,524)	LCI (PCR)	Low[a]
Kissling *et al.*, 2016	Germany, Spain, France, Hungary, Ireland, Italy, Poland, Portugal, and Romania 2010–2011 to 2014–2015	TND	Individuals with ILI (n=23,167) Primary care	IIV (n=2,224)	Unvaccinated (n=20,943)	LCI (PCR)	Low[a]
Pebody *et al.*, 2016	United Kingdom 2015–2016	TND	Individuals with acute ILI (n=3,841) Primary care	LAIV (children) or IIV4 (n=892)	Unvaccinated (n=2,949)	LCI (PCR)	Low[a]
Radin *et al.*, 2016	United States 2010–2011 to 2013–2014	TND	Individuals with febrile RI (n=1,481) Outpatient health care	IIV and LAIV (n=612)	Unvaccinated (n=869)	LCI (PCR)	Moderate[a]
Ferdinands *et al.*, 2017	United States 2011–2012 to 2014–2015	TND	Individuals (≥9 years old) with ARI (n=20,825) Outpatient setting	IV (n=9,094)	Unvaccinated (n=11,731)	LCI (PCR)	Low[a]
Hergens *et al.*, 2017	Sweden and Finland 2016–2017	TND	Older adults (≥65 years old) living in Sweden (n=358,583) or Finland (n=1,144,894) Primary care and hospitals	IIV (Stockholm n=157,477, Finland n=532,076)	Unvaccinated (Sweden n=201,106, Finland n=612,818)	LCI	Low[a]
Bi *et al.*, 2024	United States 2011–2012 to 2018–2019	TND	Individuals (≥6 months) with ARI (n=55,728) Outpatient care	IIV or LAIV (n=27,986)	Unvaccinated (n=27,742)	LCI (PCR)	Moderate[a]
Chiu *et al.*, 2018	China 2016–2017	TND	Children (6 months–17 years old) with ARI (n=5,514) Hospitals	IIV3 or IIV4 (n=495)	Unvaccinated (n=5,019)	LCI hospitalization (PCR)	Moderate[a]
Feng *et al.*, 2018	China 2012–2013 to 2016–2017	TND	Children (6 months–17 years) with hospitalized for RI (n=15,695) Hospitals	LAIV3 or LAIV4 (n=1,604)	Unvaccinated (n=14,091)	LCI (DIF assay, culture, PCR)	Moderate[a]

Table 1: Characteristics of primary research studies (observational studies and clinical trials) (*continued*)

Author, year	Country, season	Study design	Study population (n) setting	Intervention (n)	Control (n)	Outcome	RoB
Intraseasonal waning of seasonal influenza vaccine protection (*continued*)							
Young *et al.*, 2018	Europe, Kenya, Thailand, Australia 2009–2016	SR-MA of TND (n=14)	Individuals with ARI Primary care facilities (n=11)	IV (NR)	Unvaccinated (NR)	LCI (PCR)	Moderate[b]
Pebody *et al.*, 2019	United Kingdom 2017–2018	TND	Individuals with acute ILI (n=3,080) Primary care	LAIV4 (children), IIV3 or IV4 (n=838)	Unvaccinated (n=2,242)	LCI (PCR)	Low[a]
Powell *et al.*, 2019	United States 2017–2018	TND	Children (6 months–17 years old) with ARI (n=3,595) Hospitals	IV (n=632)	Unvaccinated (n=3,063)	LCI hospitalization (RIT or PCR)	Low[a]
Ray *et al.*, 2019	United States 2010–2011 to 2016–2017	TND	Vaccinated individuals (≥2 years old) tested for influenza virus (n=49,272 person-year) Primary care and hospitals	IIV (n=45,184)	Time since vaccination compared to reference period (14–41 days)	LCI (PCR)	Low[a]
Regan *et al.*, 2019	Australia 2016	TND	Individuals with ILI (n=2,085) Primary care	IV (n=332)	Unvaccinated (n=1,753)	LCI (PCR)	Serious[a]
Wang *et al.*, 2020	China 2016–2017	RCT phase 3	Healthy children 3–17 years old (n=1,999) Primary care and hospitals	LAIV3 (n=996)	Placebo (n=996)	LCI (PCR)	Low[c]
Ferdinands *et al.*, 2021	United States 2015–2016 to 2018–2019	TND	Adults (≥18 years old) hospitalized for ARI (n=3,016 A(H3N2), 1,492 A(H1N1) pdm09, and 1,060 B/Yamagata) Hospital-based	IV (n=3,589)	Unvaccinated (n=1,979)	LCI hospitalization (PCR)	Low[a]
Mira-Iglesias *et al.*, 2021	Spain 2018–2019	TND	Older adults (≥65 years old) with ILI (n=992) Primary care and hospitals	IIV3 or IIV3-Adj (n=662)	Unvaccinated (n=330)	LCI hospitalization (PCR)	Low[a]
Sahni *et al.*, 2021	United States 2015–2016 to 2019–2020	TND	Children (≥6 months–<18 years old) with ARI (n=8,430) Hospitals	IV (n=4,653)	Unvaccinated (n=3,777)	LCI hospitalization (PCR)	Low[a]
Hu *et al.*, 2022	United States 2016–2017 to 2019–2020	TND	Adults (≥18 years old) with ILI (n=7,114) Outpatient care	IIV-SD (n=4,071)	Unvaccinate (n=3,043)	LCI (PCR)	Low[a]
Tenforde *et al.*, 2023	United States 2021–2022	TND	Adults (≥18 years) with visits or hospitalization for ARI (n=86,732) Hospitals (emergency department)	IV (n=45,136); approximately 5,879 had IIV-HD, 10,559 had IIV-SD and 11,721 had IIV-Adj	Unvaccinated (n=58,401)	LCI (NR)	Low[a]
Chung *et al.*, 2024	Canada 2010–2011 to 2018–2019	TND	Vaccinated individuals (≥6 months, n=53,065) Hospital-based	LAIV3 or LAIV4 (n=53,065)	Time since vaccination compared to reference period (14–41 days)	LCI (PCR)	Low[a]
Domnich *et al.*, 2024	Italy 2018–2019 to 2022–2023	TND	Individuals (≥6 months) with ILI or hospitalized for SARI (n=6,490) Primary care or hospitals	IIV-SD (Mid-October to November, n=1,571)	Unvaccinated (n=4,857)	LCI (PCR)	Low[a]
Lewis *et al.*, 2024	United States 2022–2023	TND	Adults (≥18 years old) with (n=3,707) ARI Hospitals	IIV (n=1,697), older adults likely received IIV-HD or IIV-Adj	Unvaccinated (n=2,010)	LCI hospitalization (PCR)	Low[a]
Maurel *et al.*, 2024	Croatia, France, Germany, Hungary, Ireland, the Netherlands, Portugal, Romania, Spain national, Spain Navarra region and Sweden 2022–2023	TND	Individuals with ARI or ILI (n=38,058) Primary care	IV (n=6,380)	Unvaccinated (n=31,678)	LCI (PCR)	Low[a]

Table 1: Characteristics of primary research studies (observational studies and clinical trials) (*continued*)

Author, year	Country, season	Study design	Study population (n) setting	Intervention (n)	Control (n)	Outcome	RoB
Intraseasonal waning of seasonal influenza vaccine protection (*continued*)							
Seppälä *et al.*, 2024	Norway 2022–2023	Retrospective cohort study	Older adults (≥65 years) with SARI (n=1,005,568) Hospitals	IIV4 or IIV4-Adj (n=637,827)	Unvaccinated (n=367,741)	Influenza-associated hospitalisation and death (ICD-10 codes J09, J10 or J11)	Low[a]
Zhang *et al.*, 2024	China 2022–2023	TND	Individuals (≥6 months) with ILI (n=8,301) Hospital-based	IIV3-SD or IIV4-SD (n=182)	Unvaccinated (n=8,119)	LCI hospitalization (PCR)	Low[a]
Zhu *et al.*, 2024	China 2021–2022 to 2023–2024	TND	Children (6 months–<18 years old) with ARI (n=27,670) Outpatient setting	IIV-SD or LAIV (n=2,857)	Unvaccinated (n=24,813)	LCI (PCR or culture)	Moderate[a]
Abou Chakra *et al.*, 2025	France 2023–2024	TND	Individuals with ILI (n=146,662) Primary care	IIV4-SD or IIV4-HD (n=32,740)	Unvaccinated (n=113,922)	LCI (PCR)	Moderate[a]
Lewis *et al.*, 2025	United States 2023–2024	TND	Adults (≥18 years old) hospitalized with ARI (n=7,690) Hospital-based	IV (n=3,170)	Unvaccinated (n=4,520)	LCI hospitalization (PCR)	Low[a]
Zhu *et al.*, 2025	United States 2023–2024	TND	Individuals (≥6 months) with ARI (n=1,382,142) Outpatient and hospitals	IV (n=415,390); of adults ≥65 years, 84,739 had IIV-HD, 1,260 had RIV and 64,959 IIV-Adj	Unvaccinated (n=966,752)	LCI (PCR)	Moderate[a]
Optimal timing of influenza vaccine administration							
Glinka *et al.*, 2016	United States 2005–2006 to 2012–2013	Retrospective cohort study	HIV-positive adults in care; vaccinated predominantly with IIV-SD (n=1,176 HIV-positive adults; 4,575 vaccination events across seasons) Outpatient setting	IIV-SD Early scenario: September 1–November 15	Late scenario: after November 15	Incidence of LCI or ILI	Serious[a]
Worsham *et al.*, 2024	United States 2011–2012 to 2017–2018	Retrospective cohort study	Children vaccinated between August 1 and January 31 across seasons (n=819,223 children; 1,261,164 child-seasons) MarketScan commercial insurance claims database	Vaccination timing driven by birth month (children born in October more likely vaccinated in October)	Cross comparison across birth-month groups representing earlier versus later vaccination timing (August vs October; August vs December; October vs December)	Rate of influenza diagnosis by ICD codes or oseltamivir claim (ICD-9 or ICD-10)	Low[a]

Abbreviations: ARI, acute respiratory illness; DIF, direct immunofluorescence; HCWs, healthcare workers; ICD, International Classification of Diseases; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10, International Classification of Diseases, Tenth Revision; IIV, inactivated influenza vaccine; IIV-Adj, adjuvanted inactivated influenza vaccine; IIV-HD, high-dose inactivated influenza vaccine; IIV-SD, standard-dose inactivated influenza vaccine; IIV3, trivalent inactivated influenza vaccine; IIV3-Adj, adjuvanted trivalent inactivated influenza vaccine; IIV3-SD, standard-dose trivalent inactivated influenza vaccine; IIV4, quadrivalent inactivated influenza vaccine; IIV4-Adj, adjuvanted quadrivalent inactivated influenza vaccine; IIV4-HD, high-dose quadrivalent inactivated influenza vaccine; IIV4-SD, standard-dose quadrivalent inactivated influenza vaccine; ILI, influenza like-illness; IV, influenza vaccine; LAIV, live attenuated influenza vaccine; LAIV3, trivalent live attenuated influenza vaccine; LAIV4, quadrivalent live attenuated influenza vaccine; LCI, laboratory-confirmed influenza; NR, not reported; PCR, polymerase chain reaction; RCT, randomized controlled trial; RI, respiratory illness; RIT, rapid influenza test; RIV, recombinant influenza vaccine; RoB, risk of bias; SARI, severe acute respiratory illness; SR-MA, systematic review and meta-analysis; TND, test-negative design

[a] Risk of bias was evaluated using the Risk of Bias in Non-randomized Studies of Intervention tool (ROBINS-I)
[b] Risk of bias was evaluated using the A Measurement Tool to Assess Systematic Reviews tool for systematic review (AMSTAR 2)
[c] Risk of bias was evaluated using the revised Cochrane Risk-of-Bias tool for randomized trials (ROB 2.0)

Table 2: Key characteristics and findings of modelling studies evaluating optimal timing for influenza vaccination

Author, year	Population setting	Timing scenarios compared	Key assumptions driving results	Key result relevant to timing
Lee *et al.*, 2010	Children, United States	September–October vs later	Early-season protection emphasized	September–October vaccination most cost-effective
Myers *et al.*, 2010	Pregnant individuals, United States	Early vs delayed (>November)	No explicit waning	Delaying vaccination reduced effectiveness and cost-effectiveness
Lee *et al.*, 2015	General population, United States	Earlier vs current practice	Season timing and variability	Earlier vaccination yielded modest savings; increasing coverage had larger impact
Newall *et al.*, 2018	Adults 65 years of age and older, United States	August–November	Fast vs slow waning; season variability	Optimal timing varied by season and waning rate
Costantino *et al.*, 2019	General population, Australia	Early vs delayed (by ~2–3 months)	Waning; coverage held constant vs reduced	Delayed vaccination modestly improved outcomes only if coverage remained stable; benefits lost with small coverage declines
Smith *et al.*, 2019	Adults 65 years of age and older, United States	Compressed (October–May) vs extended (August–May) season	Waning; coverage loss; season variability	Small benefit of compression offset by reduced uptake
Ferdinands *et al.*, 2020	Adults 65 years of age and older, United States	August–September vs October	Waning; influenza season timing; VE; coverage loss with delay	Delaying vaccination increased hospitalization if more than 14% missed vaccination
Kahana *et al.*, 2021	General population, Israel	Program start dates from July 1 to December 1 (e.g., September vs October start)	Coverage-dependent rollout speed; waning	Optimal timing shifted later as coverage increased
Williams *et al.*, 2022	Adults 65 years of age and older	One-dose vs two-dose; October start	Waning, second-dose uptake	Benefits depended on late peaks and high uptake
Spencer *et al.*, 2024	Multiple age groups	Early vs delayed	Initial VE, waning rate, peak timing, coverage held constant	Optimal timing highly sensitive to waning and peak timing

Abbreviation: VE, vaccine effectiveness

Overall, population-level evidence indicated progressive intraseasonal waning, with more consistent evidence available for LCI than for hospitalization outcomes, and more pronounced for influenza A than for influenza B.

Children

Eight studies reported paediatric-specific VE estimates (4,16,42–47). Overall, VE was highest shortly after vaccination and generally remained stable or declined modestly over the season. For LCI, early–late differences were small, with changes in VE of approximately 5%–8% across the season (4,16,42,43) (Supplemental material, Table S10).

Two studies assessed influenza-related hospitalization in children and reported VE declines of approximately 20% and 30% within six or nine months post-vaccination (44,45). Age-stratified analyses showed broadly similar patterns across paediatric age groups (e.g., <2 years, 3–5 years, and 6–17 years), with modest seasonal variation for LCI and larger declines observed for hospitalization outcomes (16,44,45).

Two studies reported increasing odds of influenza positivity with time since vaccination (46,47), although significant waning was observed for A(H3N2) in only one study (46). Overall, VE in children remained protective throughout the season, with limited evidence of substantial intraseasonal waning.

Adults 18 to 64 years of age

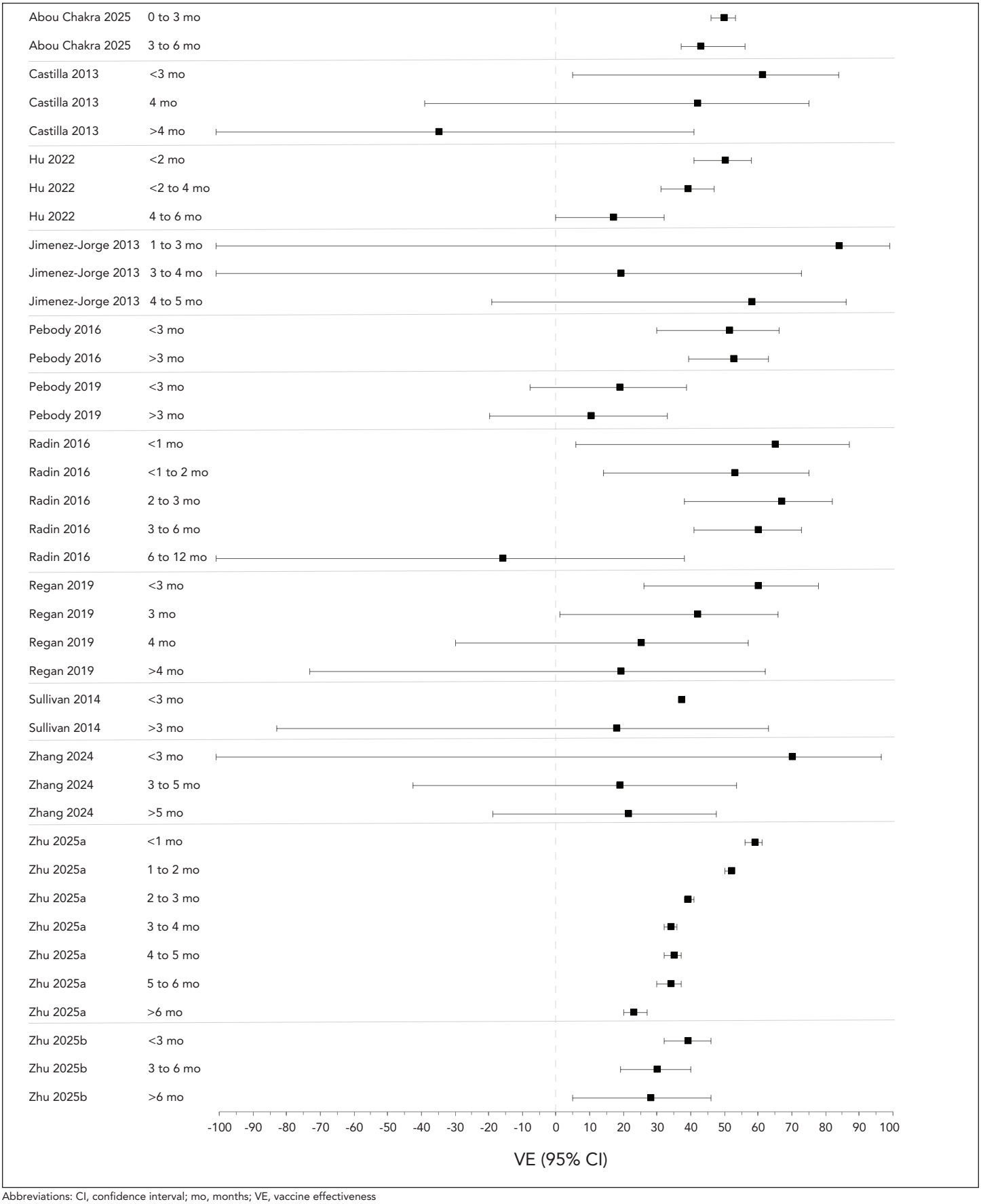
Three studies specifically assessed intraseasonal waning of influenza in adults aged 18–64 years (4,16,46). In general, VE was highest shortly after vaccination, with variable changes over time. One study reported a modest decline (~5%) at three to six months, another reported larger declines (~30%) beyond five months, and a third found no significant association between time since vaccination and influenza positivity (adjusted OR: 1.00; 95% CI: 0.95%–1.06%) (4,16,46).

Overall, evidence in this age group was limited and heterogeneous, precluding firm conclusions regarding the extend of intraseasonal waning.

Older adults

Ten studies evaluated intraseasonal waning in adults 60 or 65 years and older (4,16,19,22,24,40,46,48–50). Most reported declining VE over time, with patterns varying by outcome and strain. For LCI, VE was generally highest within one to three months post-vaccination and declined thereafter (**Table 3**), with steeper waning for A(H3N2) than influenza B in one study (24).

Figure 2: Influenza vaccine effectiveness against laboratory-confirmed infection by time since vaccination



Abbreviations: CI, confidence interval; mo, months; VE, vaccine effectiveness

Table 3: Influenza vaccine effectiveness against laboratory-confirmed influenza by time since vaccination in older adults 60 years of age and older

Study	Age groups	Time since vaccination	VE (95% CI)
Abou Chakra *et al.*, 2025	65 years and older	15 days–3 months	43.11% (37.07–48.61)
		3–6 months	39.71% (31.31–47.19)
Castilla *et al.*, 2013	65 years and older	<100 days	47% (−63–83)
		100–119 days	54% (−55–86)
		≥120 days	32% (−111–78)
Chung *et al.*, 2024	65 years and older	42–69 days	−7% (−26–9)
		70–97 days	−17% (−41–3)
		98–125 days	−30% (−60–−5)
		126–153 days	−32% (−67–−4)
		≥154 days	−32% (−78–3)
Jimenez-Jorge *et al.*, 2013	65 years and older	49–88 days	85% (18–97)
		89–127 days	33% (−102–78)
		128–166 days	−376% (−4,332–49)
Kissling *et al.*, 2016[a]	60 years and older	40 days	A(H3N2): 45% (7–67)
		80 days	A(H3N2): 33% (12–49)
		120 days	A(H3N2): 10% (−18–32)
		160 days	A(H3N2): −16% (−93–31)
		40 days	Influenza B: 62% (3–84)
		80 days	Influenza B: 55% (32–71)
		120 days	Influenza B: 41% (13–60)
		160 days	Influenza B: 24% (−39–58)

Abbreviations: CI, confidence interval; VE, vaccine effectiveness
[a] Vaccine effectiveness estimated from plots

Hospitalization outcomes showed similar temporal patterns, often with less pronounced declines and widening CIs later in the season. Mira-Iglesias *et al.* reported VE decreasing from 54% at 15–82 days to 50% at 123–177 days post-vaccination (48). In Seppälä *et al.*, VE among adults 65–79 years declined from 34% at 7–89 days to −3% beyond 180 days, whereas VE remained around 40% in adults aged 80 years and older, with CI widening over time (49).

