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ANTIVIRAL THERAPY

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ANTIVIRAL THERAPY

TABLE OF CONTENTS

Summary of the National Advisory Committee on Immunization (NACI) statement on the prevention of respiratory syncytial virus (RSV) in older adults

April Killikelly[1], Winnie Siu[1,2], Elissa M Abrams[1,3,4], Nicholas Brousseau[5] on behalf of the National Advisory Committee on Immunization (NACI)*

Abstract

Background: Respiratory syncytial virus (RSV) is a common respiratory virus. In addition to infants, older adults are at higher risk of severe outcomes due to RSV, particularly advanced-age older adults and those with chronic medical conditions. The authorization of three vaccines, one for adults 50 years of age and older (Arexvy) and two for adults 60 years of age and older (Abrysvo and mRESVIA), offers the opportunity to protect older Canadians from RSV disease. This article summarizes guidance from the National Advisory Committee on Immunization (NACI) on the prevention of RSV in older adults.

Methods: NACI established key policy questions and performed an evidence review and synthesis for three new vaccines. In consideration of the burden of illness to be prevented, safety and efficacy of the new immunizing products, economic evidence and ethics, equity, feasibility and acceptability considerations, NACI made evidence-based recommendations.

Results: The three RSV vaccines may provide similar reductions in hospitalizations associated with RSV and medically attended RSV respiratory tract infection for adults 60 years of age and older. However, evidence is limited for other outcomes. These vaccines were well-tolerated in clinical studies, with an acceptable safety profile among older adults. The duration of protection of the RSV vaccine is not yet known, and it is unclear if the protection offered by vaccination can be boosted by subsequent doses of vaccine.

Conclusion: Based on available evidence, NACI recommends RSV immunization programs for adults 75 years of age and older, particularly for older adults with chronic health conditions who are at increased risk of severe RSV disease. NACI also recommends RSV immunization programs for adults 60 years of age and older who are residents of nursing homes and other chronic care facilities. NACI recommends that receiving an RSV vaccine may be considered as an individual decision by adults 50 to 74 years of age, in consultation with their healthcare provider.

Suggested citation: Killikelly A, Siu W, Abrams EM, Brousseau N on behalf of the National Advisory Committee on Immunization (NACI). Summary of the National Advisory Committee on Immunization (NACI) Statement on the Prevention of Respiratory Syncytial Virus (RSV) in Older Adults. Can Commun Dis Rep 2025;51(8):292–6. https://doi.org/10.14745/ccdr.v51i08a01

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

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Introduction

Respiratory syncytial virus (RSV) is a common respiratory virus. In addition to infants, older adults, particularly advanced-age older adults and those with chronic medical conditions, such as cardiopulmonary disease and immunocompromise, are at higher risk of severe outcomes due to RSV (1). Patients who reside in chronic care facilities and are admitted to hospital also have a higher likelihood of severe clinical outcomes, including death, compared to patients with other living situations at hospital admission. Primary infection does not confer protective immunity against reinfections, which recur throughout life and become more serious with advanced age in older adults. In addition, adults may be at increased risk of severe RSV disease due to factors that intersect with social determinants of health.

Respiratory syncytial virus has a seasonal pattern of activity, where infections are usually more common in the winter with variation in the timing and magnitude of the peak. Prior to the COVID-19 pandemic, the RSV season in most of Canada was typically November to April, but this may vary by region.

Health Canada has recently authorized three immunization products, based on the pre-fusion stabilized F protein (preF) from RSV. An unadjuvanted vaccine, RSVpreF (Abrysvo, Pfizer) is authorized with an indication for all adults 60 years of age and over. This formulation is also authorized for pregnant women and pregnant people who are 32 to 36 weeks gestational age (wGA) to protect infants from RSV. An AS01E adjuvanted vaccine, RSVPreF3 (Arexvy, GSK) is authorized with an indication for all adults 60 years of age and over and for adults at high risk for RSV disease who are 50 to 59 years of age. Authorized for use in all adults aged 60 years and older, mRNA-1345 (mRESVIA, Moderna) delivers preF via an mRNA platform.

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with recommendations (2,3) regarding the use of vaccines and immunization products for RSV, which reflect the latest evidence for RSV epidemiology, clinical outcomes (such as immunogenicity, efficacy and effectiveness, and safety), immunization practices, and product authorization and availability in Canada. Recommendations also take into account ethics, equity, feasibility and acceptability considerations, and economic analysis. Development of this guidance was triggered by the authorization of new vaccines to protect older adults from RSV. This work was led by NACI's RSV Working Group (WG) and involved a thorough review and evaluation of the literature, as well as discussion and debate at the scientific and clinical practice levels.

Methods

The NACI RSV WG reviewed key questions and performed evidence reviews and syntheses. The WG proposed recommendations for vaccine use to NACI in consideration of the burden of illness to be prevented, safety, efficacy, ethics, equity, acceptability, feasibility and economics. All evidence was reviewed according to a Grading of Recommendations, Assessment, Development, and Evaluations (GRADE)-informed methodology and summarized in evidence tables. NACI approved specific evidence-based recommendations and summarized the rationale and relevant considerations in a statement.

Results

Efficacy

The evidence suggests that using RSVpreF, RSVPreF3 and mRNA-1345 may result in similar reductions in hospitalizations associated with RSV and medically attended RSV respiratory tract infection (RTI) for adults 60 years of age and older. However, there was limited evidence on the effect of these vaccines against death due to RSV and intensive care unit (ICU) admission associated with RSV. Larger populations may be needed to observe and assess these severe clinical outcomes. As no head-to-head trials currently exist comparing these products, there are important limitations to comparing across RSV vaccine trials for different products due to differences in trial design, including clinical endpoints and follow-up time.

In adults 75 years of age and older, protection against medically attended RSV RTI ranged from roughly 49% to 78% (4,5). In adults 75 years of age and older, protection against death, ICU admission and hospitalization was not estimable due to lack of data from clinical trials.

In adults 60 years of age and older, protection against medically attended RSV RTI ranged from roughly 66% to 86%. Data limitations did not allow for estimations of protection against death and ICU for adults 60 years of age and older. Notably, the vaccine trials were conducted during RSV seasons when public health measures due to the COVID-19 pandemic were in effect. These measures reduced the transmission of respiratory viruses, which could explain the low rate of RSV-associated outcomes observed in the trials.

Post-market data have also shown effectiveness of RSVPreF3 and RSVpreF in Phase IV studies. Real-world effectiveness data show that RSV vaccination provides protection against severe RSV disease. Vaccine effectiveness was similar to results from Phase III trials and no substantial differences in effectiveness were observed between products.

The duration of protection provided by the RSV vaccine is still unknown, and it remains unclear whether subsequent doses of vaccine can boost this protection.

Discussion

Safety

Respiratory syncytial virus vaccines were well tolerated, with an acceptable safety profile among older adults. In randomized controlled trials, most (greater than 95%) of reported adverse events (AEs) were mild to moderate. The available evidence suggests that RSVpreF may result in a slight increase in severe local AEs and little to no difference in severe systemic AEs compared to placebo. For RSVPreF3 and for mRNA-1345, data suggest that vaccination results in a slight increase in severe local and systemic AEs compared to placebo.

Early post-marketing safety data from the United States suggests a potential increased rate of Guillain-Barré syndrome in adults 60 years of age and older after administration of the RSVpreF or RSVPreF3 vaccines (6,7). However, the currently available preliminary data are subject to limitations. Additional analyses are planned to further assess this potential increased risk of Guillain-Barré syndrome.

Ethics, equity, feasibility, and acceptability

NACI considered age-based, as well as medical- and social risk-based, RSV vaccine recommendations for older adults. An age-based recommendation would improve both equity and feasibility, as it reduces access barriers, for example, by allowing vaccination in a wider range of settings and making eligibility easier to determine. Furthermore, an age-based recommendation would capture those individuals who have medical conditions that place them at increased risk of severe RSV disease but have not yet been diagnosed. However, equity could also potentially be increased through a risk-based recommendation, given that older adults at greater risk of severe illness would be prioritized.

When interpreting the epidemiological trends to inform the recommendations, equity considerations include acknowledgement that available evidence for some populations is limited and may be biased, for example, due to systemic limitations in available data for racialized groups. Consideration should be made for diverse contexts of equity-implicated communities. One example where diverse contexts may apply is Indigenous groups across various settings (e.g., urban, rural, on-reserve, off-reserve).

NACI acknowledges the feasibility concerns of the different storage temperature for mRNA-1345 and supports jurisdictions in weighing this factor alongside other vaccine characteristics when considering product selection and program design.

Economics

To support decision-making for the use of vaccines for preventing RSV in adults, NACI conducted a systematic literature review (8), developed a de novo model-based economic evaluation (9), and performed a multi-model comparison (10). The systematic review showed that, in general, without a substantial reduction in vaccine price, the use of RSV vaccines in all adults aged 60 years and older or 65 years and older was unlikely to be cost-effective at commonly used cost-effectiveness thresholds. The model-based economic analysis showed that medical risk-based vaccination strategies could be cost-effective, with the age cutoff for such a policy dependent on model assumptions. Age-based vaccination strategies may offer a positive net health benefit compared to no vaccination; however, they are not resource-efficient compared to medical risk-based strategies. The results of the multi-model comparison were consistent with the de novo model-based economic evaluation. Using currently available vaccine efficacy data, mRNA-1345 may be less cost-effective than other authorized RSV vaccines. If the assumption of lower vaccine efficacy for mRNA-1345 compared to protein subunit vaccines is accurate, a lower vaccine price for mRNA-1345 would reduce the difference in cost-effectiveness. However, true differences in efficacy remain uncertain.

For individuals who may seek vaccination outside of a public health program, NACI recommends that RSV vaccines may be considered as an individual decision by adults 50 to 74 years of age, in consultation with their healthcare provider. It is unknown at this time if these vaccines can be boosted by subsequent doses, and therefore, healthy individuals under 75 years of age may wish to discuss with their healthcare provider whether to defer vaccination until they are at greater risk. If an individual over the age of 75 is not included in a publicly funded program, NACI recommends vaccination for these individuals, particularly for those adults at increased risk of severe RSV disease.

The RSV vaccine is optimally administered just before the start of the RSV season. Jurisdictions are encouraged to define the RSV season and administer RSV vaccines based on local epidemiology (before the COVID-19 pandemic, the RSV season was typically November to April).

Limitations

Given the need for older adults to be protected from multiple vaccine-preventable diseases, some of which are seasonal, concurrent administration of an RSV vaccine with other adult vaccines is acceptable and supported. If possible, RSV vaccines should be given at least six weeks before or after non-seasonal vaccines (e.g., shingles or diphtheria-tetanus vaccines) to avoid inadvertently attributing an adverse event from another vaccine to the RSV vaccine or vice versa.

Recommendations

NACI recommends RSV immunization programs for adults 75 years of age and older, particularly for older adults with

chronic health conditions who are at increased risk of severe RSV disease. Adults with chronic health conditions, who are at increased medical risk for severe RSV disease, are highlighted in **List 1**. Indigenous Peoples may experience a disproportionate burden of illness due to social, environmental, and economic factors, rooted in the history of colonization and systemic racism (i.e., structural inequity). In First Nations, Métis, and Inuit communities, autonomous decisions should be made by Indigenous Peoples with the support of healthcare and public health partners.

List 1: Clinically significant chronic health conditions for which respiratory syncytial virus 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

NACI also recommends RSV immunization programs for adults 60 years of age and older who are residents of nursing homes and other chronic care facilities.