Continuous-time analyses generally supported waning (40,46,50). Domnich *et al.* reported a significant 6%–7% increase in odds of influenza per week since vaccination for any influenza and A(H3N2), starting 14 days post-vaccination (46). Ferdinands *et al.* estimated average declines in VE of approximately 10% per 30 days post-vaccination for hospitalization (40). However, another study observed seasonal declines in VE, but sensitivity analyses accounting for calendar week and time since vaccination did not demonstrate a clear gradual decline, with overlapping CIs across weekly VE estimates (50).

Overall, VE in older adults was highest shortly after vaccination and declined over the course of the season, with considerable heterogeneity across studies.

Optimal timing of influenza vaccine administration

Twelve studies assessed optimal vaccination timing, including ten modelling studies and two observational studies (Table 1 and Table 2) (51–62). Modelling studies evaluated vaccination timing under varying assumptions related to VE, intraseasonal waning, season timing, and vaccination coverage (Table 2), while observational studies compared influenza outcomes following earlier versus later vaccination in specific population (Table 1).

Modelling results suggested that under some late-peaking or fast-waning scenarios, delaying vaccination by one to two months could reduce influenza burden when coverage was held constant (51–53,57,58,60). However, the estimated gains were generally small, typically corresponding to less than a 5% difference in prevented cases or hospitalizations between timing scenarios (51,57,58). Several models further showed that even modest reductions in vaccination coverage associated with delayed uptake could offset or reverse these potential benefits (51,52,58). Economic modelling favoured earlier fall vaccination, particularly for children and pregnant individuals (54–56). Models of compressed vaccination periods (e.g., October–May vs August–May) or two-dose schedules in older adults showed benefits under select late-

peaking or fast-waning scenarios, which diminished when coverage or adherence declined (58,59).

Two observational studies reported mixed findings. Glinka *et al.* observed higher influenza-related outcomes among HIV-infected individuals vaccinated earlier (before mid-November) compared with later (after mid-November) vaccination (61). In contrast, a population-based cohort study in young children found that those born in October, who were disproportionately vaccinated in October, were least likely to receive an influenza diagnosis, particularly compared with children born in August, who tended to be vaccinated earlier, and those born in December, who tended to be vaccinated later (62). Both studies were subject to potential residual confounding.

Overall, modelling evidence suggests that the impact of modifying vaccination timing is highly sensitive to assumptions about waning, season timing, and vaccination coverage, with potential gains from delayed strategies generally small and easily negated by reductions in uptake, while observational evidence remains limited and inconsistent.

Discussion

This scoping review synthesized evidence on intraseasonal waning of influenza VE and its implications for seasonal vaccination timing, addressing gaps identified in recent national evidence syntheses. Across age groups and study designs, VE was generally highest within one to three months after vaccination and declined progressively over the influenza season (e.g., 3–6 months post-vaccination). Waning was most consistently observed for influenza A, particularly A(H3N2), and among older adults. Evidence for hospitalization outcomes was more limited than for LCI, but available studies suggested similar temporal patterns with greater uncertainty.

These findings align with earlier evidence syntheses, including the 2017 meta-analysis by Young *et al.* and a prior systematic review and meta-analysis of immunogenicity and antibody persistence, which demonstrated biologically plausible declines in vaccine-induced immunity by six months post-vaccination (6,63). However, the magnitude and consistency of waning varied across studies, likely reflecting differences in circulating strains, season timing, population characteristics, and analytic approaches. Importantly, observed late season declines may reflect not only waning immunity but also antigenic drift and reduced vaccine-strain match, particularly during A(H3N2)-dominant seasons (64).

Evidence on vaccination timing suggested that potential benefits of delaying vaccination are context-dependent and generally modest. Modelling studies indicated that in specific scenarios (e.g., late-peaking seasons or rapid waning), later vaccination could reduce influenza burden when coverage was held constant (51–53,57,58,60). However, projected gains were small and highly sensitive to assumptions about waning, season timing, and uptake, with several models showing that modest coverage reductions could negate benefits (51,52,58). Observational studies examining vaccination timing reported mixed findings and were subject to residual confounding (61,62).

Overall, maintaining high vaccination coverage appears to be a dominant determinant of population-level impact. While waning is a consistent feature of influenza VE, the implications for modifying vaccination timing remain uncertain and vary by population, outcome, and season. Early-season vaccination provides protection across most seasons, whereas delayed strategies may leave individuals unprotected during early circulation, given variability in season onset and peak timing.

Limitations

Interpretation should consider methodological limitations. Most studies relied on observational designs and were susceptible to residual confounding, time-varying biases and misclassification. Heterogeneity in definition of time since vaccination and adjustment for calendar time and circulating strains further complicates comparisons. Fewer studies assessed hospitalization outcomes, often with widening CIs later in the season. Modelling studies additionally depend on assumptions that may not reflect real-world conditions.

This review provides a comprehensive synthesis across multiple seasons, regions, age groups, and outcomes, integrating evidence on waning with vaccination timing. However, heterogeneity across studies, and limited data for certain populations, including pregnant individuals and immunocompromised persons, remain important gaps.

Conclusion

Intraseasonal waning of influenza VE is consistently observed, particularly for influenza A and among older adults, but represents a gradual decline that does not typically undermine season-long effectiveness. Although timing adjustments may theoretically influence protection under specific scenarios, current evidence does not demonstrate substantial or consistent population-level benefits from modifying vaccination timing. These findings highlight the importance of considering waning alongside seasonal variability, strain dynamics, and programmatic factors, and underscore the need for further research on how these elements interact to influence influenza outcomes.

Authors' statement

Both, Pamela Doyon-Plourde and Fazia Tadount contributed equally to the conceptualization, analysis and writing of the manuscript.

PD-P — Conceptualization, data curation, formal analysis, methodology, validation, visualization, writing–original draft, writing–review & editing
FT — Conceptualization, investigation, formal analysis, methodology, validation, writing–original draft, writing–review & editing
AG — Conceptualization, investigation, writing–review & editing
CL — Investigation, validation, writing–review & editing
M-MU — Investigation, validation, writing–review & editing
NS — Conceptualization, writing–review & editing
WS — Conceptualization, writing–review & editing
AS — Conceptualization, supervision, writing–review & editing

Competing interests
None.

ORCID numbers

Pamela Doyon-Plourde — 0000-0002-8738-0055
Fazia Tadount — 0009-0001-4867-5942
Anabel Gil — 0009-0001-6179-0371
Calin Lazarescu — 0000-0001-5778-9362
Marie-Michelle Ursu — 0009-0004-4541-2567
Winnie Siu — 0009-0001-5772-1509
Angela Sinilaite — 0009-0001-4488-7454

Acknowledgements

This review was developed and conducted at the request and under the guidance of the National Advisory Committee on Immunization (NACI) Influenza Working Group (IWG). The authors gratefully acknowledge the contributions of NACI IWG content experts in refining the protocol to support the feasibility and relevance of the review for key knowledge users. The authors also thank Katarina Gusic for her assistance with screening and study selection.

Funding

This work was supported by the Public Health Agency of Canada.

References

1. Public Health Agency of Canada. Statement on seasonal influenza vaccines for 2026-2027. Ottawa, ON: PHAC; 2026. https://publications.gc.ca/collections/collection_2026/aspc-phac/HP37-45-2026-eng.pdf

2. Grohskopf LA, Blanton LH, Ferdinands JM, Reed C, Dugan VG, Daskalakis DC. Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices - United States, 2025-26 Influenza Season. MMWR Morb Mortal Wkly Rep 2025;74(32):500–7. DOI PubMed

3. Government of the UK. JCVI statement on influenza vaccines for 2025 to 2026. London, UK: GOVUK; 2024. https://www.gov.uk/government/publications/flu-vaccines-2025-to-2026-jcvi-advice/jcvi-statement-on-influenza-vaccines-for-2025-to-2026

4. Chung H, Campitelli MA, Buchan SA, Campigotto A, Crowcroft NS, Gubbay JB, Jung JK, Karnauchow T, Katz K, McGeer AJ, McNally JD, Richardson DC, Richardson SE, Rosella LC, Russell ML, Schwartz KL, Simor A, Smieja M, Sundaram ME, Warshawsky BF, Zahariadis G, Kwong JC; Canadian Immunization Research Network (CIRN) Provincial Collaborative Network (PCN) Investigators. Measuring waning protection from seasonal influenza vaccination during nine influenza seasons, Ontario, Canada, 2010/11 to 2018/19. Euro Surveill 2024;29(8):2300239. DOI PubMed

5. Young BE, Mak TM, Ang LW, Sadarangani S, Ho HJ, Wilder-Smith A, Barkham T, Chen M. Influenza vaccine failure in the tropics: a retrospective cohort study of waning effectiveness. Epidemiol Infect 2020;148:e299. DOI PubMed

6. Doyon-Plourde P, Przepiorkowski J, Young K, Zhao L, Sinilaite A. Intraseasonal waning immunity of seasonal influenza vaccine - A systematic review and meta-analysis. Vaccine 2023;41(31):4462–71. DOI PubMed

7. Young B, Sadarangani S, Jiang L, Wilder-Smith A, Chen MI. Duration of Influenza Vaccine Effectiveness: A Systematic Review, Meta-analysis, and Meta-regression of Test-Negative Design Case-Control Studies. J Infect Dis 2018;217(5):731–41. DOI PubMed

8. McLean HQ, Belongia EA. Influenza Vaccine Effectiveness: New Insights and Challenges. Cold Spring Harb Perspect Med 2021;11(6):a038315. DOI PubMed

9. Peters MD, Marnie C, Tricco AC, Pollock D, Munn Z, Alexander L, McInerney P, Godfrey CM, Khalil H. Updated methodological guidance for the conduct of scoping reviews. JBI Evid Synth 2020;18(10):2119–26. DOI PubMed

10. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, Moher D, Peters MD, Horsley T, Weeks L, Hempel S, Akl EA, Chang C, McGowan J, Stewart L, Hartling L, Aldcroft A, Wilson MG, Garritty C, Lewin S, Godfrey CM, Macdonald MT, Langlois EV, Soares-Weiser K, Moriarty J, Clifford T, Tunçalp Ö, Straus SE. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and Explanation. Ann Intern Med 2018;169(7):467–73. DOI PubMed

11. Tadount F, Sinilaite A. Intraseasonal Waning of Influenza Vaccine Effectiveness and Optimal Timing for Seasonal Influenza Vaccination Programs - Scoping Review Protocol. 2025. DOI

12. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A,Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JP. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898. DOI PubMed

13. Risk of bias tools. ROBINS-I V2 tool. 2024. https://www.riskofbias.info/welcome/robins-i-v2

14. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, Henry D, Altman DG, Ansari MT, Boutron I, Carpenter JR, Chan AW, Churchill R, Deeks JJ, Hróbjartsson A, Kirkham J, Jüni P, Loke YK, Pigott TD, Ramsay CR, Regidor D, Rothstein HR, Sandhu L, Santaguida PL, Schünemann HJ, Shea B, Shrier I, Tugwell P, Turner L, Valentine JC, Waddington H, Waters E, Wells GA, Whiting PF, Higgins JP. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 2016;355:i4919. DOI PubMed

15. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ 2017;358:j4008. DOI PubMed

16. Abou Chakra CN, Blanquart F, Vieillefond V, Enouf V, Visseaux B, Haim-Boukobza S, Josset L, Rameix-Welti MA, Lina B, Nunes MC, Bal A; RELAB Study group. Vaccine effectiveness dynamics against influenza and SARS-CoV-2 in community-tested patients in France 2023-2024. Emerg Microbes Infect 2025;14(1):2466699. DOI PubMed

17. Andrews N, McMenamin J, Durnall H, Ellis J, Lackenby A, Robertson C, von Wissmann B, Cottrell S, Smyth B, Moore C, Gunson R, Zambon M, Fleming D, Pebody R. Effectiveness of trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2012/13 end of season results. Euro Surveill 2014;19(27):5–13. DOI PubMed

18. Bi Q, Dickerman BA, Nguyen HQ, Martin ET, Gaglani M, Wernli KJ, Balasubramani GK, Flannery B, Lipsitch M, Cobey S; US Flu Vaccine Effectiveness Network Investigators. Reduced Effectiveness of Repeat Influenza Vaccination: Distinguishing Among Within-Season Waning, Recent Clinical Infection, and Subclinical Infection. J Infect Dis 2024;230(6):1309–18. DOI PubMed

19. Castilla J, Martínez-Baz I, Martínez-Artola V, Reina G, Pozo F, García Cenoz M, Guevara M, Morán J, Irisarri F, Arriazu M, Albéniz E, Ezpeleta C, Barricarte A; Primary Health Care Sentinel Network; Network for Influenza Surveillance in Hospitals of Navarre. Decline in influenza vaccine effectiveness with time after vaccination, Navarre, Spain, season 2011/12. Euro Surveill 2013;18(5):20388. DOI PubMed

20. Gherasim A, Pozo F, de Mateo S, Gamarra IA, García-Cenoz M, Vega T, Martínez E, Giménez J, Castrillejo D, Larrauri A; cycEVA team and the VEVA Working Group. Waning protection of influenza vaccine against mild laboratory confirmed influenza A(H3N2) and B in Spain, season 2014–15. Vaccine 2016;34(20):2371–7. DOI PubMed

21. Hu W, Sjoberg PA, Fries AC, DeMarcus LS, Robbins AS. Waning Vaccine Protection against Influenza among Department of Defense Adult Beneficiaries in the United States, 2016–2017 through 2019–2020 Influenza Seasons. Vaccines (Basel) 2022;10(6):888. DOI PubMed

22. Jiménez-Jorge S, de Mateo S, Delgado-Sanz C, Pozo F, Casas I, Garcia-Cenoz M, Castilla J, Pérez E, Gallardo V, Rodriguez C, Vega T, Quiñones C, Martínez E, Vanrell JM, Giménez J, Castrillejo D, Serrano MC, Ramos JM, Larrauri A; Spanish Influenza Sentinel Surveillance System. Effectiveness of influenza vaccine against laboratory-confirmed influenza, in the late 2011-2012 season in Spain, among population targeted for vaccination. BMC Infect Dis 2013;13(1):441. DOI PubMed

23. Kissling E, Valenciano M, Larrauri A, Oroszi B, Cohen JM, Nunes B, Pitigoi D, Rizzo C, Rebolledo J, Paradowska-Stankiewicz I, Jiménez-Jorge S, Horváth JK, Daviaud I, Guiomar R, Necula G, Bella A, O'Donnell J, Głuchowska M, Ciancio BC, Nicoll A, Moren A. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case-control study. Euro Surveill 2013;18(5):20390. DOI PubMed

24. Kissling E, Nunes B, Robertson C, Valenciano M, Reuss A, Larrauri A, Cohen JM, Oroszi B, Rizzo C, Machado A, Pitigoi D, Domegan L, Paradowska-Stankiewicz I, Buchholz U, Gherasim A, Daviaud I, Horváth JK, Bella A, Lupulescu E, O Donnell J, Korczyńska M, Moren A; I-MOVE case–control study team. I-MOVE multicentre case-control study 2010/11 to 2014/15: is there within-season waning of influenza type/subtype vaccine effectiveness with increasing time since vaccination? Euro Surveill 2016;21(16). DOI PubMed

25. Lewis NM, Zhu Y, Peltan ID, Gaglani M, McNeal T, Ghamande S, Steingrub JS, Shapiro NI, Duggal A, Bender WS, Taghizadeh L, Brown SM, Hager DN, Gong MN, Mohamed A, Exline MC, Khan A, Wilson JG, Qadir N, Chang SY, Ginde AA, Mohr NM, Mallow C, Lauring AS, Johnson NJ, Gibbs KW, Kwon JH, Columbus C, Gottlieb RL, Raver C, Vaughn IA, Ramesh M, Johnson C, Lamerato L, Safdar B, Casey JD, Rice TW, Halasa N, Chappell JD, Grijalva CG, Talbot HK, Baughman A, Womack KN, Swan SA, Harker E, Price A, DeCuir J, Surie D, Ellington S, Self WH; Investigating Respiratory Viruses in the Acutely Ill (IVY) Network. Vaccine Effectiveness Against Influenza A-Associated Hospitalization, Organ Failure, and Death: United States, 2022–2023. Clin Infect Dis 2024;78(4):1056–64. DOI PubMed

26. Lewis NM, Harker EJ, Cleary S, Zhu Y, Grijalva CG, Chappell JD, Rhoads JP, Baughman A, Casey JD, Blair PW, Jones ID, Johnson CA, Halasa NB, Lauring AS, Martin ET, Gaglani M, Ghamande S, Columbus C, Steingrub JS, Duggal A, Felzer JR, Prekker ME, Peltan ID, Brown SM, Hager DN, Gong MN, Mohamed A, Exline MC, Khan A, Ferguson SA, Mosier J, Qadir N, Chang SY, Ginde AA, Zepeski A, Mallow C, Harris ES, Johnson NJ, Gibbs KW, Kwon JH, Vaughn IA, Ramesh M, Safdar B, Surie D, Dawood FS, Ellington S, Self WH. Vaccine Effectiveness Against Influenza A(H1N1), A(H3N2), and B-Associated Hospitalizations, United States, 1 September 2023 to 31 May 2024. J Infect Dis 2025;232(4):e626–36. DOI PubMed

27. Maurel M, Pozo F, Pérez-Gimeno G, Buda S, Sève N, Oroszi B, Hooiveld M, Gomez V, Domegan L, Martínez-Baz I, Ilić M, Carnahan AS, Mihai ME, Martínez A, Goerlitz L, Enouf V, Horváth JK, Dijkstra F, Rodrigues AP, Bennett C, Trobajo-Sanmartín C, Mlinarić I, Latorre-Margalef N, Ivanciuc A, Lopez A, Dürrwald R, Falchi A, Túri G, Meijer A, Melo A, O'Donnell J, Castilla J, Vučina VV, Hagey TS, Lazar M, Kaczmarek M, Bacci S, Kissling E; VEBIS study team. Influenza vaccine effectiveness in Europe: Results from the 2022-2023 VEBIS (Vaccine Effectiveness, Burden and Impact Studies) primary care multicentre study. Influenza Other Respir Viruses 2024;18(1):e13243. DOI PubMed

28. Pebody R, Djennad A, Ellis J, Andrews N, Marques DF, Cottrell S, Reynolds AJ, Gunson R, Galiano M, Hoschler K, Lackenby A, Robertson C, O'Doherty M, Sinnathamby M, Panagiotopoulos N, Yonova I, Webb R, Moore C, Donati M, Sartaj M, Shepherd SJ, McMenamin J, de Lusignan S, Zambon M. End of season influenza vaccine effectiveness in adults and children in the United Kingdom in 2017/18. Euro Surveill 2019;24(31):1800488. DOI PubMed

29. Pebody R, Warburton F, Andrews N, Ellis J, von Wissmann B, Robertson C, Yonova I, Cottrell S, Gallagher N, Green H, Thompson C, Galiano M, Marques D, Gunson R, Reynolds A, Moore C, Mullett D, Pathirannehelage S, Donati M, Johnston J, de Lusignan S, McMenamin J, Zambon M. Effectiveness of seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2014/15 end of season results. Euro Surveill 2015;20(36):30013. DOI PubMed

30. Pebody R, Warburton F, Ellis J, Andrews N, Potts A, Cottrell S, Johnston J, Reynolds A, Gunson R, Thompson C, Galiano M, Robertson C, Byford R, Gallagher N, Sinnathamby M, Yonova I, Pathirannehelage S, Donati M, Moore C, de Lusignan S, McMenamin J, Zambon M. Effectiveness of seasonal influenza vaccine for adults and children in preventing laboratory-confirmed influenza in primary care in the United Kingdom: 2015/16 end-of-season results. Euro Surveill 2016;21(38):30348. DOI PubMed

31. Pebody R, Andrews N, McMenamin J, Durnall H, Ellis J, Thompson CI, Robertson C, Cottrell S, Smyth B, Zambon M, Moore C, Fleming DM, Watson JM. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection. Euro Surveill 2013;18(5):20389. DOI PubMed

32. Radin JM, Hawksworth AW, Myers CA, Ricketts MN, Hansen EA, Brice GT. Influenza vaccine effectiveness: maintained protection throughout the duration of influenza seasons 2010–2011 through 2013–2014. Vaccine 2016;34(33):3907–12. DOI PubMed

33. Ray GT, Lewis N, Klein NP, Daley MF, Wang SV, Kulldorff M, Fireman B. Intraseason Waning of Influenza Vaccine Effectiveness. Clin Infect Dis 2019;68(10):1623–30. DOI PubMed

34. Regan AK, Fielding JE, Chilver MB, Carville KS, Minney-Smith CA, Grant KA, Thomson C, Hahesy T, Deng YM, Stocks N, Sullivan SG. Intraseason decline in influenza vaccine effectiveness during the 2016 southern hemisphere influenza season: A test-negative design study and phylogenetic assessment. Vaccine 2019;37(19):2634–41. DOI PubMed

35. Sullivan SG, Komadina N, Grant K, Jelley L, Papadakis G, Kelly H. Influenza vaccine effectiveness during the 2012 influenza season in Victoria, Australia: influences of waning immunity and vaccine match. J Med Virol 2014;86(6):1017–25. DOI PubMed

36. Tenforde MW, Weber ZA, DeSilva MB, Stenehjem E, Yang DH, Fireman B, Gaglani M, Kojima N, Irving SA, Rao S, Grannis SJ, Naleway AL, Kirshner L, Kharbanda AB, Dascomb K, Lewis N, Dalton AF, Ball SW, Natarajan K, Ong TC, Hartmann E, Embi PJ, McEvoy CE, Grisel N, Zerbo O, Dunne MM, Arndorfer J, Goddard K, Dickerson M, Patel P, Timbol J, Griggs EP, Hansen J, Thompson MG, Flannery B, Klein NP. Vaccine Effectiveness Against Influenza-Associated Urgent Care, Emergency Department, and Hospital Encounters During the 2021-2022 Season, VISION Network. J Infect Dis 2023;228(2):185–95. DOI PubMed