Conclusion

NACI continues to recommend RSV vaccination for adults 75 years of age and older and adults 60 years of age and older living in long-term care. Respiratory syncytial virus vaccination is particularly recommended for adults at increased risk of RSV disease. NACI will continue to monitor additional evidence, as it emerges, on RSV disease burden and RSV vaccine efficacy and safety in younger age groups.

Authors' statement

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

None.

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Evaluation of a real-time hospital surveillance system for respiratory syncytial virus, Ontario, Canada, 2022–2023

Michelle Murti[1,2]*, Ania Sarnocinska[1], Mahnaz Alavinejad[1], Aidin Kerem[1], Kamil Malikov[1], Kevin Brown[2,3], Tiffany Fitzpatrick[2,3], Michael Hillmer[1,4]

Abstract

Background: Respiratory syncytial virus (RSV) surged in the 2022–2023 respiratory season after low activity during the pandemic. To monitor the RSV season in real time and support healthcare planning, Ontario introduced daily hospital bed census reporting of RSV hospitalizations by age group (0–17, 18–64, 65 years and older).

Objectives: To assess the completeness and quality of the newly introduced real-time surveillance compared to end-of-season ICD-10 coded hospitalization discharge abstract data (DAD) from November 22, 2022, to March 31, 2023.

Methods: Respiratory syncytial virus hospitalizations from both data sources were compared to RSV laboratory positivity to assess concordance with overall RSV activity. A longitudinal comparison by age group was assessed by time-lagged cross-correlation of the daily submission data versus DAD data, including cross correlation coefficients for each time lag, confidence bound and the highest correlation value.

Results: Both data sources followed trends in RSV positivity. Data by age groups showed an early peak of paediatric admissions followed by a peak in adult and older adult hospitalizations. Daily surveillance consistently underestimated hospitalizations with a peak of 430 beds by DAD on January 7, 2023, versus 322 beds (75%) for daily reporting on the same day. The maximum correlation coefficient values were 0.67 (all ages), 0.57 (0–17 years), 0.66 (18–64 years) and 0.63 (65 years and older).

Conclusion: Implementation of daily hospital reporting provided accurate trending in RSV hospitalizations by age group to inform within season healthcare and public health planning.

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Introduction

Respiratory syncytial virus (RSV) is one of the most common causes of respiratory infection among children under five years old globally, with over 100,000 RSV-attributable deaths worldwide annually (1). Older adults are also susceptible to morbidity and mortality from RSV, with an estimated 470,000 hospitalizations in adults 60 years and older in high-income countries (2). In Ontario, RSV hospitalization rates for children younger than five years old is 4.2 per 1,000 person-years, and 29.6 per 1,000 person-years for infants aged one month old (3). During the COVID-19 pandemic, non-pharmaceutical interventions interrupted usual seasonal patterns of respiratory infections, and there had been very low levels of RSV during the 2020–2021 respiratory season in Ontario (4,5). However, by mid-2022, there were indications of

a significant RSV resurgence globally, and an early and severe season in Australia, with high morbidity among children younger than five years old (6). Along with early and elevated cases of influenza and the ongoing COVID-19 pandemic, the "triple threat" was causing significant strain on the healthcare system in Australia and other parts of the southern hemisphere (7). Given this pattern of illness, there was concern for a similar early respiratory season in the fall/winter of 2022–2023 in the northern hemisphere with disproportionate impacts on the paediatric population from overlapping peaks of RSV, influenza and COVID-19 that could overwhelm the paediatric healthcare system.

Individual cases of RSV are not reportable to public health authorities in Ontario, Canada. Surveillance is based on reporting of RSV outbreaks in institutions and public hospitals to public health authorities (8), and testing of data from hospital and public health laboratories based on respiratory multiplex testing of admitted patients as well as paediatric patients in the emergency department (9). Real-time surveillance for severity impacts from RSV did not exist in Ontario, resulting in an inability to detect, within the season, healthcare system surges related to RSV. Therefore, in the fall of 2022, in anticipation of atypically early and high levels of RSV, the Ontario Ministry of Health added daily hospital bed census reporting of admissions and cases for RSV by age group to the ongoing COVID-19 and influenza daily bed census reporting by hospitals. Initiation of real-time surveillance subsequently enabled the Ministry of Health to develop forecasting models for public health and health system decision-making throughout the 2022–2023 season. While there was high utility from the newly implemented surveillance system for informing public health and healthcare decision-making, the completeness and quality of the newly implemented data reporting were unknown.

The primary objective of this study was to evaluate the completeness and cross-correlation of the newly implemented hospital-reported daily bed census reporting data on RSV admissions by age group in Ontario to validated RSV-coded hospitalization discharge data.

Methods

Data sources

Hospital-reported bed census data was obtained from the Ontario Ministry of Health, including the daily number of hospital beds occupied by RSV patients by age group (0–17, 18–64, 65 years and older) from initiation of the surveillance on November 24, 2022, until March 31, 2023, when RSV activity returned to inter-seasonal levels. All 138 acute care hospital sites in Ontario were instructed to submit daily the total number of beds occupied by RSV inpatients each day using the following question: "As of 12 midnight, what is the total number of confirmed RSV inpatients in your facility?" There were approximately 20,000 total acute care beds amongst the 138 sites. Data submitted were based on data accurate as of the date they were reported and were not subsequently updated or corrected.

Data from the Canadian Institute for Health Information's Discharge Abstract Database (CIHI DAD) was obtained for all acute care separations in Ontario from November 24, 2022, to March 31, 2023, with ICD-10 codes J12.1, J21.0, J20.5 or B97.4 in any of the diagnostic fields. The CIHI DAD data were linked to the Ontario Registered Persons Database file to assign age group categories for admissions (0–17, 18–64, 65 years and older). Admissions that occurred after midnight and discharged prior to the following midnight (i.e., length of stays fewer than 24 hours) were not included in the hospital-reported daily data; therefore, corresponding CIHI DAD RSV admissions were obtained by removing admissions of fewer than two calendar days.

Respiratory syncytial virus testing data by age group (0–17, 18–64, 65 years and older) for the period of September 1, 2022, to March 31, 2023, was obtained from the Provincial Public Health Laboratory System. Individuals with unknown age were excluded from the dataset. All specimens and test methods for RSV were included for calculation of daily percent positivity by age group. Admissions were compared to laboratory testing positivity over the reporting period for descriptive analysis of hospitalizations relative to RSV activity.

Analysis

Respiratory syncytial virus rates based on the daily bed census data by age group were calculated per 100,000 population using Ontario population estimates for the year 2022 projected from the 2016 census. Peak bed volume days by age group were compared between the two datasets to assess completeness.

A longitudinal comparison of the data sources for all of Ontario and by age group was assessed by time-lagged cross-correlation of the daily submission data versus CIHI DAD data. The augmented Dickey-Fuller (ADF) test showed that the time series was not stationary. The 28-day rolling average was subtracted to detrend both series for an accurate cross-correlation analysis. The cross-correlation coefficients for each time lag, including the confidence bound and the highest correlation value, was assessed with coefficients >0.5–1.0 indicating strong correlation.

All analysis was completed using SAS EG Version 7.13 and Python 3.10.

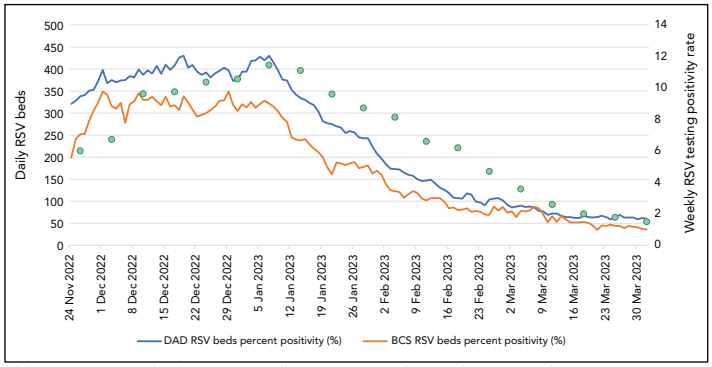
Data access and ethics approval

Public Health Ontario's Research Ethics Board assessed this study to be of minimal risk and waived the requirement for review.

Results

Figure 1 shows daily RSV hospitalizations of all ages in Ontario based on the daily hospital-reported data and the CIHI DAD data over the 2022–2023 respiratory season, along with RSV activity in the province based on provincial RSV positivity. As hospital RSV reporting was initiated later in the season, hospital admissions were already high at the end of November and continued to remain elevated until early January and began declining steadily to inter-seasonal levels by the end of February 2023. This corresponded to RSV positivity in the province that peaked in the first week of January 2023 and then declined steadily. While hospital-reported RSV bed counts followed the same trend fluctuations as CIHI DAD data, they were consistently lower than CIHI DAD admissions throughout the season, with a peak of 430 CIHI DAD beds on January 7, 2023, versus 322 (75%) on the same day from hospital reporting. While hospitals were instructed to start reporting as of November 24, 2022, hospital-reported beds appear to rise rapidly over the first week of reporting as more hospitals began reporting.

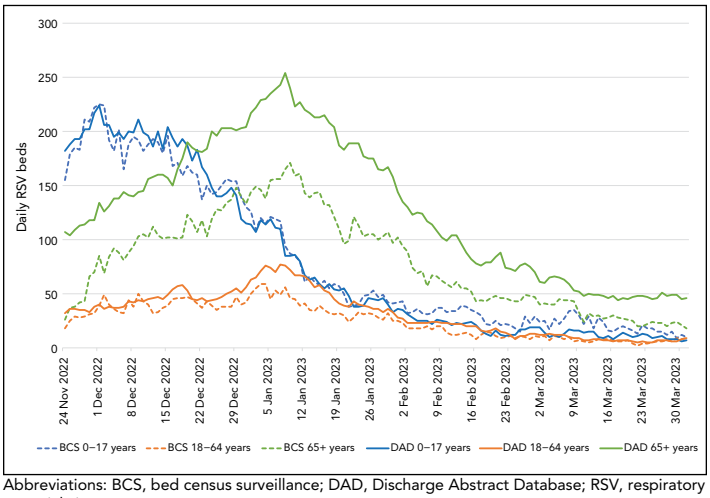
Figure 1: Daily number of hospital beds occupied by patients with respiratory syncytial virus (RSV) hospitalizations, as compared to the provincial daily RSV testing positivity rate, November 22, 2022–March 31, 2023[a]



Abbreviations: BCS, bed census surveillance; DAD, Discharge Abstract Database; RSV, respiratory syncytial virus
[a] As reported by daily real-time reporting during the season, and by Canadian Institute for Health Information Discharge Abstract Database

Figure 2 shows RSV admissions in both data systems by reported age groups. When reporting started at the end of November 2022, RSV admissions were driven by those 0–17 years of age, with a peak at the beginning of December 2022 (peak 224, CIHI DAD), followed by a steady decline for the rest of the season. After the end of January, daily bed reporting for paediatric beds was higher than CIHI DAD data, although total beds from both data sources were low. Respiratory syncytial virus admissions among individuals aged 65 years and older rose steadily from the start of reporting until

Figure 2: Daily number of hospital beds occupied by patients with respiratory syncytial virus by age group[a] hospitalizations, November 22, 2022–March 31, 2023[b]



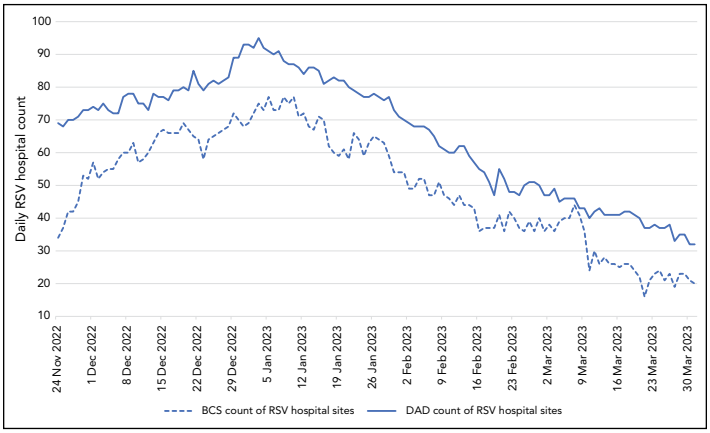
Abbreviations: BCS, bed census surveillance; DAD, Discharge Abstract Database; RSV, respiratory syncytial virus
[a] Age groups were 0–17, 18–64 and 65 years and older
[b] As reported by daily real-time reporting during the season, and by Canadian Institute for Health Information Discharge Abstract Database

early January 2023 (peak 254, CIHI DAD), declining through the rest of the season. Admissions for adults 18–64 years of age peaked at a similar time as admissions among those aged 65 years and older and contributed a small proportion of total RSV admissions (peak 77, CIHI DAD) throughout the season. Daily reported admissions for those aged 65 years and older were consistently undercounted compared to CIHI DAD data throughout the season, with a peak bed count of 254 by CIHI DAD on January 8, 2023, versus 165 beds (65%) reported by hospitals that day.

To assess the impact of non-reporting by some hospitals, **Figure 3** shows the number of hospital sites reporting in the daily real-time surveillance, as compared to the number represented each day in the CIHI DAD data. There was an initial ramp-up phase through November to mid-December, when more hospitals started participating in the daily bed reporting. Throughout the season, hospitals contributing to the daily real-time surveillance were consistently lower than hospitals in CIHI DAD data. There was also a decline in the hospitals providing daily surveillance data at the end of December, corresponding to the peak holiday period in Ontario.

Cross-correlation analysis found that the highest value of the correlation coefficient is obtained at lag=0 for all ages and for ages 0–17 years, and at lag=−1 for ages 18–64 years and 65 years and older. The maximum correlation coefficient values were 0.67 (all ages), 0.57 (0–17 years), 0.66 (18–64 years) and 0.63 (65 years and older). **Figure 4** shows the cross-correlation plots after detrending by age group.

Figure 3: Number of hospital sites represented in daily respiratory syncytial virus admissions, all ages, November 22, 2022–March 31, 2023[a]



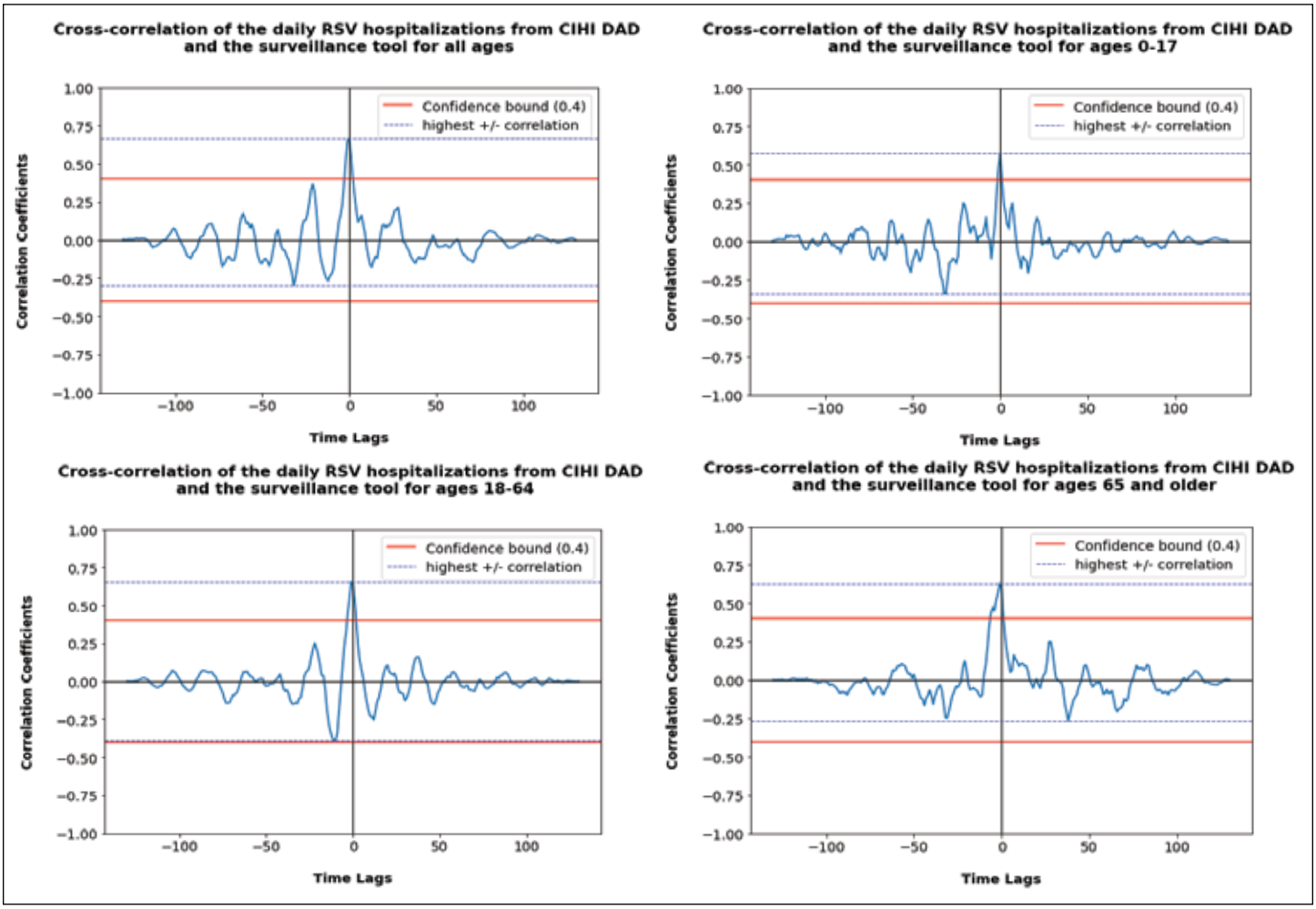
Abbreviations: BCS, bed census surveillance; DAD, Discharge Abstract Database; RSV, respiratory syncytial virus
[a] As reported by daily real-time reporting during the season, and by Canadian Institute for Health Information Discharge Abstract Database

Discussion

Respiratory syncytial virus contributed to substantial pressures on the paediatric healthcare system in the 2022–2023 respiratory season, along with influenza and COVID-19 (10). Initiation of Ontario hospital daily bed census reporting in November 2022 for RSV admissions enabled real-time surveillance of its impacts on the healthcare system over the season. The Ministry of Health and health system partners were able to utilize this surveillance to inform hospital mitigation measures, particularly in paediatric hospitals that experienced significant pressures between November–December 2022 (11).

This evaluation demonstrates that the newly implemented real-time surveillance provided strong correlation (coefficients >0.5–1) with overall trends in RSV admissions among the different age groups when compared to ICD-10-coded admission data (12). Real-time hospital-based surveillance underrepresented the true

Figure 4: Cross-correlation plots after detrending data on respiratory syncytial virus hospitalizations for all age groups[a,b]



Abbreviations: BCS, bed census surveillance; CIHI DAD, Canadian Institute for Health Information Discharge Abstract Database; RSV, respiratory syncytial virus
[a] Detrending for the daily real-time surveillance compared to Canadian Institute for Health Information Discharge Abstract Database data
[b] Age groups were 0–17, 18–64 and 65 years and older

magnitude of the hospital pressures, as it was consistently lower than CIHI DAD admissions for adults and older adults throughout the reporting period, and represented only 75% of beds at the peak day for CIHI DAD beds. Conversely, daily census reporting overestimated hospital beds for paediatric patients in the later part of the season from late January 2023 to the end of the reporting period, when total beds by both data sources were low (fewer than 50 beds daily).

Overall, under-representation was mostly driven by beds for those 65 years and older, where, on the peak day according to CIHI DAD data, hospital-reported beds were only 65%. The undercounting was at least partly due to incomplete submissions, as there were consistently fewer hospitals reporting compared to all acute care hospitals with RSV-admitted patients in the CIHI DAD data. Hospital reporting may also be lower than CIHI DAD data due to delays in RSV laboratory result reporting, where patients were admitted but had not yet been identified as an RSV-related admission. Additionally, hospitals may have omitted admissions where RSV was not the most responsible diagnosis and only a contributing diagnosis in their daily reporting. Potential reasons for overestimation of paediatric beds are less clear, but may reflect syndromic clinical diagnoses of RSV in admitted patients that were not coded as RSV admissions in CIHI DAD.

As RSV hospitalizations are reportable neither nationally nor in Ontario, there are no surveillance systems for RSV admissions to guide within season healthcare and hospital planning. In the United States, RSV hospitalization surveillance is conducted by RSV-NET, a network of sites across 12 states (5). Sentinel-based surveillance, such as RSV-NET, provides important real-time information on epidemiological trends, but is insufficient to support fulsome hospital capacity planning within the season as reporting is only representative and does not capture all hospitals. As far as we are aware, this analysis is the first report assessing the implementation of a province-wide real-time RSV hospitalization surveillance system.

Limitations

Limitations of the analysis include the incompleteness of the data in that daily reporting surveillance only began at the end of November 2022, when RSV activity was already high. While it is possible to assess which hospitals reported RSV hospitalizations in real time, it is not possible to fully distinguish whether hospitals did not report because they omitted reporting, or if there were "zero" admissions reported that day. As aggregate data were not provided by sex or narrower age bands, more refined analyses of sex differences and impacts in children younger than one year or younger than five years of age were not available for analysis.

While this analysis has shown strong correlation of trends and reasonable completeness of the newly implemented real-time daily hospital reporting, it does not include an assessment of other aspects of a surveillance system, such as feasibility and acceptability of reporting. Daily reporting by all hospital sites is time-consuming and human-resource intensive. The provision of the data throughout the season is an additional demand on hospitals; however, hospitals have also recognized the value of the data in providing intelligence locally, regionally and provincially regarding hospital capacity for planning and resource management purposes. At a provincial level, the data have been leveraged to support weekly forecasting of hospital bed projections for RSV, along with COVID-19 and influenza, to support senior-level decision-making at the Ontario Ministry of Health and Ontario Health. Ongoing reporting has also been incorporated into publicly reported provincial surveillance on RSV hospital bed occupancy as part of severe outcome surveillance of respiratory viruses in Ontario (4). Future evaluations are needed to assess the feasibility, acceptability, costs and sustainability of this surveillance system, and an assessment of completeness and correlation in the 2023–2024 and 2024–2025 seasons.

Conclusion

Implementation of a province-wide real-time surveillance system for RSV hospitalizations in Ontario in the fall of 2022 was a successful initiative providing reliable and accurate trending by age groups over the respiratory season. Compared to ICD-10-coded hospital admissions, the real-time surveillance under-reported total admissions, particularly for those aged 65 years and older, that should be taken into consideration for within-season hospital bed planning. Without any other real-time surveillance to provide data on RSV admissions, these data provide valuable insights for Ontario to guide local, regional and provincial level hospital planning during the respiratory season.