37. Zhang L, Lu G, Ma C, Zhang J, Li J, Duan W, Ma J, Shi W, Wang Y, Sun Y, Zhang D, Wang Q, Huo D. Influenza Vaccine Effectiveness against Influenza A-Associated Outpatient and Emergency-Department-Attended Influenza-like Illness during the Delayed 2022–2023 Season in Beijing, China. Vaccines (Basel) 2024;12(10):1124. DOI PubMed

38. Zhu L, Han Y, Lu J, Tan J, Liao C, Guo C, He Q, Qiu Y, Lu H, Zhou Y, Wei J, Hu D. Evaluation of Influenza Vaccine Effectiveness from 2021 to 2024: A Guangdong-Based Test-Negative Case-Control Study. Vaccines (Basel) 2024;13(1):4. DOI PubMed

39. Zhu S, Quint J, León TM, Sun M, Li NJ, Yen C, Tenforde MW, Flannery B, Jain S, Schechter R, Hoover C, Murray EL. Estimating Influenza Vaccine Effectiveness Against Laboratory-Confirmed Influenza Using Linked Public Health Information Systems, California, 2023–2024 Season. J Infect Dis 2025;232(5):1249–57. DOI PubMed

40. Ferdinands JM, Gaglani M, Martin ET, Monto AS, Middleton D, Silveira F, Talbot HK, Zimmerman R, Patel M. Waning Vaccine Effectiveness Against Influenza-Associated Hospitalizations Among Adults, 2015–2016 to 2018–2019, United States Hospitalized Adult Influenza Vaccine Effectiveness Network. Clin Infect Dis 2021;73(4):726–9. DOI PubMed

41. Ferdinands JM, Fry AM, Reynolds S, Petrie J, Flannery B, Jackson ML, Belongia EA. Intraseason waning of influenza vaccine protection: Evidence from the US Influenza Vaccine Effectiveness Network, 2011-12 through 2014-15. Clin Infect Dis 2017;64(5):544–50. DOI PubMed

42. Wang S, Zheng Y, Jin X, Gan Z, Shao Y, Zhu C, Hu X, Liang Z, Chen Y, Xing B, Lv H, Xu N. Efficacy and safety of a live attenuated influenza vaccine in Chinese healthy children aged 3–17 years in one study center of a randomized, double-blind, placebo-controlled phase 3 clinical trial, 2016/17 season. Vaccine 2020;38(38):5979–86. DOI PubMed

43. Powell L, Bégué R. 2732. Estimate of the Effectiveness of Influenza Vaccine among Children for the 2017–2018 Season. Open Forum Infect Dis 2019;6(Supp 2):S961–2. DOI

44. Feng S, Chiu SS, Chan EL, Kwan MY, Wong JS, Leung CW, Chung Lau Y, Sullivan SG, Malik Peiris JS, Cowling BJ. Effectiveness of influenza vaccination on influenza-associated hospitalisations over time among children in Hong Kong: a test-negative case-control study. Lancet Respir Med 2018;6(12):925–34. DOI PubMed

45. Chiu SS, Kwan MY, Feng S, Wong JS, Leung CW, Chan EL, Chan KH, Ng TK, To WK, Cowling BJ, Peiris JS. Influenza Vaccine Effectiveness Against Influenza A(H3N2) Hospitalizations in Children in Hong Kong in a Prolonged Season, 2016/2017. J Infect Dis 2018;217(9):1365–71. DOI PubMed

46. Domnich A, Orsi A, Signori A, Chironna M, Manini I, Napoli C, Rizzo C, Panatto D, Icardi G. Waning intra-season vaccine effectiveness against influenza A(H3N2) underlines the need for more durable protection. Expert Rev Vaccines 2024;23(1):380–8. DOI PubMed

47. Sahni LC, Naioti EA, Olson S, Campbell AP, Michaels MG, Williams JV, Allen Staat M, Schlaudecker EP, Halasa NB, Stewart LS, Englund JA, Klein EJ, Szilagyi PG, Weinberg GA, Harrison CJ, Selvarangan R, Azimi PH, Singer MN, Piedra P, Munoz FM, Patel M, Boom JA. 1178. Sustained Vaccine Effectiveness Against Influenza-Associated Hospitalization in Children: Evidence from the New Vaccine Surveillance Network, 2015-2016 Through 2019-2020. Open Forum Infect Dis 2021;8(Supp 1):S681–2. DOI

48. Mira-Iglesias A, López-Labrador FX, García-Rubio J, Mengual-Chuliá B, Tortajada-Girbés M, Mollar-Maseres J, Carballido-Fernández M, Schwarz-Chavarri G, Puig-Barberà J, Díez-Domingo J. Influenza Vaccine Effectiveness and Waning Effect in Hospitalized Older Adults. Valencia Region, Spain, 2018/2019 Season. Int J Environ Res Public Health 2021;18(3):1129. DOI PubMed

49. Seppälä E, Dahl J, Veneti L, Rydland KM, Klüwer B, Rohringer A, Meijerink H. Covid-19 and influenza vaccine effectiveness against associated hospital admission and death among individuals over 65 years in Norway: A population-based cohort study, 3 October 2022 to 20 June 2023. Vaccine 2024;42(3):620–8. DOI PubMed

50. Hergens MP, Baum U, Brytting M, Ikonen N, Haveri A, Wiman Å, Nohynek H, Örtqvist Å. Mid-season real-time estimates of seasonal influenza vaccine effectiveness in persons 65 years and older in register-based surveillance, Stockholm County, Sweden, and Finland, January 2017. Euro Surveill 2017;22(8):30469. DOI PubMed

51. Costantino V, Trent M, MacIntyre CR. Modelling of optimal timing for influenza vaccination as a function of intraseasonal waning of immunity and vaccine coverage. Vaccine 2019;37(44):6768–75. DOI PubMed

52. Ferdinands JM, Alyanak E, Reed C, Fry AM. Waning of Influenza Vaccine Protection: Exploring the Trade-offs of Changes in Vaccination Timing Among Older Adults. Clin Infect Dis 2020;70(8):1550–9. DOI PubMed

53. Kahana D, Yamin D. Accounting for the spread of vaccination behavior to optimize influenza vaccination programs. PLoS One 2021;16(6):e0252510. DOI PubMed

54. Lee BY, Tai JH, Bailey RR, Smith KJ, Nowalk AJ. Economics of influenza vaccine administration timing for children. Am J Manag Care 2010;16(3):e75–85. PubMed

55. Lee BY, Bartsch SM, Brown ST, Cooley P, Wheaton WD, Zimmerman RK. Quantifying the economic value and quality of life impact of earlier influenza vaccination. Med Care 2015;53(3):218–29. DOI PubMed

56. Myers ER, Misurski DA, Swamy GK. Influence of timing of seasonal influenza vaccination on effectiveness and cost-effectiveness in pregnancy. Am J Obstet Gynecol 2011;204(6 Suppl 1):S128-40. DOI PubMed

57. Newall AT, Chen C, Wood JG, Stockwell MS. Within-season influenza vaccine waning suggests potential net benefits to delayed vaccination in older adults in the United States. Vaccine 2018;36(39):5910–5. DOI PubMed

58. Smith KJ, France G, Nowalk MP, Raviotta JM, DePasse J, Wateska A, Shim E, Zimmerman RK. Compressed Influenza Vaccination in U.S. Older Adults: A Decision Analysis. Am J Prev Med 2019;56(4):e135–41. DOI PubMed

59. Williams KV, Krauland MG, Harrison LH, Williams JV, Roberts MS, Zimmerman RK. Can a Two-Dose Influenza Vaccine Regimen Better Protect Older Adults? An Agent-Based Modeling Study. Vaccines (Basel) 2022;10(11):1799. DOI PubMed

60. Spencer JA, Smith MZ, Osthus D, Alexander PC, Del Valle SY. When to vaccinate for seasonal influenza? Check the peak forecast. Research Square 2024. DOI

61. Glinka ER, Smith DM, Johns ST. Timing Matters - Influenza Vaccination to HIV-Infected Patients. HIV Med 2016;17(8):601–4. DOI PubMed

62. Worsham CM, Bray CF, Jena AB. Optimal timing of influenza vaccination in young children: population based cohort study. BMJ 2024;384:e077076. DOI PubMed

63. Young B, Zhao X, Cook AR, Parry CM, Wilder-Smith A, I-Cheng MC. Do antibody responses to the influenza vaccine persist year-round in the elderly? A systematic review and meta-analysis. Vaccine 2017;35(2):212–21. DOI PubMed

64. Redlberger-Fritz M, Kundi M, Popow-Kraupp T. Heterogeneity of Circulating Influenza Viruses and Their Impact on Influenza Virus Vaccine Effectiveness During the Influenza Seasons 2016/17 to 2018/19 in Austria. Front Immunol 2020;11:434. DOI PubMed

Appendix

Supplemental material is available upon request to the author: naci-ccni@phac-aspc.gc.ca

Economic evaluation of wastewater surveillance in Ontario, Canada, using COVID-19 as a case study

Yeva Sahakyan[1], David Champredon[2], Prakathesh Rabeenthira[2,3], Alex Rodriguez Barizonte[4], Manon Fleury[2], Beate Sander[1,5,6,7]*

Abstract

Background: The COVID-19 pandemic has stimulated the use of wastewater surveillance (WWS) in Canada.

Objective: To inform continued investment, the study assessed the cost-utility of WWS, alongside conventional surveillance, compared to conventional surveillance alone, using COVID-19 in Ontario as an example.

Methods: This model-based cost-utility analysis measured WWS effectiveness by increased lead time of 1–10 days for public health response using the Ontario health system perspective. The model integrated SARS-CoV-2 transmission dynamics, SARS-CoV-2 RNA concentration in the sewage system, and disease progression. The analysis considered year-round surveillance with an outbreak occurring once in a decade, assuming WWS benefits accrue only in the outbreak year. At the individual-level, a lifetime time horizon was used and future health outcomes (quality-adjusted life years [QALYs]) and cost were discounted at 1.5%. The model was informed by population-based administrative data and was calibrated to real-world Ontario surveillance data.

Results: For Omicron/BA.1-like outbreaks, a WWS program with a $15 million CAD/year budget maintained over 10 years would be cost-effective at a $50,000 CAD/QALY threshold if it detects an outbreak three or more days earlier, and cost-saving if it detects an outbreak 10 or more days earlier than conventional surveillance. For a less severe outbreak with lower transmission rates, e.g., XBB-like, the WWS program would be cost-effective if at least six outbreaks occur in a decade.

Conclusion: The study findings suggest that long-term investments in WWS are likely cost-effective for low-frequency but high-impact outbreaks. Maintaining WWS infrastructure will enhance Canada's emergency preparedness for emerging and re-emerging pathogens.

Suggested citation: Sahakyan Y, Champredon D, Rabeenthira P, Barizonte AR, Fleury M, Sander B. Economic evaluation of wastewater surveillance in Ontario, Canada, using COVID-19 as a case study. Can Commun Dis Rep 2026;52(6):246–55. https://doi.org/10.14745/ccdr.v52i06a04

Keywords: economic evaluation, cost-utility, epidemic model, SARS-CoV-2, COVID-19, outbreak, wastewater surveillance

Affiliations

[1] Health Systems and Policy Research Collaborative Centre, University Health Network, Toronto, ON

[2] National Microbiology Laboratory, Public Health Agency of Canada, Guelph, ON

[3] VHA Home HealthCare, Toronto, ON

[4] Faculty of Arts & Science, University of Toronto, Toronto, ON

[5] Public Health Ontario, Toronto, ON

[6] Institute of Health Policy, Management, and Evaluation, University of Toronto, Toronto, ON

[7] ICES, Toronto, ON

***Correspondence:**
beate.sander@uhn.ca

Introduction

As of December 2024, the COVID-19 pandemic has imposed substantial global burden with over 777 million cases, over seven million reported deaths (1) and a profound impact on health system expenditures (2,3). In Canada, as of September 2023, at least 374,106 hospital admissions have occurred due to COVID-19, of which 64,623 included intensive care unit (ICU) admissions and 46,472 resulted in death (4–7). The total expenditure incurred by the Canadian healthcare system was estimated to be over $9 billion CAD (4–7).

To guide public health interventions to mitigate the impact of COVID-19, surveillance data must be collected quickly and

affordably (8). While polymerase chain reaction (PCR) testing is essential for individual-level detection, it has limitations for large-scale surveillance during major public health events (9). These include 1) reduced testing among individuals with mild or asymptomatic condition leading to underestimation of disease prevalence (10,11), 2) limited availability of PCR or point-of-care testing and capacity for laboratory personnel, as well as 3) the time lag between infection, testing and reporting that delays detection of community transmission (11).

The need for reliable and efficient population-level monitoring has highlighted the potential of wastewater surveillance (WWS) for tracking infectious disease prevalence and spread (12–14). Studies have shown that SARS-CoV-2 fecal viral load rises shortly after infection and peaks around symptom onset (15,16); therefore, PCR testing on wastewater samples may provide insights into infection trends in a population (17). Wastewater surveillance may complement conventional surveillance, by enabling earlier detection of community transmission, and capturing data from individuals with mild, presymptomatic and asymptomatic infection, often missed by conventional surveillance.

Beginning in September 2020, the Public Health Agency of Canada (PHAC) launched the National Wastewater Monitoring of Pathogens program, a systematic effort to collect and analyze wastewater from communities across Canada (18). As of early 2025, this program routinely samples from more than 90 municipal sites, covering an estimated 36.6% of the Canadian population. In Ontario, eight sites provide data for an estimated 31.1% of the provincial population. In addition to the federal program, many provinces and territories in Canada have also launched their own wastewater programs.

Wastewater surveillance implementation and maintenance requires resources; for example, the Ontario provincial WWS program reached a total operating expense of $15 million CAD in 2023–2024, which reflected a system with 59 monitored sites with sampling conducted three to five times per week (19,20).

To inform continued investment into WWS, this study assessed the cost-utility of WWS in addition to conventional surveillance compared to conventional surveillance alone, using COVID-19 in Ontario as an example. While the focus was on SARS-CoV-2, the framework may be applicable to other infectious pathogens that can be monitored through wastewater and is intended to inform long-term public health surveillance strategies.

Methods

A model-based cost-utility analysis was conducted from the Ontario health system perspective, following Canadian guidance on economic evaluation in health (21,22). Because the timing of a future outbreak is unknown, the analysis considered year-round surveillance over 10 years with an outbreak occurring once in a decade. An outbreak was characterized by one major wave within the outbreak year. Individuals infected during the outbreak year were followed over their lifetime time to capture downstream health outcomes (i.e., life years, quality adjusted life years [QALYs] and cost, discounted by 1.5% as recommended (22)). Although WWS is maintained for each of the 10 years, the model conservatively assumed benefits from WWS occur only in the outbreak year, with no benefits during non-outbreak years.

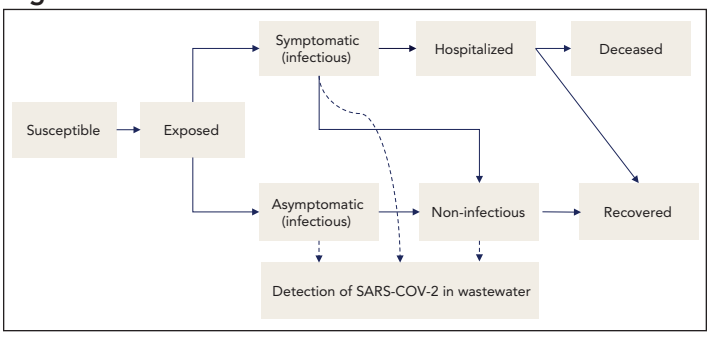
Population

The modelled population reflects epidemiological and demographic characteristics of the Ontario population who experienced COVID-19 infection, hospitalization, ICU admission, or death during selected waves of the recent COVID-19 pandemic or remained uninfected with COVID-19.

Model structure and assumptions

The analysis was based on the epidemic model previously developed by the PHAC (23), which integrates both the transmission dynamics of SARS-CoV-2 at the population-level and the concentration of SARS-CoV-2 RNA in the sewage system following viral shedding by infected individuals. Disease progression was captured through several health states: susceptible; exposed (infected but not yet infectious); asymptomatically or symptomatically infected; hospitalized; recovered and no longer infectious but still shedding virus; fully recovered and permanently immune and no longer shedding the virus; and deceased (**Figure 1**). Infection occurred at a time-dependent transmission rate, which was simultaneously calibrated on clinical reports, hospital admissions and wastewater concentrations using real-world surveillance data from Ontario during the Omicron and XBB waves of the pandemic. The weekly clinical report and hospitalizations were retrieved from Public Health Ontario (24,25), and the SARS-CoV-2 RNA concentration in wastewater was sourced from the PHAC's National Wastewater Monitoring of Pathogens program covering Toronto, Ontario. The key model parameters are summarized in **Table 1**.

Figure 1: Model structure



Strategies

The analysis assumed that WWS operated in addition to the conventional surveillance program and did not account for

Table 1: Key parameters

Transmission	Value	Source
Reproductive number[a]	Calibrated	Calibrated to match reported cases. (Gov. of ON) (24)
Average latency duration (not infectious yet), days	6	(PHAC, 2021) (26)
Symptomatic individuals who will not be hospitalized in future, days	12	(PHO, 2021) (27)
Average duration among symptomatic individuals who will be hospitalized in future, days	15	(PHO, 2021) (27)
Average duration among asymptomatic individuals, days	10	(PHO, 2021) (27)
Average duration of shedding after infectiousness, days	21	(Li, 2022), (Zhang, 2021) (28,29)
Proportion asymptomatic cases	0.33	(Oran, 2021), (Sah, 2021) (30,31)
Proportion of hospitalization[a]	Calibrated	Calibrated to match reported cases. (Gov. of ON) (25)
Average LOS in hospital, days	13	(CIHI, 2023) (5)
Days required to build immunity	40	(Carazo, 2023) (32)
Time horizon		
Individual level, years	Lifetime	(CADTH, 2017) (22)
Program level, years	10	Assumption
Case counting during the first wave of Omicron, days	120	Wave duration, (Gov. of Can, 2024) (18)
Case counting during the first wave of XBB, days	270	Wave duration, (Gov. of Can, 2024) (18)
Age and life expectancy		
Individuals with COVID-19		
Non-hospitalized	40	Statista Research Department (33)
Hospitalized (no-ICU)	65	(CIHI, 2023) (5)
ICU admitted	62	(CIHI, 2023) (5)
Died	84	(CIHI, 2023) (5)
Life expectancy	Age-dependent	Lifetables[b]
Utilities		
General population	Age-dependent	(Yan, 2024) (34)[b]
Individuals with COVID-19, estimated 360 day average		
Non-hospitalized	0.838	(Mao, 2024) (35)
Hospitalized (no-ICU)	0.827	(Mao, 2024) (35)
ICU admitted	0.746	(Mao, 2024) (35)
COVID-19 attributable costs (2023 CAD)[c]		
No hospital stay	$295	(Sander, 2025) (36)
Hospital stay (no-ICU), alive at end of follow up	$30,030	(Sander, 2025) (36)
Hospital stay (no-ICU), died before end of follow up	$30,610	(Sander, 2025) (36)
ICU stay, alive at end of follow up	$114,945	(Sander, 2025) (36)
ICU stay, died before end of follow up	$91,091	(Sander, 2025) (36)
Post-COVID-19 condition	$275	(Sander, 2025) (36)
Average annual costs for general population (2023 CAD)	Age-dependent	Estimated based on CIHI expenditures and lifetables[b]
WWS annual cost (2023 CAD)	$15 M	Gov. of ON (19)

Abbreviations: CAD, Canadian dollar; CADTH, Canadian Agency for Drug and Technology in Health; CIHI, Canadian Institute for Health Information; Gov. of Can, Government of Canada; Gov. of ON, Government of Ontario; ICU, intensive care unit; LOS, length of stay; PHAC, Public Health Agency of Canada; PHO, Public Health Ontario; WWS, wastewater surveillance

[a] Reproductive number and proportion of hospitalization (of those who were symptomatic) were calibrated separately for the Omicron and XBB waves

[b] Data available upon request from corresponding author

[c] COVID-19 attributable healthcare costs inpatient hospitalizations, outpatient hospital visits, emergency department visits, publicly funded drugs (for everyone aged 65 years and select younger individuals based on means) physician services, rehabilitation services, complex care, homecare, long-term care, and other (e.g., laboratory tests/services, assistive devices), rounded to the nearest dollar, from index to 360 days of follow-up or death, whichever occurred first

potential cost-savings from reduced reliance on patient-level testing. The impact of WWS relative to conventional surveillance was determined by increased lead time of one, three, five or 10 days for public health response (37,38) assuming that transmission would be reduced by 75% due to interventions/restrictions. This assumption was based on calibration of the epidemic model to the Omicron wave of the COVID-19 pandemic (November 2021–2022) in Ontario (24,25).

Outcomes

Outcomes included the number of individuals who are asymptomatic, symptomatic and treated in the outpatient setting, hospitalized, admitted to ICU and died due to COVID-19. The analysis also considered life years, QALYs and health system cost associated with COVID-19 management. The incremental cost-effectiveness ratio, a measure of cost-effectiveness, was estimated assuming the annual cost of WWS to be $15 million CAD (19), along with the maximum expenditure at which a WWS program would still be cost-effective. Cost-effectiveness was assessed at the commonly used threshold of $50,000 CAD per QALY gained (39).