Authors' statement

MM — Conceptualization, interpretation, writing–original draft
AS — Formal analysis, interpretation
MA — Formal analysis, interpretation
AK — Formal analysis, interpretation
KM — Formal analysis, interpretation
KB — Formal analysis, interpretation, writing–review & editing
TF — Formal analysis, writing–review & editing
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Competing interests

None.

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QUALITATIVE STUDY

Implementation of the COVID-19 antiviral therapy Nirmatrelvir/Ritonavir (Paxlovid™) across Canada in 2022: A qualitative analysis of key facilitating factors and challenges

Aklile Workneh[1], Camilia Thieba[1], Nadine Sicard[2]*

Abstract

Background: The COVID-19 antiviral Nirmatrelvir/Ritonavir (Paxlovid™, N/R) was approved for use in Canada in January 2022, with the Government of Canada assuming a procurement role and provinces, territories, and federal departments implementing usage within their respective healthcare systems. The objective of this analysis is to describe how N/R was implemented across various jurisdictions in the first six months after it was available for use and identify promising implementation practices.

Methods: Fourteen semi-structured discussions in small group settings were conducted with jurisdictional representatives involved in the implementation of N/R. A descriptive analysis of the eligibility criteria and service delivery model was conducted. A thematic analysis using the Consolidated Framework for Implementation Research and cluster analysis of the codes were then undertaken on NVivo 12 to identify key themes.

Results: Overall, the eligibility criteria were similar across jurisdictions, and three types of service delivery models were identified. Ten main themes emerged as facilitators and eight as challenges to the implementation. Partnership, collaboration, communication and flexibility were among the facilitators identified, while the complexity of the intervention (e.g., drug-drug interactions), perceived evidence gaps in effectiveness by prescribers, and resource limitations were identified as key implementation challenges.

Conclusion: While there were jurisdictional variations in the implementation of N/R, communication and collaboration, and the availability of rapid testing for COVID-19 emerged as key facilitators. Drug-drug interactions, resource pressures and limited evidence were some of the key challenges. Overall, these facilitators and challenges were similar across jurisdictions and may help inform future therapeutic implementation plans for pandemic preparedness.

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Introduction

Nirmatrelvir/Ritonavir (Paxlovid™, N/R) is an oral antiviral for treatment of SARS-CoV-2 in adults with mild to moderate symptoms at high-risk of progressing to severe disease or death. On January 17, 2022, Health Canada authorized its use following the interim results of the Phase 2/3 double-blind placebo-controlled EPIC-HR (Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients) trial demonstrating reduction in COVID-19-related hospitalization and all-cause mortality (1,2). Nirmatrelvir/Ritonavir was the first oral antiviral approved to treat COVID-19 in Canada. The Government of Canada assumed the

role of procurement, with jurisdictions responsible for delivering the treatment to their populations. Given the unprecedented context of the fast-changing COVID-19 pandemic and the novel role of procurement, the Public Health Agency of Canada (PHAC) developed an evaluation framework in conjunction with jurisdictional stakeholders. One of the components of the framework aimed to address questions on best practices in light of the limited experience with this new therapeutic option, and to inform implementation, which this study focuses on. The evaluation of the implementation aimed to describe how the rollout of N/R took place across Canada and to identify the facilitators and challenges associated with its implementation.

Evaluation objectives

The overarching aim of this evaluation was to answer the following questions:

1. How has N/R been administered across Canada?

2. What are the most promising strategies to deliver therapeutics in outpatient settings?

Methods

Adopting a qualitative methodology, this study employed semi-structured group discussions as the primary method of data collection. Informed by the Donabedian framework (3), the Consolidated Framework for Implementation Research (CFIR) (4), the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework (5), and behavioural science theory models (6,7), a structured questionnaire guided the discussions, covering key topics such as eligibility, service delivery, communication, training, and procurement experiences.

Participants were identified and recruited from various federal, provincial, and territorial (FPT) working groups using a snowball sampling technique, ensuring a diverse representation that included managers and healthcare professionals in COVID-19 therapeutics planning. Ultimately, of all jurisdictions invited, 12 provinces and territories and two federal departments participated.

One-hour interviews were conducted, and each session was recorded, transcribed, and summarized. These summaries, validated by participants, served as the foundation for descriptive and thematic analyses guided by the CFIR. The approach primarily followed a deductive method aligning with CFIR domains and constructs, while remaining open to inductive additions to the coding scheme as necessary. All factors of the CFIR were included in the initial deductive coding scheme. Each coded passage was further assigned a sentiment indicating the direction of the influencing factor (i.e., barrier or facilitator). Passages detailing the participating jurisdictions' eligibility criteria and service delivery models were not coded but summarized.

The CFIR is a theoretical framework developed to systematically explore the intricate factors influencing the successful implementation of innovations in various organizational contexts. The CFIR's five domains examine critical elements, including intervention characteristics, outer and inner organizational settings, individual traits, and the implementation process. Within these domains, there are 39 CFIR constructs and subconstructs, representing the evidence-based factors most likely to impact the implementation of interventions. The CFIR was used to code the data and organize emerging themes post-data collection. For the analysis, the jurisdiction responsible for the implementation was the reference unit. Nirmatrelvir/Ritonavir was coded as the innovation; the provincial, territorial, and federal healthcare organizations were coded as the inner setting; and the federal government and any other external institution as the outer setting.

The data analysis process involved initial coding through NVivo 12 (8) using the CFIR. This was followed by a cluster analysis to uncover patterns among the coded items based on their co-occurrence (Pearson coefficient) and, finally, matrix coding queries for constructs that were coded as positive (facilitator) or negative (challenge). Thematic analysis, inspired by Guest and Mclelan (9), was conducted to identify overarching themes when numerous salient themes emerged from the dataset. The findings were synthesized through a multi-step process, beginning with the identification of overarching themes through cluster analysis. Sentiments analysis was used to distinguish between facilitators and barriers, and major and minor themes were developed based on recognition of patterns within the data. The analysis included triangulation, member checking, and inter-observer reliability to bolster the credibility and transferability of the findings. Iterative rounds of analysis and refinement ensured a nuanced understanding of the complex implementation process.

Ethics approval

The PHAC policy on research activities was followed, however, a consultation with the Research Ethics Board was not required since the implementation evaluation is within PHAC's standard practices of assessing its programs. Consultations took place with the Privacy Management Division to ensure any personal information that might be disclosed during the evaluation was handled as per federal regulations and departmental policies.

Results

Two main phases to the rollout of N/R were identified during the interviews: the first, at the beginning of the rollout, when the supply of N/R was limited; and the second characterized by increased and stable supply. These phases directly impacted the decision-making processes and access of N/R for Canadians.

Eligibility criteria

At the start of the rollout, jurisdictions based their eligibility criteria for treatment with N/R on PHAC and the Canadian Agency for Drugs and Technology in Health (CADTH) guidance (10), the EPIC-HR trial results (2), the product monograph (11), and advice from expert advisory committees. Given the limited supply context and short lead time from drug authorization to implementation, prioritization of drug usage focused on individuals at highest risk of severe outcomes, including older, under- or unvaccinated individuals, Indigenous peoples, and those with immunosuppression, specific risk factors, or comorbidities (e.g., BMI ≥30, diabetes, lung and cardiovascular diseases). There was inter-jurisdictional variability within these criteria in regard to age thresholds for eligibility in conjunction with vaccination status and comorbidities, the number of comorbidities required for eligibility (one to three), and the comorbidities included (e.g., smoking, hypertension, chronic kidney disease).

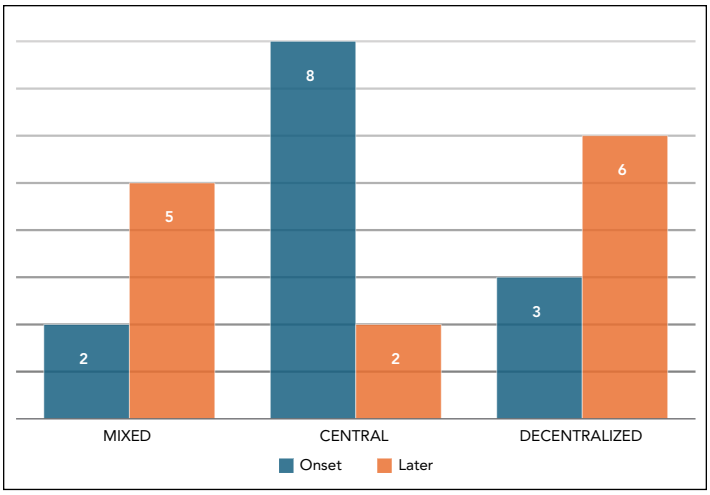
As supply increased, most jurisdictions expanded their eligibility criteria, with a couple transitioning from defined criteria to guidance for prescribers. Changes included lowering age thresholds, inclusion of vaccinated populations, refinement of the definition of vaccination status (e.g., booster doses), and lists of comorbidities. Factors driving these changes included increased supply, new research findings (e.g., EPIC-SR trial results (12)), evidence of a reduction in the effectiveness of neutralizing monoclonal antibodies (e.g., sotrovimab) against the new variants of concerns, and evolving epidemiology studies within the jurisdictions.

Service delivery models

The service delivery models varied between jurisdictions due to differences in health system infrastructure, resulting in three main models of service delivery: centralized, decentralized, and mixed, which combines both (see **Figure 1**). Initially, most jurisdictions relied on a centralized model, enabling more oversight on distribution, which was influenced by limited supply, logistical considerations, and limited evidence to support expanded usage. However, as supply increased with time, many transitioned to a decentralized or mixed model.

Authorized prescribers varied based on jurisdictional regulations, with physicians, nurse practitioners, and pharmacists authorized to prescribe N/R. Several jurisdictions amended regulations to expand the pool of designated healthcare providers authorized to prescribe and dispense the antiviral. At the time of the data collection, five jurisdictions permitted prescriptions by pharmacists, while one allowed community nurses to prescribe in an expanded role (the numbers have since increased). The expansion of access points and authorized prescribers was noted to have increased prescribing and access to N/R by some jurisdictions.

Figure 1: Distribution of service delivery models (SDMs) at the start of the rollout and after at least six months



Distribution of service delivery models at the start of the rollout versus later (data for 13 jurisdictions). At the start of the Nirmatrelvir/Ritonavir (N/R) implementation, eight participating jurisdictions used a centralized prescription model, characterized by designated points of access and/or designated prescribers for N/R. After the initial rollout, two jurisdictions transitioned to a decentralized model, and four transitioned to a mixed model (keeping the centralized model in place for unaffiliated patients or patients that could not access their healthcare providers in a timely manner, while using a decentralized model for the majority of other patients). Three jurisdictions used a decentralized model from the beginning and continued with this approach. Two jurisdictions used a mixed model initially, with one of them transitioning to a decentralized prescription model

Thematic analysis

Based on the analysis of code relationships and their frequency of co-occurrence, seven essential themes emerged, defining the key drivers of N/R implementation in Canada (**Table 1**). The examination of barriers and facilitators to N/R implementation in Canada uncovered several key factors common across jurisdictions. These are summarized in **Table 2**, organized by CFIR domain.

Table 1: General themes identified from cluster analysis

Theme number	Description
Theme 1	Availability of supply, support system, and receptivity
Theme 2	Identifying needs and communicating availability
Theme 3	Coordinated efforts for efficient testing and administration
Theme 4	Overarching alignment and resolve to deliver the intervention
Theme 5	Organizational/structural synergy to facilitate intervention delivery
Theme 6	Adaptability of the implementation processes/systems
Theme 7	Concerted efforts and stakeholder engagement to prioritize high-risk populations (leveraging pre-existing systems)

Table 2: Consolidated Framework for Implementation Research domains and the facilitators and challenges identified (matrix coding) related to the implementation of Nirmatrelvir/Ritonavir with corresponding illustrative quotes

CFIR domain plus constructs	Facilitators Subthemes	Challenges Subthemes
Characteristic: Individual domain	**Patient and provider motivation to use the product (anecdotal)** **Quote 1:** Prescribers were happy to have access to Paxlovid™, especially during the outbreak that occurred in XX from January to March 2022. **Provider capability to administer (assess and prescribe) the product** **Quote 1:** With time, as prescribers became more familiar with Paxlovid™, the uptake increased.	**Perceived lack of benefits from intervention** **Quote 1:** Overall, the response and perception from healthcare practitioners (HCP) to Paxlovid™ and COVID-19 therapies varied from wanting everyone to have access to concerns on the paucity of evidence.
Roles: Individual domain	**Systems in place to prioritize high risk populations – equity considerations** **Quote 1:** XX prioritized the First Nations (FN) communities in the eligibility criteria by reducing the age requirements to receive Paxlovid™ and ensuring that there were access points close to the communities. **Quote 2:** The XX pathway is recommended for complex cases or unattached patients that cannot access a HCP or patients that cannot access their PCP. **Quote 3:** The XX was important in operationalizing the timely access to Paxlovid™ in long-term care facilities.	N/A
Implementation: Process domain	**Flexibility of the intervention and the implementation processes to fit the context and needs** **Quote 1:** [...]. Support [from the public health organizations] was important to provide access to the vulnerable populations. As well, [...] the option of telehealth to access Paxlovid™, increasing the reach and the uptake. **Development of screening and reporting tools to support the administration** **Quote 1:** The dissemination of the education sessions, order sets and protocol facilitated the rollout. The updates to the guideline were quick as were the approvals. The Office of Public Health shared information on COVID updates; Teams channels were created to post memos and documents from the various tables and committees. **Availability of alternate vs PCR testing modalities for N/R eligibility (rapid antigen tests, ID NOW, Lucera)** **Quote 1:** Furthermore, RATs have been an important tool as they are available to people in their homes and are easily accessible. This has tremendously helped the uptake of COVID-19 [treatments] by removing potential barriers in access. **Multilateral collaborative practices** **Quote 1:** The collaboration with regional medical officers of Public Health was key to the rollout. As they strategized with pharmacy leads for distribution of Paxlovid™, this collaboration helped identify gaps in distribution. The rollout created new partnerships with centres to widen reach and work in collaboration to close gaps, if any, in the service delivery of Paxlovid™. **Quote 2:** The excellent collaboration between pharmacists, physicians and nurses was fundamental to the success of the rollout. There was a medical advisory committee consisting of key stakeholders (pharmacists, physicians, and nurses) and there were numerous collaborative discussions to not deplete the Paxlovid™ supply quickly.	**Administration processes (from screening to dispensing)** **Quote 1:** A distribution network was needed to get access to Paxlovid™ in communities and facilities that may be over 2 to 3 hours away, with a courier system and taxi services to ensure that the course was started within 24 hours. **Quote 2:** There were some challenges initially as the ordering process had to be adjusted from injectable COVID-19 therapies acquired directly by the hospital for use to oral treatments, such as Paxlovid™, that could be distributed and used outside of the hospital. **PCR testing** **Quote 1:** As well, the timeline and the timeliness of test results were a barrier for access as some patients may be not feel sick enough to consider testing or are tested more than 5 days post symptom onset for example, and by the time they seek care they are no longer eligible for Paxlovid™. **Quote 2:** There were some challenges with ensuring that patients were tested and identified within the 5-day timeframe. There were some laboratory capacity issues creating delays with the PCR tests.

Table 2: Consolidated Framework for Implementation Research domains and the facilitators and challenges identified (matrix coding) related to the implementation of Nirmatrelvir/Ritonavir with corresponding illustrative quotes (*continued*)

CFIR domain plus constructs	Facilitators Subthemes	Challenges Subthemes
Inner setting domain	**Leveraging of pre-existing channels for dissemination of information to healthcare professionals** **Quote 1:** There were also targeted communication within networks. In effect, networks such as [healthcare professional associations] disseminated Paxlovid™ communication internally through their respective newsletters to reach divisions of family practice and NPs. **Quote 2:** As well, XX and the option of telehealth to access Paxlovid™, increasing the reach and the uptake. XX was able to leverage pre-existing communication pathways to disseminate information on Paxlovid™ to the community, and there was also clear communication from the MOH. **Development of training and guidance materials for prescribers** **Quote 1:** [...] There were also training programs for physicians organised through presentation (in both English and French for physicians and pharmacists as the service delivery model was expanding. **Quote 2:** The guidance documents and supplementation guidance on prescribing to patients with severe kidney disease, created by the XX health renal network, was helpful as well. With time, as prescribers became more familiar with Paxlovid™, the uptake increased. **Creation of new infrastructures bolstered by pre-existing pathways to facilitate implementation (e.g., IT, work processes)/ Leveraging pre-existing infrastructures (IT or systems)** **Quote 1:** This network was put in place at the start of the pandemic and oversees all therapeutic recommendation approvals and the implementation processes are also discussed at the network. This has allowed for an ongoing evaluation of the process and quick responses when there were concerns with the implementation. This collaborative approach was fundamental to the rollout. **Quote 2:** The possibility to modify the regulation to allow pharmacists to prescribe was instrumental to the rollout.	**Unavailability of pre-existing IT and work infrastructures processes to respond to implementation needs (e.g., storage, workflow)** **Quote 1:** One of the main challenges to the rollout in XX was the limited resources, especially during the peak of COVID-19 infections, which coincided with the beginning of the roll out. Given the limited capacity, meeting the 5-day timeline for prescriptions was demanding, with some calls from patients frustrated because they were going to miss the treatment deadline. Providers were working overtime to ensure that patients were receiving their prescription, which also led to provider fatigue. Initially, there was no ability to follow-up on patients; now, nurses have been able to conduct day 2 and day 6 follow-ups. **Quote 2:** XX had to rely on their hospital pharmacy infrastructure to deliver the stock to community pharmacies, adding strain to resources that are not organized to perform such activities. **Quote 3:** The main deterrent from stocking Paxlovid™ has been storage space as some community pharmacies do not have the space to stock high volumes given the low usage.
Innovation domain	N/A	**Perceived insufficient level of evidence on treatment effectiveness** **Quote 1:** […] the benefits of Paxlovid™ were shown through a single trial carried with a select population. **Quote 2:** With limited evidence on Paxlovid™, the decision-making on the eligibility and access was challenging at the onset of the rollout. **Drug-drug interactions (other products with less DDIs/ easier to manage)** **Quote 1:** The response among HCPs was divided, with some being involved in the rollout and/or requesting access to Paxlovid™ before its availability, while others expressed apprehension in prescribing Paxlovid™ given the complexity of the drug-to-drug interactions and limited support. **Quote 2:** Initially the uptake of Paxlovid™ by prescribers was slow, with some hesitancy given the complexity and the drug-to-drug interactions (DDIs).

Table 2: Consolidated Framework for Implementation Research domains and the facilitators and challenges identified (matrix coding) related to the implementation of Nirmatrelvir/Ritonavir with corresponding illustrative quotes (*continued*)

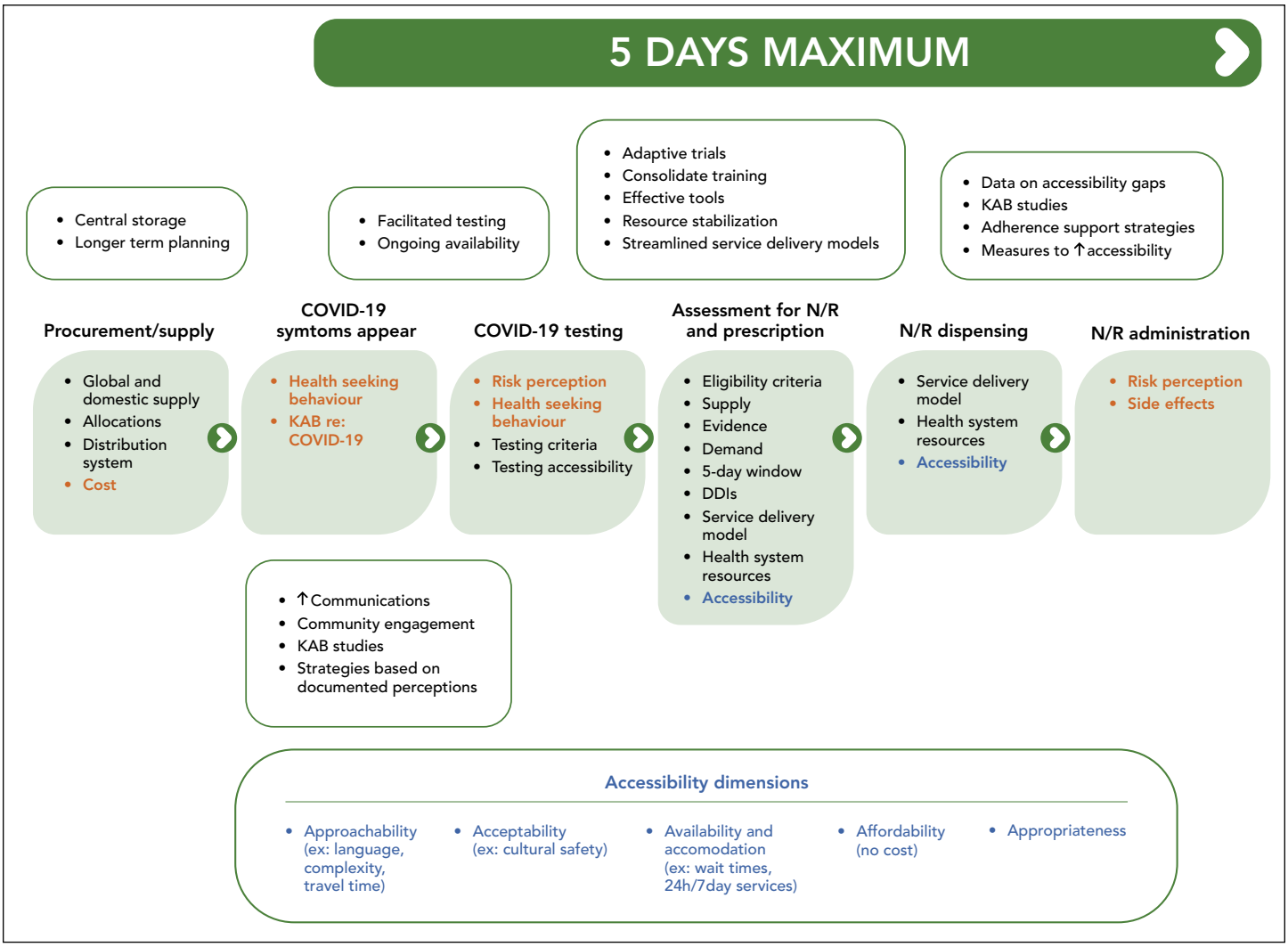
CFIR domain plus constructs	Facilitators Subthemes	Challenges Subthemes
Outer setting domain	**Multi-jurisdictional and -disciplinary collaborative practices** **Quote 1:** The willingness of the Pharmacy board to change legislation to allow pharmacists to prescribe for the treatment and prevention of COVID-19 increased access for patients and was important in rollout, especially as a proportion of the population does not have access to a HCP. The launch in the community pharmacies coupled with access to testing kits was also important in increasing access to Paxlovid™ within the 5-day timeframe. **Federal procurement and availability of the intervention** **Quote 1:** Overall, XX is appreciative of the federal government role in the procurement and for providing expedited access to Paxlovid™. There was support and guidance throughout the process; and the allocated stock is being used. **Quote 2:** XX recognizes the importance of PHAC taking the lead in the procurement, as obtaining supply for their population would not have been possible otherwise given the global supply shortages. The procurement was essential in providing access to their population. As well, the working groups fostered collaboration and transparency; issues were discussed as they arose, which facilitated the rollout.	**Global supply shortage context constricting communication and ability to implement** **Quote 1:** Additionally, with the limited supply at the beginning, planning the rollout and ensuring access to Paxlovid™ without depleting the stock was a challenge in XX. **Quote 2:** As well, when access first expanded, some patients were not aware that Paxlovid™ could be accessed through their usual providers and pharmacies; increased communication was needed to increase awareness. **Short-lead time to implement** **Quote 1:** [...] the urgency of the authorization did not follow the usual processes for clinical trials and evidence protocols. The benefits were assessed using one clinical trial and Paxlovid™ was approved and distributed very quickly.