Data

Life expectancy: Disease severity is reflected by the need for hospitalization and ICU admission. The median age of individuals who were hospitalized, including ICU admissions, was obtained from the Canadian Institute for Health Information (5). Individuals who required hospitalization were older, consistent with an age-related increase in disease severity. However, the analysis did not specifically address how hospitalizations and ICU admissions affected life expectancy beyond age-specific mortality. For individuals who were uninfected, asymptomatic and symptomatic but not hospitalized, the median age of the general Ontario population (33) was considered. Age-specific life expectancy was obtained from Statistics Canada (40) (Table 1; additional data available from corresponding author).

Quality of life: Health utility reflects the quality of life associated with a specific health state and is typically anchored at zero (death) and one (perfect health). Quality-adjusted life years are calculated as the product of utility and time spent in a specific health state (41). For uninfected and asymptomatic individuals, the utility values representative of the Canadian general population were applied, based on a study using the EQ-5D-5L instrument (34). For symptomatic individuals the mean utility 0–12 months post-infection was derived from a scoping review (35) and assumed the utility of the Canadian general population after 12 months (Table 1). The review included over 60 studies, mostly from Europe (N=39), Asia (N=15) and North America (N=8), with EQ-5D as the most frequently used instrument.

Cost: The annual cost-associated with WWS maintenance in Ontario was considered to be $15 million CAD (19). The COVID-19-attributable one-year costs (Table 1) were based on an Ontario population-based matched cohort study using health administrative data and included all publicly funded health services (36).

Zero COVID-19-attributable costs were assumed one year after infection with mean healthcare costs of the general population applied thereafter. Similarly, individuals with asymptomatic infections were assumed to incur healthcare costs equal to that of the general population. Lifetime healthcare costs for general population, were estimated considering life-expectancy and annual healthcare expenditures by age groups, based on Canadian Institute for Health Information data (40,42).

Analysis

The base-case scenario considered deterministic values for costs and utilities, assuming the Omicron wave pandemic, with no post-COVID conditions. A year-round surveillance over a 10-year period was modelled, with an outbreak occurring either in the first year or in the last year. Benefits from WWS were assumed only occurred during the outbreak year. Additionally, to address parameter uncertainty, a probabilistic analysis was conducted, using beta distributions to sample utility values, gamma distributions to sample costs, and uniform distribution to sample the outbreak year.

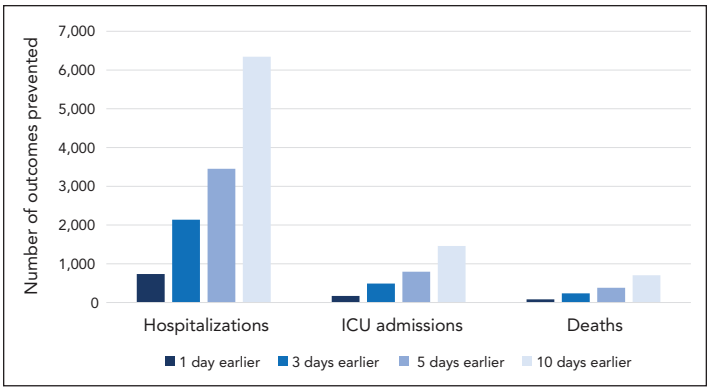
A range of scenario analyses were conducted. One scenario assumed that 15% of the infected population would experience the post-COVID-19 condition, with reduced health utility of 0.005 and increased healthcare utilization continuing one year post infection for their remaining lifetime. For these individuals, a lifetime annual cost increment of $275 was applied, based on Sander *et al.* (36) who estimated the average net cost of $7.60 per 10-day interval during months 9–12 post-infection. Best- and worst-case scenarios were conducted using the upper and lower bounds of the confidence intervals from the transmission model predictions. The cost-utility of a WWS program maintained for 20 years, where an outbreak occurs during the 20th year, was assessed as the most conservative scenario. Finally, the cost-effectiveness of the WWS was estimated assuming an outbreak with a lower transmission rate similar to the XBB wave, that may occur once or more frequently per decade.

Results

Scenario considering the Omicron wave

Compared to conventional surveillance, a WWS program that detects Omicron/BA.1-like outbreaks one to 10 days earlier could prevent, on average, 735 (95% CI: 566–939) to 6,345 (95% CI: 4,794–8,071) hospitalizations, including 169 (95% CI: 130–216) to 1,459 (95% CI: 1,103–1,856) ICU admissions, and avert 81 (95% CI: 66–89) to 702 (95% CI: 557–795) deaths (**Figure 2**; additional data available from corresponding author), assuming a single wave of an outbreak once in a decade, and no other major events in the remaining nine years.

Figure 2: Hospitalizations, intensive care unit admissions and deaths averted per 14 million (i.e., Ontario) simulated population (base-case scenario)[a]



Abbreviation: ICU, intensive care unit
[a] Comparator strategies provide 1, 3, 5 and to 10 days earlier detection of outbreaks, and, as such, 1 to 10 days earlier implementation of infection-control measures compared to conventional surveillance

A WWS program with an annual budget of $15 million CAD (in addition to conventional surveillance) maintained over 10 years would be considered cost-effective at a $50,000/QALY threshold if it detects an outbreak three or more days earlier, and cost-saving if it detects an outbreak 10 or more days earlier than conventional surveillance, regardless of which year the outbreak occurs (**Table 2**). Probabilistic analysis showed that WWS providing a three-day lead time detection was cost-effective in 77% of simulations compared to conventional surveillance (data available from corresponding author).

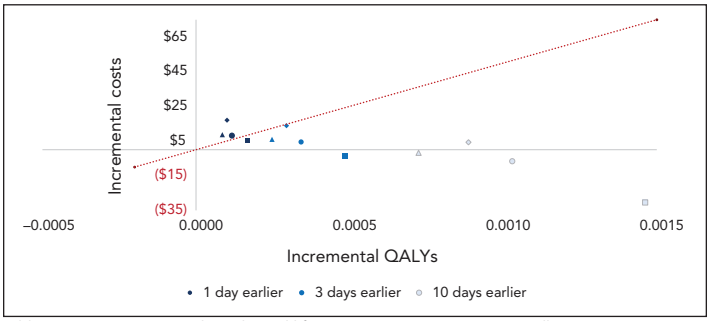
When lifetime disutility and costs associated with the post-COVID-19 condition are considered, a program that detects outbreaks three or more days earlier becomes cost-saving (**Figure 3**, Table 2). Summary for the outcomes for best- and worst-case scenarios are available from corresponding author. With a longer program horizon of 20 years, one outbreak in year 20th, and an annual budget of $15 million CAD, a WWS

Table 2: Expected quality-adjusted life years, and costs (2023 Canadian dollars) per person

Scenarios	QALY	Δ QALYs	Costs	Δ Costs	ICUR[a]	Max. annual program cost[b]
Outbreak occurring during the 1st year						
Conventional surveillance	27.1267	Ref.	$296,863	Ref.	Ref.	Ref.
1 day earlier[c]	27.1269	0.00013	$296,861	−$2.20	$58,448	$13,308,549
3 days earlier[c]	27.1271	0.00039	$296,857	−$6.41	$9,250	$38,847,772
5 days earlier[c]	27.1274	0.00063	$296,853	−$10.36	Cost-saving	$62,949,902
10 days earlier[c]	27.1279	0.00118	$296,844	−$19.11	Cost-saving	$116,599,789
Outbreak occurring during the 10th year						
Conventional surveillance	23.7248	Ref.	$259,635	Ref.	Ref.	Ref.
1 day earlier[c]	23.7250	0.00012	$259,633	−$1.93	$69,186	$11,639,553
3 days earlier[c]	23.7252	0.00034	$259,629	−$5.61	$12,926	$33,975,960
5 days earlier[c]	23.7254	0.00055	$259,625	−$9.07	1,737	$55,055,496
10 days earlier[c]	23.7259	0.00103	$259,618	−$16.71	Cost-saving	$101,977,270
Outbreak occurring during the 1st year, assuming lifetime post-COVID-19 condition						
Conventional surveillance	27.1198	Ref.	$297,248	Ref.	Ref.	Ref.
1 day earlier[c]	27.1200	0.00019	$297,242	−$5.28	$24,982	$22,108,811
3 days earlier[c]	27.1203	0.00056	$297,232	−$15.42	Cost-saving	$64,588,401
5 days earlier[c]	27.1207	0.00090	$297,223	−$25.00	Cost-saving	$104,732,688
10 days earlier[c]	27.1214	0.00167	$297,201	−$46.32	Cost-saving	$194,308,753
Outbreak occurring during the 10th year, assuming lifetime post-COVID-19 condition						
Conventional surveillance	23.7187	Ref.	$259,971	Ref.	Ref.	Ref.
1 day earlier[c]	23.7189	0.00017	$259,966	−$4.62	$32,553	$19,336,195
3 days earlier[c]	23.7192	0.00049	$259,957	−$13.49	Cost-saving	$56,488,515
5 days earlier[c]	23.7195	0.00079	$259,949	−$21.86	Cost-saving	$91,598,396
10 days earlier[c]	23.7202	0.00146	$259,930	−$40.51	Cost-saving	$169,940,927

Abbreviations: CAD, Canadian dollar; ICUR, incremental cost-effectiveness ratio; max., maximum; Ref., reference category; QALYs, quality-adjusted life years; Δ, incremental
[a] Incremental cost-utility ratio has been calculated assuming the incremental cost for the wastewater surveillance program of $15 million annually
[b] Wastewater surveillance program operational maximum annual cost for the strategy to remain cost-effective at a $50,000 CAD/QALY gained threshold, if maintained over 10 years
[c] Wastewater surveillance program that provides 1 to 10 days earlier detection of outbreaks, and, as such, 1 to 10 days earlier implementation of infection-control measures compared to conventional surveillance

Figure 3: Incremental quality-adjusted life years and healthcare costs for scenarios involving Omicron-like outbreak[a,b]



Abbreviations: QALYs, quality-adjusted life years; WWS, wastewater surveillance

[a] The graph illustrates the incremental costs in 2023 Canadian dollars (Y-axis) and incremental QALYs (X-axis) for WWS offering one, three and 10 days earlier detection of outbreaks, and, as such, one, three and 10 days earlier implementation of infection-control measures compared to conventional surveillance

[b] Symbols in the figure represent different scenarios: ♦ (rhombus) denotes the WWS 20-year scenario, ● (circle) represents the base case scenario, ▲ (triangle) indicates the worst-case scenario and ■ (quadrant) accounts for the post-COVID condition. All scenarios assume a 10-year WWS maintenance period, with an outbreak occurring in the 10th year, except for the "WWS for 20 years" scenario, the most conservative, where the WWS program is maintained for 20 years, and an Omicron-like outbreak occurs in the 20th year. A strategy that detects outbreak five-day earlier and a best-case scenario were not plotted for better visualisation. The diagonal red line represents the $50,000 cost-effectiveness threshold, below which the WWS strategy is considered cost-effective

program would be considered cost-effective at a $50,000/QALY threshold if it detects an outbreak three or more days earlier than conventional surveillance (Figure 3, data available from corresponding author).

Scenario considering the XBB wave

Compared to conventional surveillance, a WWS program that detects outbreaks similar to the XBB wave one to 10 days earlier could prevent 87 (95% CI: 63–98) to 901 (95% CI: 678–1,017) hospitalizations and avert eight (95% CI: 8–10) to 79 (95% CI: 79–101) deaths (data available upon request). For outbreaks like XBB, which have a lower transmission rate, WWS was not found to be cost-effective if the outbreak occurs only once per decade (data available upon request). A WWS program with an annual budget of $15 million CAD (in addition to conventional surveillance) maintained over 10 years and providing a three-day detection lead time, would be considered cost-effective if an XBB-like outbreak occurs in at least six out of the 10 years (data available upon request).

Discussion

The study findings suggest that long-term investment in WWS is likely cost-effective for low-frequency but high-impact outbreaks. In scenarios with Omicron-like outbreaks, a WWS program with an annual budget of $15 million CAD maintained over 10 or even 20 years along with the implementation of public health policies that reduce transmission by 75% during the outbreak would be considered cost-effective at a $50,000/QALY threshold if it detects outbreaks three or more days earlier than conventional surveillance. For less severe outbreaks with lower transmission rates, like the XBB sub-variant, the WWS program was generally not cost-effective, unless outbreaks were frequent. However, these findings rely on the assumption of highly effective public health policies, which may not be feasible to sustain over multiple outbreaks. The observed differences between the two epidemiological scenarios are attributable to the substantially lower transmission rate of XBB, meaning that interventions, which limit transmission, would have a smaller impact compared to outbreaks with higher transmission rates.

The study findings align with studies showing that population-wide testing may not be cost-effective for pathogens with lower transmission rates. For example, Neilan *et al.*, in their modelling study, showed that compared to testing of symptomatic cases only, PCR testing of the entire population was cost-effective when the virus' reproductive number exceeded 1.6 (43). While this study focuses on WWS for population-wide monitoring, it similarly highlights the impact of transmission rates on cost-effectiveness. Unlike large-scale testing, which can be challenging to implement, WWS provides a more feasible approach. In Canada, for example, testing in March 2020 was limited to individuals with severe infection requiring hospitalization, long-term care residents and those with respiratory symptoms (44,45). Testing of selected population was later shown to be not cost-effective than testing all symptomatic individuals (43).

Cost-effectiveness data on WWS remains limited. Yoo *et al.* evaluated the cost-benefit of COVID-19 screening with antigen tests vs. WWS in a residential facility in Japan (46). They reported that WWS was economically justifiable at moderate, but not at high or low incidence levels; however, their model was constrained to a closed environment of 100 individuals and a program duration of just four days. In contrast, the current analysis considers the operation of WWS in Ontario, a province with a population of 14 M, over a 10- to 20-year time horizon, providing estimates of cost-effectiveness for a population-based surveillance program. Similarly, Mvundura *et al.*, using an agent-based model, showed that WWS could avert 300–600 disability-adjusted life years over a six-month outbreak period and be cost-effective particularly in settings with high disease severity (47).

The effectiveness of WWS depends on several factors, including population density, wastewater infrastructure, pathogen detectability in wastewater, sampling frequency and analytical methods. Wastewater surveillance can complement conventional surveillance and enable community-wide monitoring regardless of healthcare access, healthcare-seeking behavior, testing disparities or socio-economic factors, providing a more affordable alternative to individual testing. Sanjak *et al.* compared the costs of WWS and clinical swab testing in 82 United States military bases under various outbreak scenarios, finding that WWS had $10.5 million–$18.5 million lower annual direct costs (48). Moreover, they estimated that over two-thirds of clinical swab testing could be replaced by WWS at no

additional cost when accounting for lost work time due to swab testing requirements (48).

Limitations

This study has several limitations. First, it focused solely on SARS-CoV-2, and a single outbreak within a ten-year period. This results in a conservative estimate, as Canada has experienced multiple waves of COVID-19 outbreaks spanning beyond one year (49). Second, the analysis did not incorporate the costs of downstream response measures that might follow WWS-triggered alerts; however, such public health responses would likely be implemented under conventional surveillance as well, albeit later, and therefore, incorporating these costs would likely have minimal impact on the overall cost-effectiveness conclusions. Third, the analysis did not account for the broader applicability of WWS in concurrently monitoring multiple pathogens, such as respiratory syncytial virus, influenza or enteroviruses (12,14,50). Detecting multiple pathogens using the same infrastructure could enhance public health preparedness at minimal additional cost. Furthermore, the study did not evaluate WWS from a broader societal perspective. Incorporating productivity losses would likely increase the value of WWS. Conversely, WWS may have limited value in detecting novel viruses during earlier waves of an outbreak, as assays development takes time, which can delay reliable detection.

Strengths

This study has several strengths. This is one of the few economic evaluations of WWS based on a large scale, population-wide setting. The model was calibrated using real-world data on infections, hospitalizations and deaths, which strengthens the validity of the findings. By considering high- and low-transmission outbreaks and a broad range of scenarios, the study provides valuable insights for decision-making.

Conclusion

Wastewater surveillance provides benefits that extend beyond the pandemic response, yet many of these benefits are difficult to quantify. This analysis focused on one measurable benefit for COVID-19 pandemic surveillance, where the most immediate and direct impact has been demonstrated. Wastewater surveillance appears to be cost-effective under various COVID-19 outbreak scenarios, especially for high-transmission events like Omicron/BA.1, with substantial health and economic benefits arising from early detection. However, this narrow scope likely underestimates WWS's full potential. Beyond pandemic settings, WWS could enable year-round, population-wide surveillance of multiple pathogens, potentially reducing surveillance lag and providing critical lead time for public health response. Leveraging the existing WWS infrastructure will enhance Canada's preparedness for emerging and re-emerging pathogens.

Authors' statement

YS — Conceptualization, methodology, formal analysis, data interpretation, writing–original draft
DC — Conceptualization, methodology, formal analysis, data interpretation, writing–review & editing
PR — Conceptualization, writing–review & editing
ARB — Methodology, writing–original draft
MF — Conceptualization, writing–review & editing
BS — Conceptualization, methodology, writing–review & editing

Competing interests

None.

ORCID numbers

Yeva Sahakyan — 0000-0002-7216-064X
David Champredon — 0000-0002-7090-8757
Prakathesh Rabeenthira — 0009-0001-5522-7363
Beate Sander — 0000-0003-2128-9133

Acknowledgement

The authors acknowledge Jagdesh Birdi for supporting this project through literature searches.

Funding

This project was funded by Government of Canada, through the Public Health Agency of Canada. This research was supported, in part, by a Tier 1 Canada Research Chair (CRC) in Economics of Infectious Diseases held by Beate Sander (CRC–2022–00362).

References

1. World Health Organization. WHO COVID-19 dashboard. Geneva, CH: WHO. [Accessed 2024 Dec 11]. https://data.who.int/dashboards/covid19/cases

2. Kapinos KA, Peters RM Jr, Murphy RE, Hohmann SF, Podichetty A, Greenberg RS. Inpatient Costs of Treating Patients With COVID-19. JAMA Netw Open 2024;7(1):e2350145. DOI PubMed

3. Nakhaee M, Khandehroo M, Esmaeili R. Cost of illness studies in COVID-19: a scoping review. Cost Eff Resour Alloc 2024;22(1):3. DOI PubMed

4. Canadian Institute for Health Information. COVID-19 Hospitalization and Emergency Department Statistics, 2019–2020 and 2020–2021: Update. Ottawa, ON: CIHI; August 2022.

5. Canadian Institute for Health Information. COVID-19 Hospitalization and Emergency Department Statistics, 2021–2022: Update. Ottawa, ON: CIHI; June 2023.

6. Canadian Institute for Health Information. COVID-19 Hospitalization and Emergency Department Statistics, 2022–2023: Update. Ottawa, ON: CIHI; June 2024.

7. Canadian Institute for Health Information. COVID-19 Hospitalization and Emergency Department Statistics, 2023–2024 (Q1 to Q2) — Provisional Data. Ottawa, ON: CIHI; 2024. https://www.cihi.ca/en/covid-19-hospitalization-and-emergency-department-statistics

8. Berry I, Brown KA, Buchan SA, Hohenadel K, Kwong JC, Patel S, Rosella LC, Mishra S, Sander B. A better normal in Canada will need a better detection system for emerging and re-emerging respiratory pathogens. CMAJ 2022;194(36):E1250–4. DOI PubMed

9. Rong G, Zheng Y, Chen Y, Zhang Y, Zhu P, Sawan M. COVID-19 Diagnostic Methods and Detection Techniques. Enc Sensors Biosnsors. 2023;3:17–32. DOI

10. Ibrahim NK. Epidemiologic surveillance for controlling Covid-19 pandemic: types, challenges and implications. J Infect Public Health 2020;13(11):1630–8. DOI PubMed

11. Long S, Loutfi D, Kaufman JS, Schuster T. Limitations of Canadian COVID-19 data reporting to the general public. J Public Health Policy 2022;43(2):203–21. DOI PubMed

12. Farkas K, Cooper DM, McDonald JE, Malham SK, de Rougemont A, Jones DL. Seasonal and spatial dynamics of enteric viruses in wastewater and in riverine and estuarine receiving waters. Sci Total Environ 2018;634:1174–83. DOI PubMed

13. Hellmér M, Paxéus N, Magnius L, Enache L, Arnholm B, Johansson A, Bergström T, Norder H. Detection of pathogenic viruses in sewage provided early warnings of hepatitis A virus and norovirus outbreaks. Appl Environ Microbiol 2014;80(21):6771–81. DOI PubMed

14. Mercier E, Pisharody L, Guy F, Wan S, Hegazy N, D'Aoust PM, Kabir MP, Nguyen TB, Eid W, Harvey B, Rodenburg E, Rutherford C, Mackenzie AE, Willmore J, Hui C, Paes B, Delatolla R, Thampi N. Wastewater-based surveillance identifies start to the pediatric respiratory syncytial virus season in two cities in Ontario, Canada. Front Public Health 2023;11:1261165. DOI PubMed

15. Miura F, Kitajima M, Omori R. Duration of SARS-CoV-2 viral shedding in faeces as a parameter for wastewater-based epidemiology: re-analysis of patient data using a shedding dynamics model. Sci Total Environ 2021;769:144549. DOI PubMed

16. Benefield AE, Skrip LA, Clement A, Althouse RA, Chang S, Althouse BM. SARS-CoV-2 viral load peaks prior to symptom onset: a systematic review and individual-pooled analysis of coronavirus viral load from 66 studies. medRxiv. DOI

17. Michael-Kordatou I, Karaolia P, Fatta-Kassinos D. Sewage analysis as a tool for the COVID-19 pandemic response and management: the urgent need for optimised protocols for SARS-CoV-2 detection and quantification. J Environ Chem Eng 2020;8(5):104306. DOI PubMed

18. Government of Canada. COVID-19 variants: Wastewater monitoring dashboard. Ottawa, ON: Government of Canada; 2025. [Accessed 2024 Dec 12]. https://health-infobase.canada.ca/wastewater/variants.html