Abbreviations: DDI, drug-to-drug interactions; FN, First Nations; HCP, healthcare practitioners; MOH, Ministry of Health; NP, nurse practitioners; N/A, not applicable; N/R, Nirmatrelvir/Ritonavir; PCP, primary care provider; PCR, polymerase chain reaction; PHAC, Public Health Agency of Canada; RAT, rapid antigen tests

Adaptability to the rapidly evolving context and collaboration among stakeholders emerged as crucial facilitators, evident across individual (characteristics and roles), implementation process, and inner and outer setting domains of the CFIR. The availability of guidance documents, provided by CADTH (10), PHAC and expert advisory committees, at the onset of the implementation coupled with its adaptation to jurisdictional context (e.g., prioritization of equity-seeking groups and high-risk populations) for the creation of screening and reporting tools enabled a streamlined process, facilitating efficient patient prioritization, assessment, and, in some cases, follow-up. Multi-jurisdictional and interdisciplinary collaboration facilitated the development of improved processes, aided by pre-existing systems for information dissemination, access to testing and screening tools, and timely drug dispensing. Comprehensive training, continued learning, and guidance materials for prescribers contributed significantly to the intervention's success, disseminated through various pre-existing and new channels, such as healthcare professional associations, academic institutions, and even through informal messages on a commonly used internal messaging application. The availability and admissibility of alternate testing modalities (i.e., rapid antigen and rapid molecular point-of-care tests) were instrumental in streamlining the rollout in the later stages, as well as ensuring access to N/R in remote and rural communities within the five-day eligibility window. Policies expanding the authority of pharmacists and community nurses to prescribe and administer N/R were reported as increasing uptake. Lastly, equity considerations informed the implementation of components/activities aiming to prioritize high-risk populations (e.g., long-term care residents, Indigenous populations, and racialized and marginalized individuals).

Elements contributing to barriers in N/R implementation in Canada were mainly observed across the individual (characteristic), implementation process, innovation, and inner and outer setting domains of the CFIR. The perceived lack of benefits and complexity of prescribing the drug, attributed to limited evidence and numerous drug-drug interactions, influenced attitudes towards its adoption. The short lead time and global supply constraint amidst a pandemic posed challenges for the health services infrastructure, particularly in establishing necessary administration processes, IT and work infrastructures, for timely identification of eligible and best candidate patients, as well as timely delivery of the therapy. Setting up systems for identifying positive cases through PCR testing was challenging initially, but improved with widespread use of rapid antigen tests. As it relates to procurement, some jurisdictions expressed the need for enabling centralized storage capacity and federal distribution of therapeutics, alongside expanding the FPT pandemic coordination processes to include clinical discussions. The global supply constraint also influenced communication strategies and service delivery models initially, until the Canadian supply stabilized. Infrastructural limitations and insufficient human resources, including healthcare providers, further impacted the N/R rollout in Canada. A patient trajectory to access N/R in Canada along with possible strategies to streamline the process was created base on the findings from the thematic analysis (see **Figure 2**).

Figure 2: Patient trajectory to access Nirmatrelvir/Ritonavir in Canada and possible strategies (boxes outlined in green) to optimize uptake[a]



Abbreviations: DDIs, drug-drug interactions; KAB, knowledge, attitudes and behaviours; N/R, Nirmatrelvir/Ritonavir
[a] Orange text indicates dimensions that were not explored in this evaluation; blue text indicates dimensions that were partially explored in this evaluation (7)

Discussion

This qualitative study sought to examine the implementation of N/R within the first six months of its approval in Canada during the COVID-19 pandemic. Its aim was to identify key facilitators and challenges encountered during this implementation process and derive lessons applicable to future outpatient therapeutic implementations, thereby informing pandemic preparedness readiness in the Canadian context. While there was jurisdictional variability in eligibility criteria and service delivery models, owing to differences in health system infrastructure, the findings of this evaluation have highlighted the importance of communication, partnership and collaboration, and flexibility and adaptability of policies and implementation processes to ensure equitable access to COVID-19 treatments. In effect, jurisdictions shared knowledge and resources, from guidance documents to testing and screening mechanisms, with one another to facilitate the rollout of N/R. The context in which N/R was implemented, short lead time to implementation amidst a global shortage, along with elements directly related to the therapeutic (e.g., complexity of the therapeutics due to numerous drug-drug interactions and limited evidence, and short window of eligibility), as well as infrastructural and workforce limitations, posed challenges to its implementation.

Through our analysis, 10 themes were delineated related to facilitators and eight themes related to challenges (see Table 2). While the factors affecting uptake and barriers vary by jurisdiction based on healthcare system structure, population characteristics, and data analysis capacity, synthesizing insights from participants and considering challenges and successful approaches, strategies have been proposed to address some of the barriers uncovered in this study (Figure 2). These strategies span across the N/R supply chain from procurement through

dispensing or administration to patients. Healthcare system capacity notably affected the N/R rollout, with primary care capacity being a critical factor raised by evaluation participants. While some challenges are systemic and complex, actionable strategies could include consolidating provider training, streamlining patient pathways, and ensuring continued access to rapid testing for patients eligible for treatment. Addressing cost barriers by providing free testing and treatments is crucial, especially since COVID-19 impacts are not uniformly distributed across Canadian populations (13). Although variations in implementation are to be expected, given the wide breadth of the population, with each jurisdiction facing some unique challenges. Furthermore, lessons learned from the implementation of N/R can help guide future therapeutics implementation efforts and inform ongoing federal planning to bolster Canada's readiness for public health threats as Canada updates its pandemic preparedness plan (14). These can inform logistical planning of therapeutics implementation (e.g., testing, storage, and surveillance of distribution and dispensing), as well as the facilitation of FPT and Indigenous collaboration during the decision-making processes to ensure equitable access and distribution of therapeutics in future health emergency situations.

Limitations

There was a high participation level, with almost all jurisdictions participating in the evaluation. The participants in the discussion session were diverse and included individuals that contributed to different capacities (i.e., healthcare professionals and managers). As such, experiences from across the country were captured, giving a broad understanding of the implementation processes of N/R. There are, however, potential limitations to the evaluation. the patient perspectives and perspectives of other more local/regional components of the healthcare system were not explored, and any information obtained was from the participants' experiences. The potential dynamics between participants cannot be ruled as discussion sessions were held in groups for each jurisdiction. As well, although it was communicated that the results of the evaluation would be anonymized and the acquired data handled to ensure participant privacy, the potential for desirability bias remains, as the discussion sessions were led by PHAC employees. There is also the potential for interviewees' recall bias, as the evaluation covered the experiences in the first six months of the rollout. Furthermore, while the CFIR offers great insight into the implementation processes, the complexity and scope of its 39 constructs may pose a limitation to its generalizability and consistency of its application; these limitations have been mitigated by defining the scope of the settings to ease with reproducibility.

Conclusion

Patients' health-seeking behaviours have been found to be influenced by their knowledge, attitudes, and beliefs (6,7) as well as accessibility to testing and treatment services. While this evaluation did not assess knowledge, attitudes and behaviours for patients and providers, future work in this area would further inform therapeutic implementation efforts and help understand and address some of the challenges identified in this study.

The evaluation assessed how N/R was administered in Canada in the first six months of the implementation, identifying pressure points and considerations for the initial stages of a therapeutic rollout. While jurisdictions have since modified their N/R programs, the lessons learned remain valuable for future therapeutic rollout in the context of a public health threat.

Authors' statement

AW — Project management, conceptualization, methodology, leading discussion sessions, data analysis, interpretation, writing–original draft, writing–review & editing
CT — Conceptualization, methodology, leading discussion sessions, data analysis, interpretation, writing–original draft, writing–review & editing
NS — Supervision, conceptualization, methodology, leading discussion sessions, data interpretation, writing–review & editing

Contributors

Representatives from 14 jurisdictions who contributed to the implementation evaluation project.

Competing interests

NS had some previous interactions with some of the participants of this study as part of other Public Health Agency of Canada activities.

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Effectiveness of the four-component protein-based meningococcal vaccine against *Neisseria gonorrhoeae* infections: Mounting evidence and public health implications for Canada

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Abstract

Background: In Canada, the burden of gonorrhea has been increasing steadily over the last decade with emerging multi-drug-resistant strains. There is a high genomic similarity between *Neisseria meningitidis* and *Neisseria gonorrhoeae*.

Methods: Review of published studies and on-going trials with the four-component meningococcal serogroup B vaccine (4CMenB–Bexsero®).

Results: Observational studies have shown protection against gonorrhea infection ranging from 35% to 59% for up to three years after the administration of 4CMenB. Several randomized clinical trials are also under way. Results from the DOXYVAC trial have been published but the sample size was too small to exclude a protective effect in the 30%–50% range. Recommendations on the use of 4CMenB for individuals at high risk of gonorrhea infection have been issued in the United Kingdom and New York state based on results of observational studies.

Conclusion: If results of observational studies are confirmed by randomized trials with an acceptable cost-effectiveness profile in the Canadian context, a targeted immunization program using 4CMenB could be implemented.

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Introduction

In Canada, the burden of gonorrhea has been increasing steadily over the last decade, with a reported rate almost tripling from 2010 (33.5 per 100,000 population) to 2019 (94.3 per 100,000 population) (1,2). Because of the COVID-19 pandemic, the years 2020 and 2021 were atypical, with reduced travel and contacts among individuals, hesitancy to seek medical care, and diagnostic test shortages (3). Males account for 56% of all cases diagnosed and the most commonly affected age group consists of those 15 to 39 years old, accounting for 82% of total cases (2). The incidence of sexually transmitted infections is particularly high in street youth, sex workers, men who have sex with men, users of hard drugs, incarcerated persons, and some Indigenous people (4). The proportion of multi-drug-resistant strains has also increased from 8.6% in 2015 to 12.4% in 2019, a source of concern for treatment effectiveness (2).