19. Ontario's Ministry of the Environment Conservation and Parks. Expenditure Estimates for the Ministry of Environment, Conservation and Parks (2023–24). Toronto, ON: MECP; 2025. [Accessed 2024 Dec 12]. https://www.ontario.ca/page/expenditure-estimates-ministry-environment-conservation-and-parks-2023-24#section-4

20. Public Health Ontario. Technical Notes: COVID-19 Wastewater Surveillance in Ontario. Toronto, ON: PHO; 2023. [Accessed 2025 Jul 29]. https://www.publichealthontario.ca/-/media/Data-Files/wastewater-surveillance-technical-notes.pdf?sc_lang=en&rev=58f16fdb7b6f424b977a54a720174edc&hash=881FFCE8F4DB27D54928A0D3BB2FEE98

21. Public Health Agency of Canada. National Advisory Committee on Immunization (NACI): Guidelines for the Economic Evaluation of Vaccination Programs in Canada. Ottawa, ON: PHAC; 2023. https://www.canada.ca/en/public-health/services/immunization/national-advisory-committee-on-immunization-naci/methods-process/incorporating-economic-evidence-federal-vaccine-recommendations/guidelines-evaluation-vaccination-programs-canada.html

22. Canada's Drug Agency. Guidelines for the economic evaluation of health technologies: Ottawa, ON: CDA; 2021. https://www.cda-amc.ca/guidelines-economic-evaluation-health-technologies-canada-0

23. Nourbakhsh S, Fazil A, Li M, Mangat CS, Peterson SW, Daigle J, Langner S, Shurgold J, D'Aoust P, Delatolla R, Mercier E, Pang X, Lee BE, Stuart R, Wijayasri S, Champredon D. A wastewater-based epidemic model for SARS-CoV-2 with application to three Canadian cities. Epidemics 2022;39:100560. DOI PubMed

24. Government of Ontario. Confirmed positive cases of COVID-19 in Ontario. Toronto, ON: Government of Ontario; 2024. [Accessed 2025 Apr 23]. https://data.ontario.ca/dataset/confirmed-positive-cases-of-covid-19-in-ontario

25. Government of Ontario. COVID-19 cases in hospital and ICU, by Ontario Health (OH) region. Toronto, ON: Government of Ontario; 2024. [Accessed 2025 Apr 23]. https://data.ontario.ca/dataset/covid-19-cases-in-hospital-and-icu-by-ontario-health-region

26. Public Health Agency of Canada. Evidence brief of SARS-CoV-2 incubation periods (August 2021). Ottawa, ON: PHAC; 2024. [Accessed 2024 Aug 12]. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/canadas-reponse/summaries-recent-evidence/evidence-brief-sars-cov-2-incubation-periods.html

27. Public Health Ontario. COVID-19 Overview of the Period of Communicability – What We Know So Far. Toronto, ON: PHO; 2021. [Accessed 2024 Aug 12]. https://www.publichealthontario.ca/-/media/documents/ncov/covid-wwksf/2021/03/wwksf-period-of-communicability-overview.pdf

28. Li WT, Zhang Y, Liu M, Liu YQ, Ma X. Prolonged viral shedding in feces of children with COVID-19: a systematic review and synthesis of data. Eur J Pediatr 2022;181(12):4011–7. DOI PubMed

29. Zhang Y, Cen M, Hu M, Du L, Hu W, Kim JJ, Dai N. Prevalence and Persistent Shedding of Fecal SARS-CoV-2 RNA in Patients With COVID-19 Infection: A Systematic Review and Meta-analysis. Clin Transl Gastroenterol 2021;12(4):e00343. DOI PubMed

30. Oran DP, Topol EJ. The Proportion of SARS-CoV-2 Infections That Are Asymptomatic : A Systematic Review. Ann Intern Med 2021;174(5):655–62. DOI PubMed

31. Sah P, Fitzpatrick MC, Zimmer CF, Abdollahi E, Juden-Kelly L, Moghadas SM, Singer BH, Galvani AP. Asymptomatic SARS-CoV-2 infection: A systematic review and meta-analysis. Proc Natl Acad Sci USA 2021;118(34):e2109229118. DOI PubMed

32. Carazo S, Skowronski DM, Brisson M, Barkati S, Sauvageau C, Brousseau N, Gilca R, Fafard J, Talbot D, Ouakki M, Gilca V, Carignan A, Deceuninck G, De Wals P, De Serres G. Protection against omicron (B.1.1.529) BA.2 reinfection conferred by primary omicron BA.1 or pre-omicron SARS-CoV-2 infection among health-care workers with and without mRNA vaccination: a test-negative case-control study. Lancet Infect Dis 2023;23(1):45–55. DOI PubMed

33. Statista Research Department. Median age of the resident population of Canada in 2023, by province (July 2024). NY, NY: Statista; 2025. [Accessed 2024 Aug 12]. https://www.statista.com/statistics/444816/canada-median-age-of-resident-population-by-province/

34. Yan J, Xie S, Johnson JA, Pullenayegum E, Ohinmaa A, Bryan S, Xie F. Canada population norms for the EQ-5D-5L. Eur J Health Econ 2024;25(1):147–55. DOI PubMed

35. Mao Z, Li X, Jit M, Beutels P. COVID-19-related health utility values and changes in COVID-19 patients and the general population: a scoping review. Qual Life Res 2024;33(6):1443–54. DOI PubMed

36. Sander B, Mishra S, Swayze S, Sahakyan Y, Duchen R, Quinn K, Janjua N, Sbihi H, Kwong J. Population-Based Matched Cohort Study of COVID-19 Healthcare Costs, Ontario, Canada. Emerg Infect Dis 2025;31(4):710–9. DOI PubMed

37. Kumar M, Jiang G, Kumar Thakur A, Chatterjee S, Bhattacharya T, Mohapatra S, Chaminda T, Kumar Tyagi V, Vithanage M, Bhattacharya P, Nghiem LD, Sarkar D, Sonne C, Mahlknecht J. Lead time of early warning by wastewater surveillance for COVID-19: geographical variations and impacting factors. Chem Eng J 2022;441:135936. DOI PubMed

38. Schenk H, Rauch W, Zulli A, Boehm AB. SARS-CoV-2 surveillance in US wastewater: leading indicators and data variability analysis in 2023-2024. PLoS One 2024;19(11):e0313927. DOI PubMed

39. Grosse SD. Assessing cost-effectiveness in healthcare: history of the $50,000 per QALY threshold. Expert Rev Pharmacoecon Outcomes Res 2008;8(2):165–78. DOI PubMed

40. Statistics Canada. Table 13-10-0114-01: Life expectancy and other elements of the complete life table, three-year estimates, Canada, all provinces except Prince Edward Island. Ottawa, ON: StatCan; 2024. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310011401

41. Whitehead SJ, Ali S. Health outcomes in economic evaluation: the QALY and utilities. Br Med Bull 2010;96:5–21. DOI PubMed

42. Fraser Research. Aging and Expenditures on Health Care. Vancouver, BC: Fraser Inst; 2021. [Accessed 2024 Aug 12]. https://www.fraserinstitute.org/sites/default/files/aging-and-expenditures-on-health-care.pdf

43. Neilan AM, Losina E, Bangs AC, Flanagan C, Panella C, Eskibozkurt GE, Mohareb A, Hyle EP, Scott JA, Weinstein MC, Siedner MJ, Reddy KP, Harling G, Freedberg KA, Shebl FM, Kazemian P, Ciaranello AL. Clinical Impact, Costs, and Cost-effectiveness of Expanded Severe Acute Respiratory Syndrome Coronavirus 2 Testing in Massachusetts. Clin Infect Dis 2021;73(9):e2908–17. DOI PubMed

44. Thiara S, Henry B, Patrick D, Kanji H. British Columbia's COVID-19 experience. BCMJ. 2020;62(8):277–9. https://bcmj.org/sites/default/files/BCMJ_Vol62_No8_covid-19.pdf

45. Public Health Ontario. Enhanced Epidemiological Summary. COVID-19 in Ontario: a summary of wave 1 transmission patterns and case identification. Toronto, ON: PHO; 2020. [Accessed 2025 Jan 7]. https://www.publichealthontario.ca/-/media/documents/ncov/epi/2020/08/covid-19-wave-1-transmission-patterns-epi-summary.pdf?sc_lang=en

46. Yoo BK, Iwamoto R, Chung U, Sasaki T, Kitajima M. Economic Evaluation of Wastewater Surveillance Combined with Clinical COVID-19 Screening Tests, Japan. Emerg Infect Dis 2023;29(8):1608–17. DOI PubMed

47. Mvundura M, Ngwira LG, Shrestha KB, Tuladhar R, Gauld J, Kerr C, Barnes K, Anscombe C, Sharma B, Feasey N. Cost-effectiveness of wastewater-based environmental surveillance for SARS-CoV-2 in Blantyre, Malawi and Kathmandu, Nepal: A model-based study. PLOS Glob Public Health 2025;5(4):e0004439. DOI PubMed

48. Sanjak JS, McAuley EM, Raybern J, Pinkham R, Tarnowski J, Miko N, Rasmussen B, Manalo CJ, Goodson M, Stamps B, Necciai B, Sozhamannan S, Maier EJ. Wastewater Surveillance Pilot at US Military Installations: Cost Model Analysis. JMIR Public Health Surveill 2024;10:e54750. DOI PubMed

49. Public Health Agency of Canada. Federal/provincial/territorial public health response plan for ongoing management of COVID-19. Ottawa, ON: PHAC; 2022. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/guidance-documents/federal-provincial-territorial-public-health-response-plan-ongoing-management-covid-19.html

50. Lehto KM, Länsivaara A, Hyder R, Luomala O, Lipponen A, Hokajärvi AM, Heikinheimo A, Pitkänen T, Oikarinen S; WastPan Study Group. Wastewater-based surveillance is an efficient monitoring tool for tracking influenza A in the community. Water Res 2024;257:121650. DOI PubMed

Mycobacterium abscessus soft tissue infections associated with subcutaneous injection of lipolytic agents: An outbreak report and novel molecular epidemiology analysis approach

Xavier Quan-Nguyen[1,2], Nicholas Waglechner[3,4,5], Maxime Veillette[1,2], Pier-Alexandre Vasil[2,6], Floriane Point[1], Bouchra Tannir[1,2], Melissa Zarandi-Nowroozi[2], Catherine Tsimiklis[7,8], Nadine Pétrin[9], Marty Teltscher[10], Anna Urbanek[6], Pierre-Marie Akochy[11], Joseph Cox[6,12,13], Robyn Lee[5,14,15], Simon Grandjean Lapierre[1,7]*

Abstract

Background: Management of *Mycobacterium abscessus* (*M. abscessus*) skin and soft tissue infections outbreaks require collaboration between clinicians, public health authorities and reference laboratories providing bacterial molecular identification and genotyping.

Objective: This study reports on a *M. abscessus* skin and soft tissue outbreak linked to mesotherapy treatments in Montréal, Canada. We present an innovative approach combining Nanopore long read and Illumina short read whole-genome sequencing data with a novel open access bioinformatic molecular epidemiology pipeline to support public health investigations by identifying genomically related isolates.

Methods: Public health investigations and physician questionnaires were used for outbreak identification and investigation. The complete genomes of six isolates from four individuals were sequenced. Nanopore and Illumina data were combined to assemble genomes *de novo* using a hybrid approach. Single nucleotide polymorphisms (SNPs) were identified within each genome by mapping the short reads to a reference genome. Single nucleotide polymorphisms distances among isolates, and between isolates and the reference genome were used alongside core SNP alignment analyses to evaluate genetic similarity between isolates and other contemporary *M. abscessus* genomes.

Results: Identified individuals had received mesotherapy injections from the same esthetician within a one-month period. Outbreak isolates were genomically nearly identical, differing by only 0–2 SNPs when using the earliest collected isolate as a reference. A phylogenetic tree revealed genetic distinctness between outbreak isolates and other contemporary *M. abscessus* isolates from Montréal.

Conclusion: Genomic sequencing and the presented bioinformatic approach can identify *M. abscessus* genomic relatedness suggestive of clinical outbreaks. This approach can support public health investigations, particularly when epidemiological links are uncertain.

Suggested citation: Quan-Nguyen X, Waglechner N, Veillette M, Vasil P-A, Point F, Tannir B, Zarandi-Nowroozi M, Tsimiklis C, Pétrin N, Teltscher MS, Urbanek A, Akochy P-M, Cox J, Lee R, Grandjean Lapierre S. *Mycobacterium abscessus* soft tissue infections associated with subcutaneous injection of lipolytic agents: An outbreak report and novel molecular epidemiology analysis approach. Can Commun Dis Rep 2026;52(6):256–63. https://doi.org/10.14745/ccdr.v52i06a05

Keywords: *Mycobacterium abscessus*, skin and soft tissue infection, mesotherapy, whole genome sequencing, molecular epidemiology

Affiliations

See Appendix

***Correspondence:**
simon.grandjean.lapierre@umontreal.ca

Introduction

Nontuberculous mycobacteria are ubiquitous organisms that can be found in healthcare and other environments and cause outbreaks of skin and soft tissue, pulmonary, lymph nodes, and joint infections (1–4). Diagnosis and treatment of *Mycobacterium abscessus* (*M. abscessus*) soft tissue infections is particularly challenging due their frequently atypical nodular and mildly inflammatory presentation, the inability of conventional bacterial cultures to identify this rapidly growing mycobacteria and its innate and acquired resistance to available antimicrobial agents (3,5). Outbreaks of *M. abscessus* skin and soft tissue infections have been previously reported in immunosuppressed individuals, following exposure to contaminated water, as post-operative complication of plastic surgery or following tattooing, acupuncture and mesotherapy treatments—a procedure in which multiple injections of pharmaceuticals or vitamins are delivered into the mesodermal layer of skin tissues to promote the loss of fat or cellulitis (5–7). Past outbreak investigations required coordinated efforts between public health, clinical professionals and reference laboratories providing bacterial molecular identification and genotyping (8,9).

The increased availability of next-generation sequencing platforms and the development of semi-automated data analysis pipelines support the increased uptake of next-generation sequencing-based molecular typing for outbreak investigation by public health and clinical microbiology laboratories (10). Bacterial whole-genome sequencing (WGS) allows much greater discrimination of epidemiologically clustered isolates and therefore helps support or refute the results of standard public health investigations (11–13). By combining WGS and epidemiological investigations, Olawoye *et al.* recently showed that health care-associated human-to-human transmission of *M. abscessus* was rare on the island of Montréal (14). In a multi-country study comparing strains from distinct global *M. abscessus* outbreaks, Tettelin *et al.* highlighted that while strains from the same outbreak were clustered together, high genomic relatedness could also be observed between epidemiologically unrelated isolates (15). Next-generation sequencing-based molecular typing systems must be well adapted to pathogens' intrinsic genomic diversity and evolution to best complement public health investigations and accurately support or refute the relatedness of isolates.

We report on the investigation of a *M. abscessus* skin infections outbreak associated with mesotherapy procedures in Québec. We also describe a unique innovative approach combining long read and short read sequence data to improve the resolution of our molecular epidemiology analysis. This novel bioinformatic pipeline for the phylogenetic analysis of *M. abscessus* isolates is openly accessible.

Methods

Public health investigation

In 2021, an infectious disease clinician reported a case of disseminated panniculitis lesions associated with mesotherapy injections to the Montréal public health department. Although *M. abscessus* infections are not a mandatory reportable disease in Québec, the attending physician had perceived a potential risk for the public since aesthetic injections were the only identifiable risk factor. An investigation was initiated to identify and attempt to eliminate the infection source. An interview with the esthetician was conducted to catalog the injection products that were used and to review infection control practices. A detailed list of past clients having underwent mesotherapy procedures using the same injectable product and procedures was obtained. Putative outbreak cases were defined as individuals with microbiologically confirmed *M. abscessus* skin and soft tissue infections having been injected with the same product by the same esthetician. Cases were identified by reviewing the clients' medical charts, including skin infections and positive culture results for *M. abscessus*. Attending physicians of all newly identified infected individuals were asked to complete a questionnaire collecting basic epidemiology, clinical presentation and microbiology data (**Appendix**, **Supplementary material**).

Genomic sequencing and bioinformatic analysis

Mycobacterial isolates had initially been cultured by hospital-based clinical laboratories and referred to the *Laboratoire de santé publique du Québec* for *M. abscessus* speciation using 16s RNA sequencing. All available isolates from all individuals were retrieved and included in the molecular analysis. One randomly selected contemporary *M. abscessus* clinical isolate (control X) from Montréal was included as control for laboratory procedures and bioinformatic analyses. Mycobacterial DNA was extracted from pure culture and sequenced using Illumina and Oxford Nanopore next-generation sequencing platforms (Appendix, Supplementary material). All isolates passed sequencing quality controls including pre-alignment genomic coverage and absence of contaminating data (Appendix, Supplementary material).

Sequencing data was analyzed following previously described methods from Waglechner *et al.* (13). Both Nanopore and Illumina sequencing data were analyzed together using the Snakemake workflow engine (version 7.32.4) to execute the following pipeline using the "hybrid" branch (16). Kraken2 v2.1.3, using a prebuilt MiniKraken database (version k2_plusfp_20220908_16) containing bacterial, viral, human, archaeal, vector, plasmid, protozoa and fungal sequences, was used for taxonomic assignment and contamination checking of each raw sequence data set (Nanopore and Illumina) for each

sample (17,18). Using short read data, *de novo* assembly was performed and assigned to the most appropriate subspecies using mashtree along with reference sequences of *Mycobacterium tuberculosis* H37Rv (outgroup) (NC_000962) and the three *M. abscessus* subspecies: *M. abscessus* subspecies *abscessus* ATCC 19977 (NCBI GCF_000069185.1), *M. abscessus* subspecies *massiliense* CCUG 48898/ JCM 15300 (NCBI GCF_000497265.2) and *M. abscessus* subspecies *bolletii* BD (NCBI GCF_003609715.1) (18). A hybrid *de novo* assembly was also prepared for each sample with long and short read data using dragonfly v1.2.1 with three rounds of short read polishing with polypolish v0.6.0 (19,20).

First, to assess outbreak individuals' isolates relatedness, samples' short read *de novo* assemblies for cases A through D were mapped against 1) the *M. abscessus* subspecies *massiliense* CCUG 48898 and 2) the hybrid short-read polished assembly of the putative outbreak earliest case (case B) using bwa-mem2 v2.2.1 with default parameters (19). Single nucleotide polymorphisms (SNPs) were identified using samtools mpileup v1.14 (15). Variants were extracted into an alignment and subjected to recombination correction using gubbins v3.3.0 and counted using snp-dists v0.8.2 to assess relatedness of isolates (21). Core SNP alignments were analyzed by iqtree v2.3.6 with ultrafast bootstraps to examine the relatedness of outbreak isolates in the context of using either an outbreak isolate (case B hybrid assembly) or a subspecies type (*M. abscessus* subspecies *massiliense* CCUG 48898) as the reference genome. ETE (v3.1.1) was used to visualize maximum likelihood phylogenetic trees (22).

Second, to confirm outbreak isolates' clustering within local circulating *M. abscessus* strains, a core genome was estimated from predicted open reading frames present in 99% or more of all assemblies from the outbreak isolates and 220 additional recent Montréal *M. abscessus* genomes from Olawoye *et al.* using the pangenome workflow from bactopia v3.1.0 using default parameters (14,23).

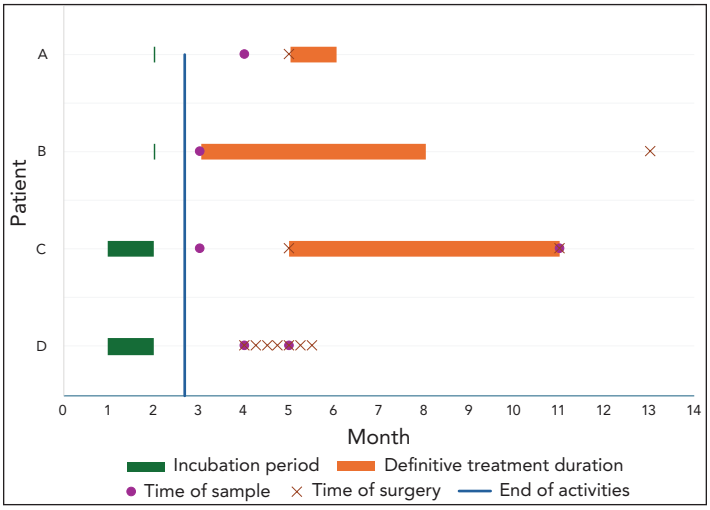
Data availability

Whole genome sequencing data is available on the National Center for Biotechnology Information GenBank database (bioproject ID 1221978).

Public health investigation

The initial investigation included only the first two clients and revealed that an esthetician had performed mesotherapy injections in a rented commercial space. Esthetic services were advertised on social media as part of a spa package and were performed in a total of five clients during a one-month period. Among those, the public health investigation and medical chart review concluded that four clients were infected (**Figure 1**). Within days following the injection procedures, all four individuals had presented with subcutaneous, erythematous nodules at various sites where injections occurred, including

Figure 1: Montréal *Mycobacterium abscessus* outbreak timeline derived from medical records and attending clinical reports[a]



[a] Months are numbered based on the first clients' injections (month 0). Incubation period refers to the time between injection and first reported symptoms. Definitive treatment duration refers to the length of *Mycobacterium abscessus* specific treatment following positive culture. Time of sample refers to the months in which the clinical samples were collected. Repeated sampling was performed for two individuals due to persistent skin lesions. Time of surgery refers to the months in which a surgical intervention was performed for the panniculitis lesions. End of activities refers to cessation of at risk injection treatments by the esthetician

the waist, lower back and thighs, accompanied by systemic symptoms (fever, chills, fatigue). Infected individuals had no other risk factors for mycobacterial infection, such as immunosuppression, implanted foreign material or other surgeries. Skin biopsy cultures had confirmed *M. abscessus* as the etiologic agent in all four individuals, including two with two distinct cultured isolates each (C–1 and C–2, D–1 and D–2). Each individual's clinical management and treatment were retrieved (Appendix, Supplementary material).