In this commentary, results of studies on the impact of the four-component meningococcal serogroup B (4CMenB) vaccination on gonorrhea risk are presented, along with the biological plausibility and cost-effectiveness analyses. The public health implications of these findings are discussed in terms of product information and possible recommendations for specific high-risk groups in Canada.

Methods

A review was performed of published observational studies and on-going trials on the protein-based 4CMenB (Bexsero®, Glaxo-Smith-Kline) aiming to protect against *Neisseria gonorrhoeae* infection and disease. A PubMed search was performed on October 5, 2023, using the following combination of terms: (meningococcal vaccine OR 4CMenB) AND gonorrhea. A total of 121 hits was obtained. Titles and abstracts were reviewed using inclusion and exclusion criteria. Inclusion criteria were quantitative studies in humans aiming to evaluate the effect of vaccination on the occurrence of *N. gonorrhoeae* infection by comparing 4CMenB vaccination with a control group. An exclusion criterion was any ecological study design using before-after comparisons without ascertainment of the immunization status of each individual. When several manuscripts described results of a same study, the latest analysis was selected. A similar search was performed in Google Scholar, PubMed and Clinicaltrial.gov and results were completed by information provided by the 4CMenB manufacturer.

Results

Epidemiological studies

In 2009, a mass immunization campaign was implemented in the Saguenay–Lac-Saint-Jean region of Québec to control an increase of serogroup B invasive meningococcal disease using 4CMenB. The vaccination campaign reached 86% of the target population aged six months to 20 years, with most receiving two doses (5). Following the mass campaign, an unexpected decrease in the number of gonococcal infections among persons aged ≤20 years was observed in the region (6). Such a decrease was not seen among adults aged >20 years, and there was also a clear continuing upward trend in the number of *Chlamydia trachomatis* infections in all age groups. The review identified five other observational studies on this issue and results described in **Table 1** support the hypothesis of a cross-protection against gonorrhea generated by 4CMenB in the 35% to 59% range for up to three years after vaccination (7–11).

Clinical trials

As shown in **Table 2**, five randomized clinical trials (RCTs) aiming to demonstrate the efficacy of 4CMenB in preventing gonorrhea in different high-risk groups are underway and one has been completed (12). In the DOXYVAC trial in France, the incidence of a first episode of gonorrhea (main outcome) was 58.3 per 100 person-years (103 events in 274 participants) in the 4CMenB vaccine group and 77.1 per 100 person-years (122 events in 270 participants) in the no vaccine group (adjusted hazard ratio=0.78 (95% CI: 0.60%–1.01%) (13). When the analysis was restricted to participants not receiving doxycycline post-exposure prophylaxis to exclude any interference between the two interventions, the incidence was 76.0 per 100 person-years (40 events in 93 participants) in the 4CMenB vaccine group and 105.3 per 100 person-years (48 events in 90 participants) in the no vaccine group (adjusted hazard ratio=0.76 (95% CI: 0.50%–1.15%). Because this trial was underpowered from the outset and prematurely terminated, a vaccine protection in the 30%–50% range cannot be excluded. Research is also underway to develop a specific *N. gonorrhoeae* vaccine that could induce high-level protection of long duration (14). It could, however, take many years to have an *N. gonorrhoeae* vaccine authorized and commercialized in Canada.

Table 1: Observational studies aiming to assess the effectiveness of the four-valent serogroup B meningococcal vaccine (4CMenB) against gonorrhea

Reference	Setting	Study design	Main results
Wang *et al.*, 2023 (7)	In 2018, a publicly funded 4CMenB program was introduced in South Australia: infants are offered three doses, and two doses for grade 10 school students (about 15 years of age).	Vaccine impact was assessed using a Poisson or negative binomial regression model, and vaccine effectiveness (VE) was estimated using screening and case-control methods. Chlamydia controls were used to control potential confounding effects such as high-risk sexual behaviour associated with sexually transmitted infections.	Two-dose VE was 33.2% (95% CI: 15.9%–47.0%). The VE estimate after 36 months post-vaccination was 23.2% (95% CI: 0%–47.5%) compared to 34.9% (95% CI: 15.0%–50.1%) within 6–36 months).
Abara *et al.*, 2022 (8)	Gonorrhea rates in New York City and Philadelphia are among the highest in the United States. Since 2015, ACIP has recommended immunization with a serogroup B meningococcal vaccine for adolescents and young adults aged 16–23 years based on shared clinical decision-making to provide short-term protection against meningococcal disease.	Cohort approach using laboratory-confirmed gonorrhea and chlamydia infections cases among individuals aged 16–23 years identified in sexually transmitted infection surveillance records in New York City and Philadelphia from 2016 to 2018 that were linked to immunization registry records to determine 4CMenB vaccination status at infection. Adjusted VE was estimated using log-binomial regression with generalized estimating equations to account for correlations between multiple infections per patient.	Complete 4CMenB vaccination series VE was 40% (95% CI: 23%–53%) effective and partial vaccination series was 26% effective (95% CI: 12%–37%).

Table 1: Observational studies aiming to assess the effectiveness of the four-valent serogroup B meningococcal vaccine (4CMenB) against gonorrhea (*continued*)

Reference	Setting	Study design	Main results
Robinson *et al.*, 2023 (9)	Mass vaccination campaigns were prompted by serogroup B meningococcal disease outbreaks at University of Oregon in 2015 and Oregon State University in 2016, each used both available meningococcal B vaccines.	Case-control study based on vaccine recipients aged 18–29 years who were reported to Oregon's ALERT Immunization Information System, linked with gonorrhea cases reported to public health authorities from one month to two years after vaccination.	Overall 4CMenB VE was 47% (95% CI:13%-68%). Among those aged 18–19 years, two-dose VE was 59% (95% CI: 20%–79%).
Bruxvoort *et al.*, 2023 (10)	The Kaiser Permanente Southern-California is a prepaid healthcare system with comprehensive administrative databases including vaccinations and results of laboratory tests.	Cohort study from 2016 to 2020 among individuals 15–30 years of age: recipients of 4CMenB were matched in a ratio of 1:4 to recipients of polysaccharide-conjugate vaccines (MenACWY) and followed for incident gonorrhea using Cox proportional hazards regression, adjusting for potential confounders. The same analysis was conducted with chlamydia as a negative control outcome.	Gonorrhea rates were lower among recipients of 4CMenB vs. MenACWY (VE=46%; 95% CI: 14%–66%), but chlamydia rates were similar between vaccine groups (VE=2%; 95% CI: −17%–18%).
Raccagni *et al.*, 2023 (11)	In Italy, there is a recommendation for people living with HIV to receive two 4CMenB doses eight weeks apart since 2016.	Unmatched case-control study on men who have sex with men living with HIV, in care at San Raffaele Scientific Institute, Milan, Italy, with gonorrhea, syphilis, chlamydia, or anal human papillomavirus diagnosed between July 2016 and February 2021. For the analysis, cases were people with gonorrhea infection, and controls were people with syphilis, chlamydia, or anal human papillomavirus infection. Logistic regression was used to estimate 4CMenB VE against gonorrhea.	Adjusted VE was 44% (95% CI: 9%–65%).

Abbreviations: ACIP, Advisory Committee on Immunization Practices; HIV, human immunodeficiency virus; VE, vaccine effectiveness; 4CMenB, four-valent serogroup B meningococcal vaccine

Table 2: On-going randomized clinical trials aiming to assess the efficacy of the four-valent serogroup B meningococcal vaccine (4CMenB) against gonorrhea infection[a]

Registration	Study title	Participants	Outcome	Sponsor	Source
NTC04415424	*Efficacy Study of 4CMenB (Bexsero®) to Prevent Gonorrhoea Infection in Gay and Bisexual Men (GoGoVax)*	High-risk adults 18–40 years of age (n=730)	*N. gonorrhoeae* infection	Kirby Institute, Australia	https://clinicaltrials.gov/study/NCT04415424
ACTRN12619001478101	*MenGO: Does the licensed meningococcal vaccine Bexsero® provide cross-protection against gonorrhoea in gay and bisexual men?*	High-risk adults ≥18 years of age (n=130)	*N. gonorrhoeae* infection	Gold Coast University Hospital, Australia	https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=376715
NCT04350138	*Safety and Efficacy Study of Meningococcal Group B Vaccine rMenB+OMV NZ (Bexsero) to Prevent Gonococcal Infection*	High-risk adults 18–50 years of age (n=2,200)	*N. gonorrhoeae* infection	National Institute of Allergy and Infectious Diseases (NIAID), United States	https://clinicaltrials.gov/study/NCT04350138
NCT05294588	*Efficacy of Immunization with 4C-MenB in Preventing Experimental Urethral Infection with Neisseria gonorrhoeae*	Healthy males 19–35 years of age (n=140)	Experimental *N. gonorrhoeae* infection	University of North Carolina, Chapel Hill, United States	https://clinicaltrials.gov/study/NCT05294588
NCT05766904	*Efficacy Trial on Meningococcal B Vaccine for Preventing Gonorrhea Infections*	High-risk males 18–50 years of age (n=150)	*N. gonorrhoeae* infection	Chinese University of Hong Kong, China	https://clinicaltrials.gov/study/NCT05766904
NCT04597424	*Combined prevention of sexually transmitted infections (STIs) in men who have sex with men and using oral Tenofovir Disoproxil Fumarate/ Emtricitabine (TDF/FTC) for HIV pre-exposure prophylaxis (PrEP) (DOXYVAC)*	High-risk males ≥18 years of age (n=556)	Sexually transmitted infections, including *N. gonorrhoeae* infection	ANRS, France	https://clinicaltrials.gov/study/NCT04597424

Abbreviations: *N. gonorrhoeae*, *Neisseria gonorrhoeae*; 4CMenB, four-valent serogroup B meningococcal vaccine
[a] Trials were identified through PubMed, Google Scholar and ClinicalTrial.Gov searches complemented with information provided by GSK

Discussion

Biological plausibility

The 4CMenB vaccine that was licensed in Canada in 2014 contains four components: the outer membrane vesicle (OMV) from the NZ98/254 strain, a factor H binding protein (fHbp), neisserial heparin-binding antigen (NHBA), and the *Neisseria* adhesin A (NadA) with the accessory proteins GNA2091 and GNA1030 fused with fHbp and NHBA, respectively, to increase their immunogenicity (15). Results of DNA hybridization analyses have shown that *N. meningitidis* and *N. gonorrhoeae* share close to 90% of their genomic identity (16). The nucleotide and amino acid sequences of collections of *N. gonorrhoeae* strains were analyzed and compared with antigens included in 4CMenB and their encoding genes. The NHBA-2 peptide in 4CMenB showed moderate sequence identity (73%) to its gonococcal homolog, which is highly conserved within *N. gonorrhoeae* and predicted to be surface expressed (17). The gene encoding NadA is absent in *N. gonorrhoeae* (18). Although *N. gonorrhoeae* lacks fHbp, it encodes a distinct homolog, Ghfp, which is not expressed on the bacterial surface (19). Bioinformatic analyses have found that a homolog of 20 of the 22 major OMV proteins on the 4CMenB vaccine are present in *N. gonorrhoeae* 16 proteins having >90% identity, and 2 proteins having >80% identity (20). In mice, 4CMenB was found to elicit antibodies that bind to the surface of *N. gonorrhoeae in vitro* and promote serum bactericidal activity and opsonophagocytic killing activity using human polymorphonuclear leukocytes (21). In humans, 4CMenB elicited bactericidal immunoglobulin G (IgG) antibodies to *N. gonorrhoeae* conformational epitopes involving Hep I and Hep II glycosylated lipo-oligosaccharide structures shared between *N. meningitidis* and *N. gonorrhoeae* (22).