A registered letter based on regulations in Québec's public health law ordered the esthetician to assure a cessation of all activities. The esthetician had discarded all injection products after clients reported adverse reactions, so these products were unavailable for culture. The mesotherapy product lacked a Drug Identification Number in Health Canada's Drug Product Database and was not a licensed natural product on Health Canada's Licensed Natural Health Product Database (24,25). Health Canada's Central Triage Unit, Regulatory Operations and Enforcement Branch was alerted to the possible *M. abscessus* contamination of the product. The case was referred to the Health Product Compliance East Unit of Health Canada which performed a compliance verification for the product; however, the results of the investigation, including additional information obtained from direct communication with the manufacturer, were not shared in accordance with the *Privacy Act*. As of February 2025, the Health Product Compliance East Unit reported "no more noncompliance" for the product. Also, no recalls or safety alerts have ever been issued for the product according to the Government of Canada's Recalls and Safety Alerts database (26).

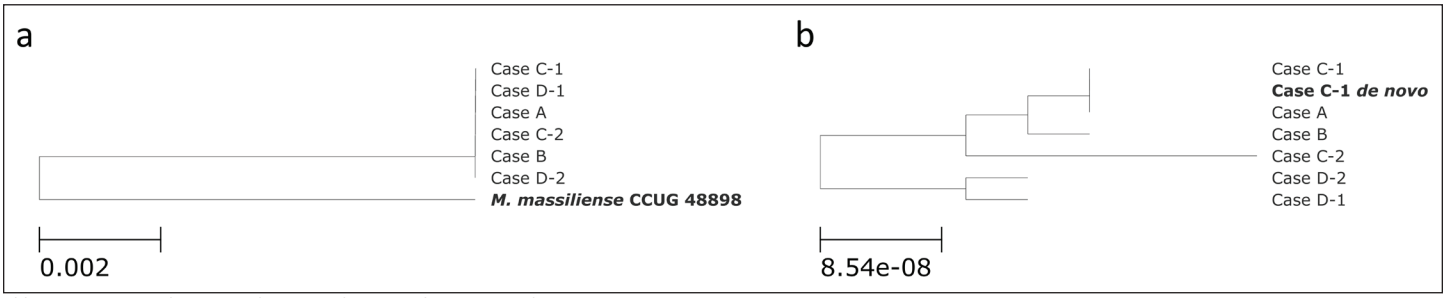
Outbreak isolates relatedness molecular analysis

All outbreak-related isolates were identified as *M. abscessus* subspecies *massiliense*. The contemporary clinical control isolate was identified as *M. abscessus* subspecies *abscessus* and excluded from further pairwise SNP comparisons using the outbreak-specific hybrid assembly reference. Short read data from the outbreak isolates mapped against a polished assembly of an early outbreak isolate (Case B) showed 100% mapping coverage. The outbreak isolates were nearly identical with each other by pairwise SNP distance, ranging from 0 to 2 SNPs. The same procedure using *M. abscessus* subspecies *massiliense* CCUG 48898 as a reference yielded pairwise SNP distances ranging from 32 to 50 SNPs between outbreak isolates, while outbreak isolates ranged from 26,612 to 26,644 pairwise SNPs apart from the reference (**Figure 2**, **Figure 3**). Sequentially cultured clinical isolates from the same individual (e.g., C–1 vs. C–2, D–1 vs. D–2) sampled up to eight months apart were not more closely related to the earliest isolate in each pair than to isolates from other individuals.

Outbreak isolates clustering amongst locally circulating strains

The pangenome was constructed using assemblies from the six outbreak isolates as well as the Control X isolate along with 220 additional *M. abscessus* isolates collected from 2010 to 2018 recently published from the island of Montréal and other Québec laboratories (5). The core genome (sequences found in 99% or more of genomes) consisted of 3,403 open reading

Figure 2: Maximum likelihood phylogenetic trees of Montréal *Mycobacterium abscessus* outbreak isolates[a]



Abbreviation: *M. massiliense*, *Mycobacterium abscessus* subspecies *massiliense*
[a] Core genome single nucleotide polymorphism (SNP) alignments were produced by mapping short read data against a) the *M. abscessus* subspecies *massiliense* CCUG 48898 reference genome and b) a *de novo* long read assembly of an early outbreak case polished with short read data. Reference sequences used for mapping in each tree are indicated in bold

Figure 3: Outbreak isolates pairwise[a] single nucleotide polymorphisms distance matrices

a)

	M. massiliense CCUG 48898	Case B	Case D–1	Case D–2	Case C–2	Case C–1	Case A
M. massiliense CCUG 48898	0	20,624	20,644	20,612	20,628	20,641	20,629
Case B	20,624	0	47	32	39	44	39
Case D–1	20,644	47	0	42	47	40	45
Case D–2	20,612	32	42	0	38	40	37
Case C–2	20,628	39	47	38	0	50	43
Case C–1	20,641	44	40	40	50	0	36
Case A	20,629	39	45	37	43	36	0

b)

	Case C–1 (*de novo*)	Case B	Case D–1	Case D–2	Case C–2	Case C–1	Case A
Case C-1 (*de novo*)	0	0	1	1	1	0	0
Case B	0	0	1	1	1	0	0
Case D–1	1	1	0	0	2	1	1
Case D–2	1	1	0	0	2	1	1
Case C–2	1	1	2	2	0	1	1
Case C–1	0	0	1	1	1	0	0
Case A	0	0	1	1	1	0	0

Abbreviation: *M. massiliense*, *Mycobacterium abscessus* subspecies *massiliense*
[a] Pairwise distances using a) Illumina data mapped against *M. massiliense* CCUG 48898, b) Illumina data mapped against *de novo* long read assembly polished with Illumina data against an early outbreak case

frames totaling 3,951,644 bp when aligned. After recombination detection and masking with ClonalFrameML, pairwise SNPs were counted from this alignment and used to produce a phylogenetic tree of 227 Montréal *M. abscessus* isolates from all three subspecies (**Figure 4**). This tree shows that the outbreak isolates are distinct from other subspecies *massiliense* isolates previously sequenced except for one. This isolate had been cultured from the respiratory track of a cystic fibrosis patient who had not received mesotherapy treatments and shared no epidemiological links with the outbreak individuals.

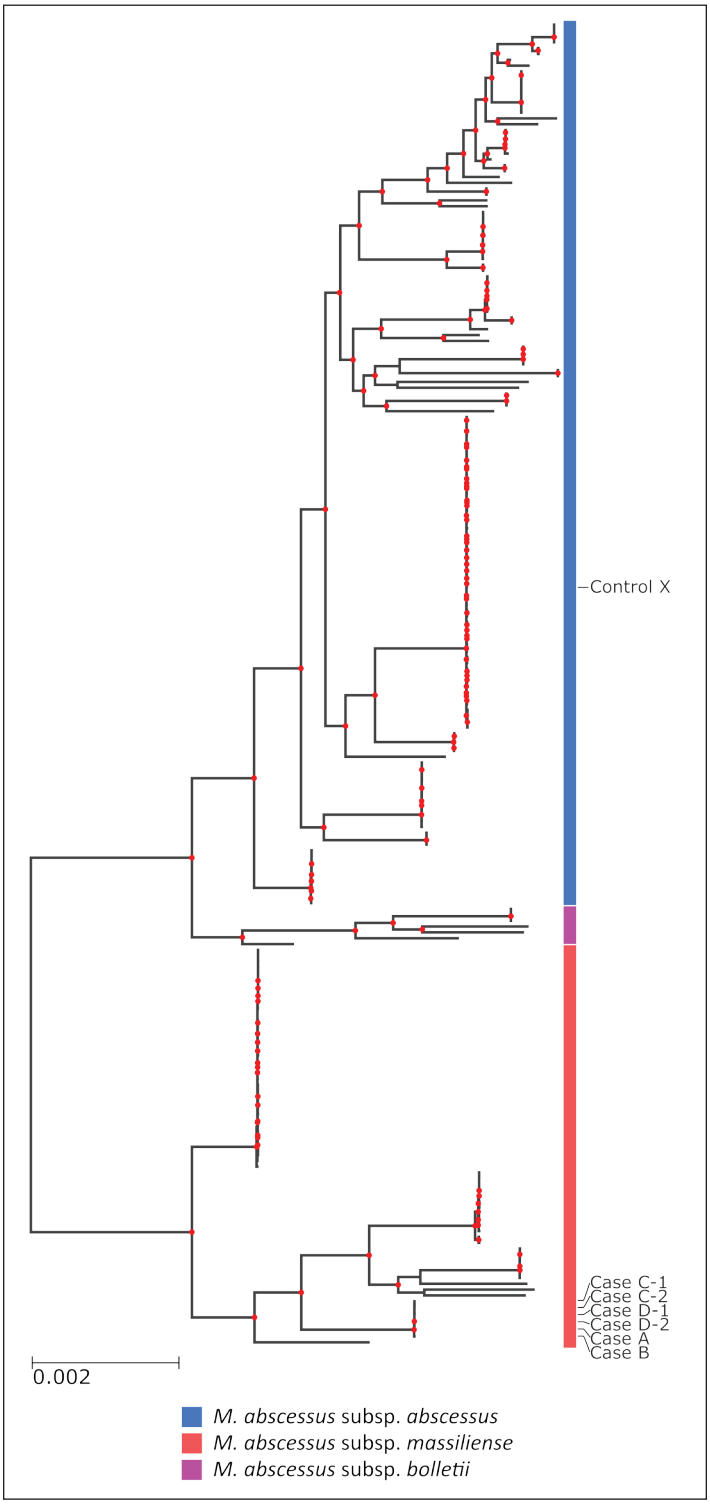
Discussion

During this *M. abscessus* infection outbreak investigation, we confirmed the ability of a conventional epidemiological investigation to comprehensively identify individuals involved in a point-source outbreak. We also developed an improved molecular approach leveraging both short (Illumina) and long (Nanopore) read sequence data to confirm the relatedness of epidemiologically linked cases and assess their bacterial isolates' molecular clustering within an extended catalog of locally circulating strains.

Esthetician services and easy access to injection products on-line do not fall under Health Canada regulations. In Québec, anyone who wishes to receive regulated product injections for cosmetic purposes must undergo a prior medical evaluation so that a doctor can establish an individualized treatment plan. A nurse or licenced practical nurse, if prescribed to do so, may undertake such treatments. Since esthetician services are not regulated, it is important for the public to be aware of the risks associated with invasive treatments which should only be provided under medical supervision. In this context, we highlight the importance of case signaling by health professionals to Public Health departments. This outbreak investigation was initiated following physicians' report of a post-injection infection. Public health authorities have a responsibility to investigate real and perceived threats to the public's health; as seen in this investigation, they use their authority under the law to order the cessation of activities or use of suspected products, until a public health investigation can be completed and the threat removed or diminished.

A strength of our investigation is the combination of traditional epidemiological investigation and multi-modal sequencing molecular epidemiology. Using clinically related isolates from this outbreak investigation, we extended our previously published *M. abscessus* bioinformatic pipeline to make use of long read data from Oxford Nanopore instruments (15). Long read data enabled the production of essentially closed and complete genome assemblies of the outbreak isolates and enabled the use a more relevant reference for pairwise SNP analysis. Before the common availability of long read sequencing, mapping relied on using the closest publicly available genome sequence

Figure 4: Core-genome single nucleotide polymorphisms phylogeny of *Mycobacterium abscessus* isolates from Montréal in 2025[a]



Abbreviations: *M. abscessus*, *Mycobacterium abscessus*; subsp., subspecies
[a] The core genome was estimated from open reading frames of the assembled outbreak isolates along with 220 additional isolates from the island of Montréal. *Mycobacterium abscessus* subsp. *massiliense* isolates cultured from the skin infection outbreak individuals exhibit high relatedness compared to the Montréal *M. abscessus* catalog

that, in practice, could result in bias in SNP calling. This bias can be seen when mapping our outbreak isolates against the *M. abscessus* subspecies *massiliense* CCUG 48898 strain where the clinical isolates were collectively approximately 28,000 SNPs apart from the reference. More importantly, bias was introduced at the mapping and SNP calling stages that exaggerated the differences between outbreak isolates. Using the complete *de novo* Case C–1 assembly as a reference 100% of the reference was covered revealing limited genomic variability between outbreak isolates where each was within 0–2 SNPs of each other.

In this study, all outbreak isolates were found to be almost genetically identical. Sequentially sampled isolates from the same infected individuals did not exhibit higher or lower genomic relatedness (e.g., C–1 and C–2, D–1 and D–2). Previous studies suggested that *M. abscessus* subspecies *massiliense* has a lower mutation rate than other *M. abscessus* (27–29). In a previous *M. abscessus* molecular epidemiology study conducted over nine years, clinical isolates collected from the same individual did preferentially clustered together (14). Bryant *et al.*, suggested that SNP distances of less than 25 were associated with related *M. abscessus* subspecies *massiliense* isolates and that SNP distances of 50 to 200 correlated with distinct clusters (27). Doyle *et al.* found median SNP distances of 2,084 within the same sequence cluster and advocated for variant calling against more genetically similar reference sequences or when unavailable, the first isolated sample, to better highlight differences between strains and decluster genetically similar sequences (30). We believe the differences between within-host bacterial evolution in lungs and soft tissue infections, the bioinformatic analytic approach and the choice of alignment reference sequence explain these differences between previously published results and ours. Among other previously reported *M. abscessus* skin and soft tissue outbreaks, one included short-read sequencing-based WGS analysis and also found related isolates to be within three SNPs of each other and source environmental isolates (6).

Conclusion

Nontuberculous mycobacteria skin infections outbreaks can be associated with aesthetic injection products. Bacterial WGS and the presented bioinformatic pipeline can support *M. abscessus* outbreak investigations. Combining Nanopore and Illumina sequencing data for molecular clustering analyses represents a novel approach to improve *M. abscessus* clinical isolates clustering analysis. Genomic sequencing is of important value when molecular clustering further supports a clinically suspected iatrogenic infectious.

Authors' statement

XQ-N — Methodology, validation, formal analysis, investigation, writing–original draft, visualization
NW — Methodology, software, validation, formal analysis, data curation, writing–original draft, visualization
MV — Investigation, formal analysis, data curation, writing–original draft
P-AV — Investigation, writing–review & editing
FP — Software, formal analysis, data curation, writing–review & editing
BT — Investigation, writing–review & editing
MZ-N — Investigation, writing–review & editing
CT — Investigation, writing–review & editing
NP — Formal analysis, investigation, writing–review & editing
MT — Investigation, writing–review & editing
AU — Investigation, writing–review & editing
P-MA — Formal analysis, investigation, writing–review & editing
JC — Formal analysis, investigation, writing–review & editing
RL — Software, validation, formal analysis, resources, supervision, writing–review & editing
SGL — Conceptualization, methodology, validation, investigation, resources, data curation, writing–review & editing, supervision, project administration

Xavier Quan-Nguyen, Nicholas Waglechner and Maxime Veillette contributed equally to this article.

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

Competing interests

The authors declare no competing interests.

ORCID numbers

Xavier Quan-Nguyen — 0009-0005-1448-4418
Maxime Veillette — 0000-0002-0493-3428
Melissa Zarandi-Nowroozi — 0000-0003-3635-4292
Joseph Cox — 0000-0002-7041-1556
Robyn Lee — 0000-0001-7120-9053
Simon Grandjean Lapierre — 0000-0003-3646-1573

Acknowledgements

None.

Funding

No dedicated funding was obtained for this study. SGL is supported by a clinical-scholar award from the *Fonds de Recherche Québec – Santé* (Award #367743).

References

1. Brown-Elliott BA, Wallace RJ Jr. Clinical and taxonomic status of pathogenic nonpigmented or late-pigmenting rapidly growing mycobacteria. Clin Microbiol Rev 2002;15(4):716–46. DOI PubMed

2. Lee MR, Sheng WH, Hung CC, Yu CJ, Lee LN, Hsueh PR. Mycobacterium abscessus Complex Infections in Humans. Emerg Infect Dis 2015;21(9):1638–46. DOI PubMed

3. Nessar R, Cambau E, Reyrat JM, Murray A, Gicquel B. Mycobacterium abscessus: a new antibiotic nightmare. J Antimicrob Chemother 2012;67(4):810–8. DOI PubMed

4. Saiman L. The mycobacteriology of non-tuberculous mycobacteria. Paediatr Respir Rev 2004;5 Suppl A:S221–3. DOI PubMed

5. Winburn B, Sharman T. Atypical Mycobacterial Disease. Treasure Island (FL): StatPearls Publishing; 2025. https://www.ncbi.nlm.nih.gov/books/NBK556117/

6. Griffin I, Schmitz A, Oliver C, Pritchard S, Zhang G, Rico E, Davenport E, Llau A, Moore E, Fernandez D, Mejia-Echeverry A, Suarez J, Noya-Chaveco P, Elmir S, Jean R, Pettengill JB, Hollinger KA, Chou K, Williams-Hill D, Zaki S, Muehlenbachs A, Keating MK, Bhatnagar J, Rowlinson MC, Chiribau C, Rivera L. Outbreak of Tattoo-associated Nontuberculous Mycobacterial Skin Infections. Clin Infect Dis 2019;69(6):949–55. DOI PubMed

7. Leto Barone AA, Grzelak MJ, Frost C, Ngaage LM, Ge S, Kolegraff K, Chopra K, Tornheim JA, Caffrey J, Lifchez SD, Rasko Y. Atypical Mycobacterial Infections After Plastic Surgery Procedures Abroad: A Multidisciplinary Algorithm for Diagnosis and Treatment. Ann Plast Surg 2020;84(3):257–62. DOI PubMed

8. Villanueva A, Calderon RV, Vargas BA, Ruiz F, Aguero S, Zhang Y, Brown BA, Wallace RJ Jr. Report on an outbreak of postinjection abscesses due to Mycobacterium abscessus, including management with surgery and clarithromycin therapy and comparison of strains by random amplified polymorphic DNA polymerase chain reaction. Clin Infect Dis 1997;24(6):1147–53. DOI PubMed

9. Zhang Y, Rajagopalan M, Brown BA, Wallace RJ Jr. Randomly amplified polymorphic DNA PCR for comparison of Mycobacterium abscessus strains from nosocomial outbreaks. J Clin Microbiol 1997;35(12):3132–9. DOI PubMed

10. Kwong JC, McCallum N, Sintchenko V, Howden BP. Whole genome sequencing in clinical and public health microbiology. Pathology 2015;47(3):199–210. DOI PubMed

11. Gilchrist CA, Turner SD, Riley MF, Petri WA Jr, Hewlett EL. Whole-genome sequencing in outbreak analysis. Clin Microbiol Rev 2015;28(3):541–63. DOI PubMed

12. Quainoo S, Coolen JP, van Hijum SA, Huynen MA, Melchers WJ, van Schaik W, Wertheim HF. Whole-Genome Sequencing of Bacterial Pathogens: the Future of Nosocomial Outbreak Analysis. Clin Microbiol Rev 2017;30(4):1015–63. DOI PubMed

13. Waglechner N, Tullis E, Stephenson AL, Waters V, McIntosh F, Ma J, Jamieson FB, Behr MA, Batt J, Lee RS. Genomic epidemiology of Mycobacterium abscessus in a Canadian cystic fibrosis centre. Sci Rep 2022;12(1):16116. DOI PubMed

14. Olawoye IB, Waglechner N, McIntosh F, Akochy PM, Cloutier N, Grandjean Lapierre S, Tannir B, Greenaway C, Matouk E, Poirier L, Levesque RC, Boyle B, Quach C, Soualhine H, Batt J, Behr MA, Lee RS, Guthrie JL. Genomic Epidemiology of Mycobacterium abscessus on the Island of Montréal Is Not Suggestive of Health Care-Associated Person-to-Person Transmission. J Infect Dis 2025;231(2):e396–406. DOI PubMed

15. Tettelin H, Davidson RM, Agrawal S, Aitken ML, Shallom S, Hasan NA, Strong M, de Moura VC, De Groote MA, Duarte RS, Hine E, Parankush S, Su Q, Daugherty SC, Fraser CM, Brown-Elliott BA, Wallace RJ Jr, Holland SM, Sampaio EP, Olivier KN, Jackson M, Zelazny AM. High-level relatedness among Mycobacterium abscessus subsp. massiliense strains from widely separated outbreaks. Emerg Infect Dis 2014;20(3):364–71. DOI PubMed

16. Köster J, Rahmann S. Snakemake--a scalable bioinformatics workflow engine. Bioinformatics 2012;28(19):2520–2. DOI PubMed

17. BenLangmead. Kraken 2, KrakenUniq and Bracken indexes. Baltimore, MD: Benlangmead; 2024. https://benlangmead.github.io/aws-indexes/k2

18. Katz LS, Griswold T, Morrison SS, Caravas JA, Zhang S, den Bakker HC, Deng X, Carleton HA. Mashtree: a rapid comparison of whole genome sequence files. J Open Source Softw 2019;4(44):10.21105/joss.01762. DOI PubMed

19. Vasimuddin MD, Misra S, Li H, Aluru S. Efficient Architecture-Aware Acceleration of BWA-MEM for Multicore Systems. 2019 IEEE International Parallel and Distributed Processing Symposium (IPDPS). Rio de Janeiro, Brazil; 2019;314–24. DOI

20. Wick RR, Holt KE. Polypolish: short-read polishing of long-read bacterial genome assemblies. PLOS Comput Biol 2022;18(1):e1009802. DOI PubMed

21. Tseemann. snp-dists. Github; 2024. https://github.com/tseemann/snp-dists

22. Huerta-Cepas J, Serra F, Bork P. ETE 3: Reconstruction, Analysis, and Visualization of Phylogenomic Data. Mol Biol Evol 2016;33(6):1635–8. DOI PubMed

23. Petit RA 3rd, Read TD. Bactopia: a Flexible Pipeline for Complete Analysis of Bacterial Genomes. mSystems 2020;5(4):e00190–20. DOI PubMed

24. Health Canada. Drug Product Database online query. Ottawa, ON: HC; 2024. [Accessed 2024 Nov 25]. https://health-products.canada.ca/dpd-bdpp/

25. Health Canada. Search licensed natural health products. Ottawa, ON: HC; 2024. [Accessed 2024 Nov 25]. https://health-products.canada.ca/lnhpd-bdpsnh/?lang=eng

26. Government of Canada. Recalls and safety alerts. Ottawa, ON: Government of Canada; 2025. [Accessed 2024 Nov 25]. https://recalls-rappels.canada.ca/en

27. Bryant JM, Grogono DM, Greaves D, Foweraker J, Roddick I, Inns T, Reacher M, Haworth CS, Curran MD, Harris SR, Peacock SJ, Parkhill J, Floto RA. Whole-genome sequencing to identify transmission of Mycobacterium abscessus between patients with cystic fibrosis: a retrospective cohort study. Lancet 2013;381(9877):1551–60. DOI PubMed

28. Kaewprasert O, Nonghanphithak D, Chetchotisakd P, Namwat W, Ong RT, Faksri K. Whole-Genome Sequencing and Drug-Susceptibility Analysis of Serial Mycobacterium abscessus Isolates from Thai Patients. Biology (Basel) 2022;11(9):1319. DOI PubMed

29. Harrison LB, Behr MA. Mutation rates and the molecular epidemiology of Mycobacterium abscessus. Proc Natl Acad Sci USA 2023;120(25):e2307499120. DOI PubMed

30. Doyle RM, Rubio M, Dixon G, Hartley J, Klein N, Coll P, Harris KA. Cross-transmission Is Not the Source of New Mycobacterium abscessus Infections in a Multicenter Cohort of Cystic Fibrosis Patients. Clin Infect Dis 2020;70(9):1855–64. DOI PubMed

Appendix

Supplemental material is available upon request to the author: simon.grandjean.lapierre@umontreal.ca

Figure S1: Data collection questionnaire
Figure S2: Mycobacterial DNA extraction and sequencing
Figure S3: Sequencing quality metrics
Figure S4: Clinical management and treatment
Table S1: *Mycobacterium abscessus* outbreak patients' treatment and clinical management

Affiliations

[1] Centre de Recherche du Centre Hospitalier de l'Université de Montréal, Université de Montréal, Montréal, QC

[2] Département de médecine, Université de Montréal, Montréal, QC

[3] Shared Hospital Laboratory, Toronto, ON

[4] Sinai Health System, Toronto, ON

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

[6] Direction régionale de santé publique, CIUSSS du Centre-Sud-de-l'île-de-Montréal, Montréal, QC

[7] Département de microbiologie, infectiologie et immunologie, Université de Montréal, Montréal, QC

[8] Hôpital du Sacré-Cœur-de-Montréal, Montréal, QC

[9] Centre hospitalier de l'Université de Montréal, Montréal, Canada

[10] Division of Infectious Diseases, Jewish General Hospital, Montréal, QC

[11] Laboratoire de santé publique du Québec, Montréal, QC

[12] Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montréal, QC

[13] Infectious Diseases and Immunity in Global Health Program, Research Institute of the McGill University Health Centre, McGill University, Montréal, QC

[14] McGill International TB Centre, McGill University, Montréal, QC

[15] Faculty of Medicine and Health Sciences, McGill University, Montréal, QC

Characteristics of outpatient nirmatrelvir/ritonavir recipients during the 2022/2023 era in Alberta, Canada: A retrospective observational population-based study

Khanh Vu[1], Jason Randall[1], Karen Martins[1], Sylvia Aponte-Hao[2,3], Lynora Saxinger[4,5], Jenine Leal[6,7,8,9], Elissa Rennert-May[7,8,9,10], Ellen Rafferty[4,11], Phuong Uyen Nguyen[3], Tyler Williamson[3,7,9,12,13], Scott Klarenbach[1,4]*

Abstract

Background: An understanding of real-world nirmatrelvir/ritonavir (NMV-r; Paxlovid™) use in Canada is needed to inform strategies for therapy access and use.

Objective: To describe the characteristics of adults who received NMV-r in Alberta, Canada.

Methods: Population-level administrative data was used to describe adults (18 years and older) who received an outpatient dispensation of NMV-r between January 2022 and March 2023 in Alberta. Omicron variants predominated during this period.

Results: Mean age of the cohort (n=11,793) was 65 years (standard deviation=18), 60.4% were female and 83.9% had one or more health condition associated with a risk for the development of severe COVID-19 outcomes. In comparison to the general Alberta population, a larger proportion of those that received NMV-r resided in urban areas (Alberta: 82.3%; NMV-r: 89.8%) and were more socioeconomically well-off (Material Deprivation Index quintile 1-Alberta: 20.0%; NMV-r: 25.8%). A total of 81.6% received three or more COVID-19 vaccine doses and 7.0% received one or no dose. The majority of dispensed NMV-r prescriptions were from physicians (83.6%), with 13.5% from pharmacists and 2.9% from other healthcare providers.

Conclusion: In Alberta, adults who received outpatient NMV-r displayed characteristics associated with risk for progression to severe COVID-19 outcomes (related to age and health conditions) and healthcare-seeking behaviour (older age, female sex, presence of health conditions, higher socioeconomic status and highly vaccinated). Provision by urban/rural and socioeconomic status were noted. Findings can be used to inform strategies for overcoming barriers and ensuring equitable access to COVID-19 therapy for all who are most likely to benefit.

Affiliations

See Appendix

***Correspondence:**
swk@ualberta.ca

Suggested citation: Vu K, Randall JR, Martins KJB, Aponte-Hao S, Saxinger L, Leal J, Rennert-May E, Rafferty E, Nguyen PU, Williamson T, Klarenbach SW. Characteristics of outpatient nirmatrelvir/ritonavir recipients during the 2022/2023 era in Alberta, Canada: A retrospective observational population-based study. Can Commun Dis Rep 2026;52(6):264–72. https://doi.org/10.14745/ccdr.v52i06a06

Keywords: Paxlovid, COVID-19, oral antiviral therapy, outpatient use, real-world, administrative data, observational, population-based

Introduction

The COVID-19 pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been the most disruptive public health crisis of the 21st century. While widespread immunization (which began December 2020 in Canada), immunity from previous infections and prevalence of newer variants associated with milder disease have contributed

to a reduction in the risk of severe COVID-19 illness (1,2), some individuals remain at high risk, particularly older adults and those living with a higher comorbid burden and certain health conditions (3). Among these individuals, antiviral therapies for the treatment of COVID-19 and prevention of severe outcomes such as hospitalization and death are valuable tools.

Nirmatrelvir/ritonavir (NMV-r; Paxlovid™), which became available in Canada on January 18, 2022, is an oral antiviral medication for the treatment of COVID-19 in adults that can be taken within five days of mild-to-moderate symptom onset in those who test positive for SARS-CoV-2 and who are at high risk for developing severe COVID-19 outcomes (4). Due to early supply constraints, initial eligibility in Canada was limited to those who were considered to benefit most, with varied provincial criteria. As knowledge and availability of therapy increased, access to NMV-r expanded with broader eligibility criteria, and inclusion of pharmacist prescribers and nurse practitioners to provide increased access to timely treatment for COVID-19 and ease pressure on the healthcare system (**Appendix**, Supplemental material, Table S1) (5–11).

Although outpatient NMV-r therapy has been shown to significantly reduce the risk of severe COVID-19 outcomes among those at high risk (12–15), previous reports from the United States have shown that NMV-r is underused in the eligible population (16–18). An understanding of real-world population-level NMV-r prescribing and use in the outpatient setting would inform strategies to improve therapy access and use, which, in turn, could reduce serious COVID-19 outcomes and attendant strain of the healthcare system. Limited information is available in Canada. Sicard *et al.* (2023) described the characteristics of NMV-r recipients from eight jurisdictions across Canada during the first several months of its availability (19). Updated and additional information describing the demographic and clinical characteristics of this population of interest in Canada, along with healthcare prescriber type would be beneficial. The objective of this study was to describe the characteristics of adults who received an outpatient dispensation for NMV-r in Alberta, Canada between January 2022 and March 2023.

Methods

Ethics approval was received from the University of Alberta (Pro00132799) and informed consent was waived. Data custodian approvals were received from Alberta Health and Alberta Health Services for the use of administrative health data. A retrospective, observational, population-based study was conducted using administrative health data from several databases in Alberta (Appendix, Supplemental material, Table S2).

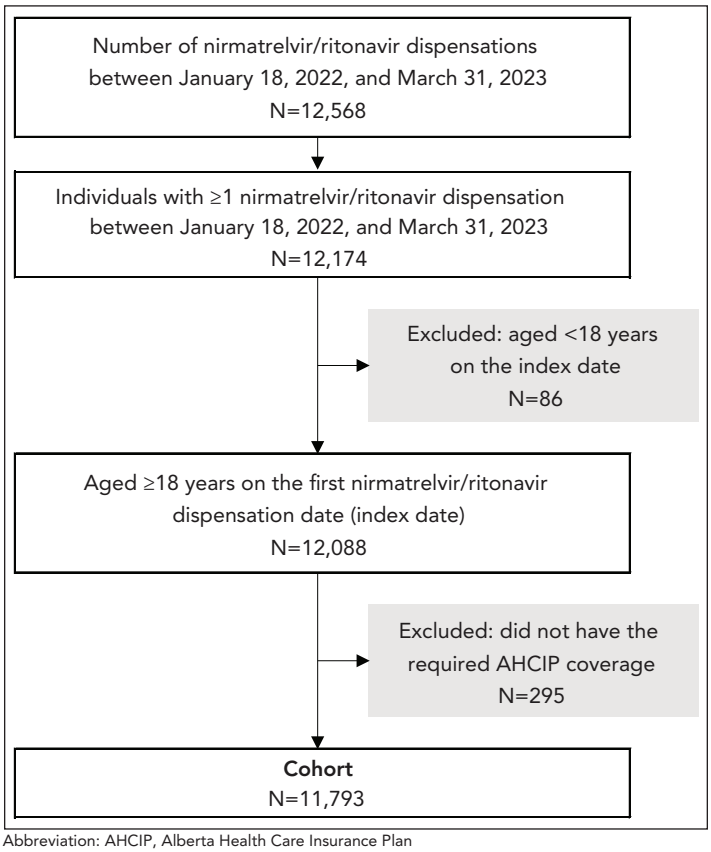
Eligibility criteria included those who 1) were 18 years of age or older on the index NMV-r dispensation date (date of the first NMV-r dispensation during the inclusion period between January 18, 2022 to March 31, 2023; Omicron BA1.1, BA.2, BA.2.12.1, BA.4, BA.5, BQ.1, BQ.1.1 and XBB.1.5 variants predominated during this period) and 2) had provincial healthcare coverage for two or more years before the index NMV-r dispensation date. Canadian provinces have single-payer health systems and provide publicly funded medically necessary care for all residents. While the majority of prescription drugs are not publicly funded, the Public Health Agency of Canada procured, allocated and paid for NMV-r during the inclusion period of this study.

Demographic characteristics recorded on the index NMV-r dispensation date included age, sex, urban/rural residence, those residing within long-term care or supportive living and socioeconomic status (20). Clinical characteristics included the Charlson Comorbidity Index score (Appendix, Supplemental material, Table S3) (21,22) and health conditions that were eligible for NMV-r in Alberta during the inclusion period (Appendix, Supplemental material, Table S4) (7,9,21,23–39). The proportion of those who had a prior infection of SARS-CoV-2, and the previous number of COVID-19 vaccine doses received, were reported. Descriptive statistics included counts and percentages for categorical variables and means and standard deviations (SDs) for continuous variables. In accordance with data custodian privacy standards, outcomes with one to nine individuals were reported as "fewer than 10" (40); where applicable, other outcomes were censored. Analysis was performed using SAS (version 9.4; SAS Institute, Cary, North Carolina).

Results

Cohort selection is shown in **Figure 1** (Appendix, Supplemental material, Figure S1 includes data linkage). Mean age of the cohort (n=11,793) was 65 years (SD=18), 60.4% were female, the majority lived in urban areas (cohort: 89.8%; Alberta general population residing in an urban area: 82.3% (41)) and 7.8% lived in long-term care or supportive living (**Table 1**). Socioeconomic status was presented based on quintiles that represent the Alberta general population (five groups with 20% in each); comparatively, the cohort was more likely to be materially well-off (Material Deprivation Index [MDI] 1: 25.8%) and less likely to be materially deprived (MDI 5: 15.1%) (Table 1). The most commonly (>10%) identified health conditions of interest that the cohort were living with were an immunocompromised status (60.0%), obesity (22.0%), chronic kidney disease (21.0%), diabetes and taking medication for the condition (17.9%), and chronic obstructive pulmonary disease (13.7%); 83.9% had ≥1 health condition of interest (**Table 2**). Most individuals received ≥3 doses of a COVID-19 vaccine on or before the index NMV-r dispensation date (81.6%), 11.4% received 2 doses, and 7.0% received ≤1 dose (0 doses: 5.9%; 1 dose: 1.1%) (Table 2).

Figure 1: Cohort selection flow diagram



Abbreviation: AHCIP, Alberta Health Care Insurance Plan

Among those with an identified prescriber type (n=10,072; 85.4% of the cohort), 83.6% (n=8,418) had NMV-r prescribed by a physician; the most common types were primary healthcare providers (78.8%; n=6,630) and emergency medicine specialists (14.2%; n=1,197) (**Table 3**). Other providers included pharmacists (13.5%; n=1,360) and other types of healthcare providers (2.9%; n=294), of whom the majority were nurse practitioners (54.1%; n=159) and those from pulmonary function laboratories (41.5%; n=122) (Table 3).

Table 1: Demographic characteristics of the total cohort

Demographic characteristics	n (%) (N=11,793)
Age, years	
Mean (SD)	65 (18.0)
Category	
18–49	2,460 (20.9%)
50–59	1,636 (13.9%)
60–69	2,428 (20.6%)
70 or older	5,269 (44.7%)
Sex	
Female	7,127 (60.4%)
Male	4,666 (39.6%)
Residence	
Urban	10,589 (89.8%)
Rural	1,204 (10.2%)
Long-term care/supportive living	916 (7.8%)
Socioeconomic status	
Material Deprivation Index	
1 (most well-off)	2,824 (25.8%)
2	2,423 (22.1%)
3	2,027 (18.5%)
4	2,033 (18.5%)
5 (most deprived)	1,657 (15.1%)
Missing	829
Social Deprivation Index	
1 (most well-off)	2,366 (21.6%)
2	1,915 (17.5%)
3	2,044 (18.6%)
4	2,255 (20.6%)
5 (most deprived)	2,384 (21.7%)
Missing	829

Abbreviation: SD, standard deviation

Discussion

This retrospective, observational, population-based study characterised adults who received outpatient NMV-r in Alberta, Canada between January 2022 and March 2023. Recipients were generally older in age and were living with health conditions associated with a high risk for the development of severe COVID-19 outcomes. This is an important finding as individuals who are at low risk have been shown to not benefit from NMV-r use (42,43). Individuals were also highly vaccinated, with 81.6% having received three or more COVID-19 vaccine doses. There was evidence of higher use among those who resided in urban areas and in areas with a higher socioeconomic status, indicating potential urban/rural and socioeconomic inequalities. The majority of dispensed NMV-r prescriptions were from physicians (83.6%), with 13.5% from pharmacists and 2.9% from other types of healthcare providers. Findings show that while NMV-r was received by adults at high risk for progression to severe COVID-19 outcomes, strategies are needed to address barriers and ensure equitable access to COVID-19 therapy for all who are most likely to benefit.

Sicard *et al.* (2023) investigated the characteristics of NMV-r recipients in Canada during the first several months of its availability (19). The authors found that 61% of individuals were 70 years of age and older, 56% were female, 67% had one or more health conditions and 84% had received three or more COVID-19 vaccine doses, with 5% unvaccinated (19). Similar results were observed in this study regarding the proportion of those who were female and COVID-19 vaccination status; differences were observed with age and health conditions. In this study, a lower proportion who received NMV-r were

Table 2: Clinical characteristics of the total cohort

Clinical characteristics	n (%) (N=11,793)
Charlson Comorbidity Index	
Overall score, mean (SD)	2.0 (2.2)
Category	
0; no comorbidity	3,066 (26.0%)
1–2; mild comorbidity	5,317 (45.1%)
3–4; moderate comorbidity	2,118 (18.0%)
5 or more; severe comorbidity	1,292 (11.0%)
Health conditions	
Type of condition	
Immunocompromised	7,073 (60.0%)
Obesity	2,600 (22.0%)
Chronic kidney disease	2,478 (21.0%)
Diabetes, taking medication	2,106 (17.9%)
COPD	1,613 (13.7%)
Asthma	1,000 (8.5%)
Congestive heart failure	832 (7.1%)
Pregnant	97 (0.8%)
Number of above conditions	
0	1,907 (16.2%)
1	4,798 (40.7%)
2	3,073 (26.1%)
3 or more	2,015 (17.1%)
COVID-19-related characteristics	
Prior SARS-CoV-2 infection	603 (5.1%)
COVID-19 vaccine doses received	
0	697 (5.9%)
1	131 (1.1%)
2	1,344 (11.4%)
3 or more	9,621 (81.6%)

Abbreviations: COPD, chronic obstructive pulmonary disorder; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation

Table 3: Healthcare prescriber type of outpatient pharmacy dispensed nirmatrelvir/ritonavir

Healthcare provider type	Prescriber type identified, n (%) (N=10,072)
Physician	**8,418 (83.6%)**
Primary healthcare provider	6,630 (78.8%)
Emergency medicine	1,197 (14.2%)
Obstetrics and gynecology	208 (2.5%)
Infectious disease	90 (1.1%)
Cardiology	78 (0.9%)
Internal medicine	57 (0.7%)
Hematology	34 (0.4%)
Mental health	33 (0.4%)
Paediatrics	17 (0.2%)
Other	fewer than 10 of each type
Pharmacist	**1,360 (13.5%)**
Other types	**294 (2.9%)**
Nurse practitioners	159 (54.1%)
Pulmonary function laboratory	122 (41.5%)
Other	fewer than 10 of each type

70 years of age and older (44.7%) and a higher proportion had one or more health condition (83.9%). The longer time frame over which the current study inclusion period occurred included broadening eligibility at younger ages (Appendix, Supplemental material, Table S1). The number and type of included health conditions, and the methodology used to define and identify these conditions differed between studies, likely contributing to the varying proportion of people living with health conditions of interest who received NMV-r.

Large retrospective, observational studies from the United States have shown that among individuals who were SARS-CoV-2-positive and eligible to receive NMV-r, the likelihood of receiving NMV-r increased with having a higher socioeconomic status (versus lower), being female and receiving COVID-19 vaccine doses (particularly three or more versus none) (18,44).

Findings from the current study extend these previous reports by indicating urban residents may also be more likely to receive NMV-r. A number of the characteristics associated with higher use of NMV-r are consistent with healthcare-seeking behaviour, which has been shown to be more prevalent in those with a higher socioeconomic status, female sex/gender, older age, the presence of chronic conditions, knowledge of illness prevention and health maintenance, and trust in healthcare providers (45). Although not investigated in this study due to data limitations, previous reports have also shown racial and ethnic disparities in the use of outpatient NMV-r (17,46). Policies and programs addressing barriers to equitable healthcare access and COVID-19 vaccine acceptance and uptake may provide insights for initiatives to reduce outpatient COVID-19 therapy disparities (47). This is of particular importance now that the Government of Canada is no longer supplying COVID-19 rapid antigen tests and NMV-r free of charge, and coverage for these costs varies across provinces and territories (48).

Although prescribing of NMV-r was expanded to pharmacists and nurse practitioners to provide increased access in Alberta, 83.6% of dispensed NMV-r prescriptions were still from physicians. Gold *et al.* (2022) found that despite a substantial increase in the number of COVID-19 oral antiviral dispensing sites in the United States, population-adjusted dispensing rates in areas with a low socioeconomic status (versus higher) were substantially lower even though these areas had the most dispensing sites (49); therefore, addressing outpatient COVID-19 therapy disparities among high risk individuals will

require initiatives beyond pharmacist prescribing and pharmacy proximity.

Although the clinical profile of individuals at high risk for severe COVID-19 outcomes has evolved since the inclusion period of this study, data support NMV-r as an ongoing first-line treatment (14,15). Consequently, addressing disparities in outpatient treatment access among this population remains a relevant need. Current guidelines suggest outpatient NMV-r treatment for those with older age, immunocompromising conditions, or multiple comorbidities, regardless of vaccination status; particularly, adults aged 75 years and older, adults of any age living with an immunocompromising condition, and adults who are immunocompetent living with multiple risk factors for progression to severe COVID-19 illness (e.g., aged 65 years and older, medical complexity, certain health conditions) (3).

Limitations

This study has several important strengths including the large size and population-based design; however, this study is also subject to limitations that should be taken into consideration when interpreting results. Retrospective claims-based studies use administrative data with consequent potential for misclassification of study cohorts or measures; validated case definitions were used, where available, to address this limitation. Socioeconomic status was determined at the neighbourhood dissemination area level (a small geographic area), as opposed to the individual living within the neighbourhood; therefore, there is a potential for misclassification of some participants within the quintiles. Race and ethnicity are not included in administrative health data and therefore could not be assessed. The Pharmaceutical Information Network database only provides information on prescription medication dispensations, and, therefore, does includes neither medications prescribed but not dispensed nor uptake by individuals.

Conclusion

Results from this real-world study showed that adults who received outpatient NMV-r in Alberta displayed characteristics consistent with a high risk for progression to severe COVID-19 outcomes (related to age and health conditions) and healthcare-seeking behaviour (older age, female sex, presence of health conditions, higher socioeconomic status and highly vaccinated). Results also suggested potential urban/rural and socioeconomic differences.

Achieving the optimal use of NMV-r will require iterative refinement of high risk criteria to reflect the evolving epidemic and evidence of benefit, ensuring high risk groups can access diagnostic testing, along with addressing barriers such as drug costs, knowledge gaps and inequities. The implementation of initiatives should be paired with assessment to confirm their effectiveness. If risk-based deployment of NMV-r is successful and barriers are overcome, serious COVID-19 outcomes and attendant strain of the healthcare system could be reduced.

Authors' statement

KV — Conceptualization, methodology, formal analysis, writing–original draft, visualization
JR — Conceptualization, methodology, writing–review & editing, project administration
KM — Conceptualization, methodology, writing–original draft, project administration
SA-H — Conceptualization, methodology, data curation, writing–review & editing
LS — Conceptualization, methodology, writing–review & editing
JL — Conceptualization, methodology, writing–review & editing
ER-M — Conceptualization, methodology, writing–review & editing
ER — Conceptualization, methodology, writing–review & editing
PUN — Conceptualization, methodology, validation, writing–review & editing, visualization
TW — Conceptualization, methodology, writing–review & editing
SK — Conceptualization, methodology, writing–review & editing, supervision, funding acquisition

The data that support the findings of this study are available from Alberta Health Services and Alberta Health, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

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

Competing interests

The author(s) declared the following potential conflicts of interest with respect to the research and authorship of this report: KV, SA-H, JR, KM, PUN, TW and SK are members of the Alberta Real World Evidence Consortium (ARWEC) and the Alberta Drug and Therapeutic Evaluation Consortium (ADTEC); these entities (comprised of individuals from the University of Alberta, University of Calgary, and Institutes of Health Economics) conduct research including academic investigator-initiated industry-funded studies (ARWEC) and government-funded studies (ADTEC). Pfizer is the manufacturer of nirmatrelvir/ritonavir, and contributed research funding to the grant held by the University of Alberta, with SK as the principal investigator. In the past three years: the University of Alberta, with SK as the principal investigator, has received research funding from Moderna (a manufacturer of COVID-19 vaccines), and the Post Market Drug Evaluation program (funded by Canada's Drug Agency) in relation to COVID-19 research; JL has received research funding from the Canadian Institutes for Health Research, Society for Healthcare Epidemiology of America, MSI Foundation, University of Calgary Department of Medicine and O'Brien Institute for Public Health, support for meeting attendance from the Canadian Institutes for Health Research, Society for Healthcare Epidemiology of America, and Research Canada, and a Pandemic EVIDENCE Collaboration fellowship from Kellogg College, Oxford University. No other conflict of interest was declared. All authors of this study had complete

autonomy over the design and execution of the study, as well as the content of this manuscript.

ORCID numbers

Khanh Vu — 0000-0002-4319-1922
Jason Randall — 0000-0002-0288-3551
Karen Martins — 0000-0002-3400-7214
Sylvia Aponte-Hao — 0000-0002-8940-4516
Lynora Saxinger — 0000-0003-4133-9337
Jenine Leal — 0000-0002-0308-4890
Elissa Rennert-May — 0000-0001-9884-6423
Ellen Rafferty — 0000-0001-9974-8016
Phuong Uyen Nguyen — 0009-0001-3948-5362
Tyler Williamson — 0000-0001-5029-2345
Scott Klarenbach — 0000-0002-8611-1056

Acknowledgements

We thank the participants in this study. This study is based in part on data from Alberta Health and AHS, which was provided by the Alberta Strategy for Patient Oriented Research (SPOR) SUPPORT Unit housed within AHS. The interpretation and conclusions contained herein are those of the researchers and do not necessarily represent the views or opinions of the Government of Alberta or AHS. Scott Klarenbach was supported by the Kidney Health Research Chair and the Division of Nephrology at the University of Alberta.

Funding

This research study was funded by a grant (232402922) from the Pfizer-Alberta Collaboration in Health with financial contributions from Pfizer Canada and the Government of Alberta that was evaluated and awarded by Alberta Innovates to the University of Alberta, with SK as the principal investigator. The funders had no role in the study design, analysis, interpretation of the data or drafting of the manuscript. The funders were provided with the opportunity to comment on the protocol and manuscript, with all final decisions remaining with SK and the other authors.

References

1. Rick AM, Laurens MB, Huang Y, Yu C, Martin TC, Rodriguez CA, Rostad CA, Maboa RM, Baden LR, El Sahly HM, Grinsztejn B, Gray GE, Gay CL, Gilbert PB, Janes HE, Kublin JG, Huang Y, Leav B, Hirsch I, Struyf F, Dunkle LM, Neuzil KM, Corey L, Goepfert PA, Walsh SR, Follmann D, Kotloff KL; NIAID-funded COVID-19 Prevention Network (CoVPN). Risk of COVID-19 after natural infection or vaccination. EBioMedicine 2023;96:104799. DOI PubMed

2. Lewnard JA, Mahale P, Malden D, Hong V, Ackerson BK, Lewin BJ, Link-Gelles R, Feldstein LR, Lipsitch M, Tartof SY. Immune escape and attenuated severity associated with the SARS-CoV-2 BA.2.86/JN.1 lineage. Nat Commun 2024;15(1):8550. DOI PubMed

3. Cohen P, Gebo K. COVID-19: Evaluation and management of adults with acute infection in the outpatient setting. UpToDate; 2025. [Accessed 2025 Dec 31]. https://www.uptodate.com/contents/covid-19-evaluation-and-management-of-adults-with-acute-infection-in-the-outpatient-setting

4. Health Canada. Health Canada authorizes PAXLOVID™ for patients with mild to moderate COVID-19 at high risk of developing serious disease. Ottawa, ON: HC; 2022. https://www.canada.ca/en/health-canada/news/2022/01/health-canada-authorizes-paxlovidtm-for-patients-with-mild-to-moderate-covid-19-at-high-risk-of-developing-serious-disease.html

5. Alberta Health. New at-home COVID-19 treatment on its way to Alberta. Edmonton, AB: Alberta Health; 2022. https://www.alberta.ca/release.cfm?xID=81782C40D5547-AD19-27C0-6D5D8405D1FD31A5

6. Alberta Health. Paxlovid to be available at more Alberta pharmacies. Edmonton, AB: Alberta Health; 2022. https://www.alberta.ca/release.cfm?xID=822359E14E00B-D965-BC47-BFD4C52D42540237

7. Alberta Health. Alberta expands access to fourth vaccine doses. Edmonton, AB: Alberta Health; 2022. https://www.alberta.ca/release.cfm?xID=822960A564540-9E17-A696-8D1B30A93143EF97#jumplinks-2

8. Alberta Health. Expanding Paxlovid accessibility. Edmonton, AB: Alberta Health; 2022. https://www.alberta.ca/release.cfm?xID=82493A9DBDEEC-B852-AA3F-6EFADF340E2ADA0A

9. Alberta Health Services. Eligibility criteria for Paxlovid and Remdesivir expanded. Edmonton, AB: Alberta Health; 2022. https://www.specialistlink.ca/assets/Outpatient-COVID-Treament-criteria-update-MEMO_May11.pdf

10. Alberta Health Services. COVID-19, FAQs for health care providers. Edmonton, AB: Alberta Health; 2023. https://www.albertahealthservices.ca/assets/info/ppih/if-ppih-covid-19-paxlovid-faq-patient.pdf

11. Alberta Blue Cross. A reference guide for federally supplied Paxlovid™: Paxlovid dispensing. Edmonton, AB: AB Blue Cross; 2022. https://www.ab.bluecross.ca/pdfs/reference-guide-for-pharmacists-dispensing-paxlovid.pdf

12. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, Baniecki M, Hendrick VM, Damle B, Simón-Campos A, Pypstra R, Rusnak JM; EPIC-HR Investigators. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med 2022;386(15):1397–408. DOI PubMed

13. Okoli GN, Askin N, Rabbani R. Nirmatrelvir/Ritonavir Regimen for Mild/Moderately Severe COVID-19: A Rapid Review With Meta-Analysis and Trial Sequential Analysis. Ann Fam Med 2024;22(4):336–46. DOI PubMed

14. Aggarwal NR, Molina KC, Beaty LE, Bennett TD, Carlson NE, Mayer DA, Peers JL, Russell S, Wynia MK, Ginde AA. Real-world use of nirmatrelvir-ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study. Lancet Infect Dis 2023;23(6):696–705. DOI PubMed

15. Aggarwal NR, Beaty LE, Bennett TD, Fish LE, Jacobs JR, Mayer DA, Molina KC, Peers JL, Richardson DB, Russell S, Varela A, Webb BJ, Wynia MK, Xiao M, Carlson NE, Ginde AA. Real-world use of nirmatrelvir-ritonavir in COVID-19 outpatients during BQ.1, BQ.1.1., and XBB.1.5 predominant omicron variants in three U.S. health systems: a retrospective cohort study. Lancet Reg Health Am 2024;31(6):100693. DOI PubMed

16. Levy ME, Burrows E, Chilunda V, Pawloski PA, Heaton PR, Grzymski J, Goldman JD, McEwen LM, Wyman D, Dei Rossi A, Dai H, Isaksson M, Washington NL, Basler T, Tsan K, Nguyen J, Ramirez J, Sandoval E, Lee W, Lu J, Luo S. SARS-CoV-2 Antiviral Prescribing Gaps Among Nonhospitalized High-Risk Adults. Clin Infect Dis 2024;78(6):1531–5. DOI PubMed

17. Boehmer TK, Koumans EH, Skillen EL, Kappelman MD, Carton TW, Patel A, August EM, Bernstein R, Denson JL, Draper C, Gundlapalli AV, Paranjape A, Puro J, Rao P, Siegel DA, Trick WE, Walker CL, Block JP. Racial and Ethnic Disparities in Outpatient Treatment of COVID-19 - United States, January-July 2022. MMWR Morb Mortal Wkly Rep 2022;71(43):1359–65. DOI PubMed

18. Malden DE, McLaughlin JM, Hong V, Lewnard J, Ackerson BK, Puzniak L, Kim JS, Takhar H, Frankland TB, Slezak JM, Tartof SY. Predictors of nirmatrelvir-ritonavir receipt among COVID-19 patients in a large US health system. Sci Rep 2024;14(1):7485. DOI PubMed

19. Sicard N, Squires S, Mullah M, Daley P. Characteristics and clinical outcomes of nirmatrelvir/ritonavir (Paxlovid™) recipients in Canada, 2022: a descriptive cohort study. Can Commun Dis Rep 2023;49(10):440–5. DOI PubMed

20. Pampalon R, Hamel D, Gamache P, Raymond G. A deprivation index for health planning in Canada. Chronic Dis Can 2009;29(4):178–91. DOI PubMed

21. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40(5):373–83. DOI PubMed

22. Lix L, Smith M, Pitz M, Ahmed R, Quon H, Griffith J, Turner D, Hong S, Prior H, Banerjee A, Koseva I, Kulbaba C. Cancer data linkage in Manitoba: expanding the infrastructure for research. Manitoba Centre for Health Policy; 2016. http://mchp-appserv.cpe.umanitoba.ca/reference/Candata_web_final.pdf

23. Tonelli M, Wiebe N, Fortin M, Guthrie B, Hemmelgarn BR, James MT, Klarenbach SW, Lewanczuk R, Manns BJ, Ronksley P, Sargious P, Straus S, Quan H; Alberta Kidney Disease Network. Methods for identifying 30 chronic conditions: application to administrative data. BMC Med Inform Decis Mak 2015;15:31. DOI PubMed

24. Gershon AS, Wang C, Guan J, Vasilevska-Ristovska J, Cicutto L, To T. Identifying individuals with physcian diagnosed COPD in health administrative databases. COPD 2009;6(5):388–94. DOI PubMed

25. Kennedy-Martin T, Boye KS, Peng X. Cost of medication adherence and persistence in type 2 diabetes mellitus: a literature review. Patient Prefer Adherence 2017;11:1103–17. DOI PubMed

26. Paterson JM, Dormuth C, Janzen D, Katz A, Ronksley P, Aponte-Hao S, Dahl M, Dawn-Scory T, Missaoui H, Lu X, Kabore JL, Benigeri M, St-Jean A, Sheng R, Wu F. Outpatient Nirmatrelvir-Ritonavir and Remdesivir Utilization in Canada. Ottawa, ON: CADTH; 2024. https://www.cda-amc.ca/sites/default/files/hta-he/HC0069_Pax_Rem_DUS_Scientific%20Report_final.pdf

27. Clement FM, James MT, Chin R, Klarenbach SW, Manns BJ, Quinn RR, Ravani P, Tonelli M, Hemmelgarn BR; Alberta Kidney Disease Network. Validation of a case definition to define chronic dialysis using outpatient administrative data. BMC Med Res Methodol 2011;11:25. DOI PubMed

28. Lix L, Plourde PJ, Larcombe L, Kinew KA, Basham CA, Derksen S, Srisakuldee W, Schultz J, McCulloch S. Exploring tuberculosis treatment, management, and prevention in Manitoba's Administrative health data. Manitoba Centre for Health Policy; 2018. http://mchp-appserv.cpe.umanitoba.ca/deliverable.php?referencePaperID=77874

29. Grosse SD, Green NS, Reeves SL. Administrative data identify sickle cell disease: A critical review of approaches in U.S. health services research. Pediatr Blood Cancer 2020;67(12):e28703. DOI PubMed

30. Antoniou T, Zagorski B, Loutfy MR, Strike C, Glazier RH. Validation of case-finding algorithms derived from administrative data for identifying adults living with human immunodeficiency virus infection. PLoS One 2011;6(6):e21748. DOI PubMed

31. Widdifield J, Bombardier C, Bernatsky S, Paterson JM, Green D, Young J, Ivers N, Butt DA, Jaakkimainen RL, Thorne JC, Tu K. An administrative data validation study of the accuracy of algorithms for identifying rheumatoid arthritis: the influence of the reference standard on algorithm performance. BMC Musculoskelet Disord 2014;15:216. DOI PubMed

32. Rezaie A, Quan H, Fedorak RN, Panaccione R, Hilsden RJ. Development and validation of an administrative case definition for inflammatory bowel diseases. Can J Gastroenterol 2012;26(10):711–7. DOI PubMed

33. Eder L, Widdifield J, Rosen CF, Alhusayen R, Cheng SY, Young J, Campbell W, Bernatsky S, Gladman DD, Paterson M, Tu K. Identifying and Characterizing Psoriasis and Psoriatic Arthritis Patients in Ontario Administrative Data: A Population-based Study From 1991 to 2015. J Rheumatol 2020;47(11):1644–51. DOI PubMed

34. Widdifield J, Ivers NM, Young J, Green D, Jaakkimainen L, Butt DA, O'Connor P, Hollands S, Tu K. Development and validation of an administrative data algorithm to estimate the disease burden and epidemiology of multiple sclerosis in Ontario, Canada. Mult Scler 2015;21(8):1045–54. DOI PubMed

35. Clemens KK, Reid JN, Shariff SZ, Welk B. Validity of Hospital Codes for Obesity in Ontario, Canada. Can J Diabetes 2021;45(3):243–248.e4. DOI PubMed

36. Bello A, Padwal R, Lloyd A, Hemmelgarn B, Klarenbach S, Manns B, Tonelli M; Alberta Kidney Disease Network. Using linked administrative data to study periprocedural mortality in obesity and chronic kidney disease (CKD). Nephrol Dial Transplant 2013;28 Suppl 4:iv57–64. DOI PubMed

37. Canadian Institute for Health Information. Bariatric surgery in Canada. Ottawa, ON: CIHI; 2014. https://www.cihi.ca/sites/default/files/document/bariatric-surgery-in-canada-22may2014-en.pdf

38. Manitoba Centre for Health Policy. Concept: teenage pregnancy / teen pregnancy. Winnipeg, MB: MCHP; 2020. [Accessed 2024 Nov 10]. http://mchp-appserv.cpe.umanitoba.ca/viewConcept.php?conceptID=1248

39. Wijeratne DT, Housin A, Lajkosz K, Lougheed MD, Xiong PY, Barber D, Doliszny KM, Archer SL. Using health administrative data to identify patients with pulmonary hypertension: A single center, proof of concept validation study in Ontario, Canada. Pulm Circ 2022;12(1):e12040. DOI PubMed

40. Alberta Health. Health data, research and standards: Health data access. Edmonton, AB: Alberta Health. [Accessed 2024 May 24]. https://www.alberta.ca/health-research

41. Statistics Canada. Focus on Geography Series, 2021 Census of Population: Alberta, Province. Ottawa, ON: StatCan; 2025. [Accessed 2025 Feb 6]. https://www12.statcan.gc.ca/census-recensement/2021/as-sa/fogs-spg/page.cfm?lang=E&topic=8&dguid=2021A000248

42. Faust JS, Kumar A, Shah J, Khadke S, Dani SS, Ganatra S, Sax PE. Oral Nirmatrelvir and Ritonavir for Coronavirus Disease 2019 in Vaccinated, Nonhospitalized Adults Aged 18-50 Years. Clin Infect Dis 2023;77(9):1257–64. DOI PubMed

43. Dormuth CR, Kim JD, Fisher A, Piszczek J, Kuo IF. Nirmatrelvir-Ritonavir and COVID-19 Mortality and Hospitalization Among Patients With Vulnerability to COVID-19 Complications. JAMA Netw Open 2023;6(10):e2336678. DOI PubMed

44. Appaneal HJ, LaPlante KL, Lopes VV, Martin C, Puzniak L, Wiemken TL, Zasowski EJ, McLaughlin JM, Caffrey AR. Nirmatrelvir/Ritonavir Utilization for the Treatment of Non-hospitalized Adults with COVID-19 in the National Veterans Affairs (VA) Healthcare System. Infect Dis Ther 2024;13(1):155–72. DOI PubMed

45. Thompson AE, Anisimowicz Y, Miedema B, Hogg W, Wodchis WP, Aubrey-Bassler K. The influence of gender and other patient characteristics on health care-seeking behaviour: a QUALICOPC study. BMC Fam Pract 2016;17:38. DOI PubMed

46. Xiao X, Alexander GC, Mehta HB. Nirmatrelvir/Ritonavir (Paxlovid) Use Among Individuals at Risk of Severe COVID-19: An Analysis of the National COVID Cohort Collaborative (N3C). Pharmacoepidemiol Drug Saf 2024;33(8):e5869. DOI PubMed

47. Public Health Agency of Canada. Immunization Partnership Fund. Ottawa, ON: PHAC; 2025. [Accessed 2024 Oct 30]. https://www.canada.ca/en/public-health/services/immunization-vaccine-priorities/immunization-partnership-fund.html

48. Public Health Agency of Canada. COVID-19: Provincial and territorial resources. Ottawa, ON: PHAC; 2022. [Accessed 2025 Mar 12]. https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/symptoms/provincial-territorial-resources-covid-19.html

49. Gold JA, Kelleher J, Magid J, Jackson BR, Pennini ME, Kushner D, Weston EJ, Rasulnia B, Kuwabara S, Bennett K, Mahon BE, Patel A, Auerbach J. Dispensing of Oral Antiviral Drugs for Treatment of COVID-19 by Zip Code-Level Social Vulnerability - United States, December 23, 2021-May 21, 2022. MMWR Morb Mortal Wkly Rep 2022;71(25):825–9. DOI PubMed

Appendix

Supplemental material is available upon request to the author: swk@ualberta.ca

Table S1: Eligibility criteria for nirmatrelvir/ritonavir in Alberta during the study inclusion period
Table S2: Administrative databases used in the study
Table S3: Health conditions and their associated codes and weights included in the Charlson Comorbidity Index
Table S4: Case definitions used for identification of health conditions
Figure S1: Selection of the study cohort with data linkage shown

Affiliations

[1] Real World Evidence Unit, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, AB

[2] Research Services, Alberta Strategy for Patient Oriented Research SUPPORT Unit (AbSPORU), Calgary, AB

[3] Centre for Health Informatics, Cumming School of Medicine, University of Calgary, Calgary, AB

[4] Department of Medicine, University of Alberta, Edmonton, AB

[5] Department of Microbiology and Immunology, University of Alberta, Edmonton, AB

[6] Infection Prevention & Control, Alberta Health Services, AB

[7] Department of Community Health Sciences, Cumming School of Medicine, University of Calgary, Calgary, AB

[8] Department of Microbiology, Immunology, and Infectious Diseases, Cumming School of Medicine, University of Calgary, Calgary, AB

[9] O'Brien Institute for Public Health, University of Calgary, Calgary, AB

[10] Department of Medicine, University of Calgary, Calgary, AB

[11] Institute of Health Economics, Edmonton, AB

[12] Libin Cardiovascular Institute, University of Calgary, Calgary, AB

[13] Alberta Children's Hospital Research Institute, University of Calgary, Calgary, AB

CCDR

CANADA COMMUNICABLE DISEASE REPORT

Public Health Agency of Canada
130 Colonnade Road
Address Locator 6503B
Ottawa, Ontario K1A 0K9
ccdr-rmtc@phac-aspc.gc.ca

To promote and protect the health of Canadians through leadership, partnership, innovation and action in public health.

Public Health Agency of Canada

Published by authority of the Minister of Health.

This publication is also available online at

https://www.canada.ca/ccdr

Également disponible en français sous le titre :
Relevé des maladies transmissibles au Canada