The evidence drawn from these observational studies meets seven of the causality criteria proposed by Austin Bradford Hill (23): i) strength of the association (a large and statistically significant effect size); ii) consistency (reproducibility of results in different studies); iii) specificity of effect (protection against gonorrhea and not against other sexually transmitted infections as shown in a study in Australia) (24); iv) temporality (the effect occurs after vaccination); v) biological gradient (effect of one vs two vaccine doses); vi) plausible biological mechanisms and coherence between epidemiological and laboratory findings (discussed in the above section); and vii) analogy (protection was also observed with another OMV meningococcal vaccine in New Zealand) (25). Evidence from RCTs is the eighth causality criteria and the most convincing one (21). There were many limitations in the only trial which results have been published and we will have to wait for results of other on-going trials to make a final judgement (13).

Cost-effectiveness evaluations

To investigate the potential public health impact of adolescent 4CMenB vaccination in England, a deterministic transmission-dynamic model of *N. gonorrhoeae* infection among heterosexual 13 to 64 year-olds was developed assuming 31% vaccine efficacy, a six-year span of protection, and 85% uptake, resulting in the prevention of 25% (95% credibility interval: 17%–33%) of heterosexual infections over 70 years (26). No cost-effectiveness evaluation was made in this analysis. In another integrated transmission-dynamic health economic model from England, strategies targeting high-risk groups only were evaluated, including vaccination on attendance for testing in sexual health clinics; vaccination on diagnosis with gonorrhea; or vaccination according to risk offered to patients diagnosed with gonorrhea plus individuals who test negative but report having more than five sexual partners per year (27). Results showed that vaccination on attendance would have the fastest and largest impact but at high cost, vaccination on diagnosis would be highly cost-effective but with a much lesser impact, whereas vaccination according to risk would have a similar impact to vaccination on attendance at a fraction of the cost and would likely be cost saving from a health services perspective at the current National Health Services costs (£8 per dose plus £10 for administration). This model was applied to test the targeted vaccination of men who have sex with men in England with one or two 4CMenB doses (28). Results indicated that both one- or two-dose strategies would be cost-saving at any uptake level and for a vaccine unit price of £8 per dose plus £10 for its administration.

Public health implications

In the United Kingdom, the Joint Committee on Vaccination and Immunization (JCVI) has recommended the implementation of a 4CMenB immunization program, the vaccine being offered on an opportunistic basis through specialized sexual health services that have vast experience in assessment and identification of those at increased risk of gonococcal infection (29). In the United States, the New York State Department of Health AIDS Institute recommends offering 4CMenB vaccination to patients at high risk of gonorrhea infection (i.e., men who have sex with men and other individuals who have had a bacterial sexually transmitted infection in the prior 12 months, commercial sex workers, and individuals engaging in condomless sex with multiple partners) (30).

Conclusion

A plausible effectiveness of 4CMenB against *N. gonorrhoeae* infections is not mentioned in the latest version of Canadian product monograph and a new submission by the manufacturer would have to be made to add this indication (15). This hypothesis is briefly mentioned in a recent National Advisory Committee on Immunization statement on meningococcal disease published in the *Canada Communicable Disease Report* (CCDR) in September 2023, and more details on scientific evidence could be easily incorporated into a revision of the Canadian Immunization Guide (31). The next step would be a careful evaluation of the integration of 4CMenB into publicly funded provincial/territorial immunization programs for high-risk groups, including the scientific evidence, expected health benefits, budgetary impact, cost-effectiveness, feasibility and

acceptability of different vaccination strategies. It is always difficult to extrapolate the country-specific results of economic evaluations and it would thus be interesting to develop a Canadian model or to adapt an existing model to the Canadian context. A first step would be an estimation of the size of high-risk groups and corresponding *N. gonorrhoeae* infections rates in Canada, as well as practical ways to reach these high-risk groups without stigmatization. In the meantime, results of adequately powered randomize RCTs will be available to hopefully support the relevance of a Canadian immunization initiative for the prevention of *N. gonorrhoeae* infections.

Authors' statement

PDW conceptualized the study and wrote the first draft of the manuscript. All authors contributed to the literature search, analyses and interpretation of results. All authors critically revised and edited the manuscript and approved the final version for submission.

Competing interests

Authors have no conflict of interests to declare.

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RAPID COMMUNICATION

Safety monitoring of Imvamune vaccine during the 2022 mpox outbreak in Canada

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Abstract

Background: In Canada in 2020, the indication for use of Imvamune was expanded to include immunization against smallpox, mpox and related *Orthopoxvirus* infection and disease in adults who are 18 years of age and older and determined to be at high risk for exposure.

Methods: Since the introduction of this new use for the vaccine and throughout the 2022 mpox outbreaks, the Public Health Agency of Canada (PHAC) has closely monitored the safety of the Imvamune vaccine through the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS).

Results: This article describes reports of adverse events following immunization (AEFI) after administration of Imvamune, submitted to the CAEFISS database between May 24, 2022 and December 11, 2022, during the activation of Canada's emergency response.

Conclusion: Monitoring of AEFI reports following immunization with Imvamune submitted to CAEFISS has not identified any new or unexpected safety concerns in the Canadian adult population. The Public Health Agency of Canada continues to monitor for potential vaccine safety signals.

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Keywords: mpox, adverse events, Imvamune, vaccine safety, outbreak

Introduction

Issue identification

In May 2022, human mpox cases were reported in the United Kingdom and other countries shortly before being identified in Canada (1,2). In July 2022, the World Health Organization declared the mpox outbreak a public health emergency of international concern (3). By December, more than 80,000 cases of mpox were reported across 110 countries (4). The severity of reported cases within this outbreak was low, with few hospitalizations and no deaths; however, cases reported considerable pain from lesions or scarring (5–7). Cases occurred predominantly within marginalized communities, specifically gay, bisexual and other men who have sex with men (GBMSM) (5). The term GBMSM aims to include people who self-identify as cisgender or transgender men whose sexual partners are cisgender and/or transgender men, regardless of their sex assigned at birth; that being said, there may be differences across surveillance systems with how gender identity, sex, and sexual orientation is defined (5). Canadian provinces and territories initiated an immunization campaign (8) following the release of interim guidance by the National Advisory Committee on Immunization (NACI) on the use of Imvamune in the context of monkeypox outbreaks in Canada (8,9). NACI further indicated that additional post-marketing safety data on Imvamune was a research priority (9).

Imvamune (modified vaccinia Ankara-Bavarian Nordic), also known outside of Canada by the brand names Jynneos and Imvanex, is a live-attenuated, non-replicating *Orthopoxvirus* vaccine (10). Health Canada initially granted approval of Imvamune in 2013 under the Extraordinary Use New Drugs (EUNDs) submission for use against smallpox infections (11). A supplement to the EUNDs in 2020 expanded the indication to include mpox and related orthopoxviral infection (11). The approval was for primary doses of the vaccine administered as two 0.5 mL doses given subcutaneously, at least four weeks apart. Imvamune can be given prior to potential exposure or as post-exposure prophylaxis for individuals who

have been exposed to the virus but do not yet have symptoms of mpox (9).

The Public Health Agency of Canada (PHAC) monitored Imvamune vaccine safety using the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS), which is a federal, provincial, and territorial public health post-market vaccine safety surveillance system coordinated by PHAC and used to continuously monitor the safety of vaccines administered in Canada (12). Reports are first submitted to a health authority (i.e., local, regional, provincial/territorial or federal authorities) by healthcare providers of individuals who experienced an adverse event following immunization (AEFI). These reports are then submitted by the federal, provincial or territorial health authorities to PHAC for inclusion in the CAEFISS database (12). Adverse events following immunization are also monitored through the Canada Vigilance Program of Health Canada, however, no reports of AEFIs with Imvamune were received through this program.

The aim of this study was to describe AEFI reports following administration of Imvamune submitted to the CAEFISS database between May 24, 2022 and December 11, 2022. This study period was defined due to the peak of the outbreaks that occurred in Canada during this year (2,5) and the national health portfolio emergency response being de-escalated in December 2022 (13).

Methods

Data were searched and extracted data from CAEFISS for deidentified AEFI reports submitted between May 24, 2022 and December 11, 2022. Data extraction was done using the "Preferred Terms" hierarchical level of the Medical Dictionary for Regulatory Activities (MedDRA) standardized terminology (14). All reports underwent systematic primary medical case review by trained health professionals. An AEFI was considered serious if it resulted in death, was life-threatening (an event/reaction in which the patient was at real, rather than hypothetical, risk of death at the time of the event/reaction), required in-patient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or resulted in a congenital anomaly/birth defect (15). Dose-administered data were also collected from relevant provincial and territorial partners.

Reporting rates of adverse events were calculated by dividing the number of adverse events by the number of doses administered. The associated 95% confidence intervals (CIs) were estimated using the Poisson exact method. The data extraction and analysis for this article were generated using R Statistical Software version 4.2.2 (16) and SAS Enterprise Guide software version 7.1. The SAS and all other SAS Institute Inc. product or service names are registered trademarks or trademarks of SAS Institute Inc., Cary, North Carolina, United States.

Results

Between May 24, 2022 and December 11, 2022, 119,826 doses of Imvamune were administered in Canada, including 95,346 (79.6%) first doses, 24,478 (20.4%) second doses, and two third doses (0.0%). The majority (93.2%) of doses were administered to males. Imvamune was administered to 80 persons aged less than 18 years.

A total of 53 AEFI reports following administration of Imvamune were submitted to PHAC for inclusion in the CAEFISS database during the period under analysis, corresponding to an overall reporting rate of 44.2 reports per 100,000 doses (95% CI: 33.1–57.9). Most reports were classified as non-serious based on the described clinical manifestations and outcomes, with AEFIs reported predominantly among males (81%), primarily in the age range of 0 to 49 years (72%) (**Table 1**). This is consistent with the recommendations for Imvamune use in the context of an active mpox outbreak, as well as the epidemiology of the 2022 outbreak (5). While most reports indicated vaccination via subcutaneous injection (53%), route of administration was not provided for many reports (Table 1). The most reported adverse events were similar between vaccinations administered subcutaneously and those where route of administration was unknown (**Table 2**).

Table 1: Characteristics of Imvamune vaccine recipients with adverse events following immunization reports submitted to CAEFISS in Canada, May 24, 2022–December 11, 2022, (n=53)

Characteristic	Number of reports (%)[a]
Sex	
Male	43 (81%)
Female	6–9
Other	<5
Age group (in years)	
0–29	12 (23%)
30–39	14 (26%)
40–49	12 (23%)
50–59	10 (19%)
60+	5 (9%)
Route of administration	
Subcutaneous	28 (53%)
Intramuscular[b]	<5
Unknown	21–24
Seriousness	
Non-serious	49–52
Serious	<5

Abbreviation: CAEFISS, Canadian Adverse Events Following Immunization Surveillance System
[a] For cells with small counts (n<5), the exact number and proportion is supressed due to potential personal identifiers
[b] This route was indicated as an immunization error

Table 2: Top 10 most frequently reported adverse events following immunization after Imvamune vaccine administration, by route of vaccine administration from CAEFISS in Canada, May 24, 2022–December 11, 2022

AEFI[a]	Number of reports[b]
Subcutaneous route of administration	
Vaccination site erythema	9 (32%)
Vaccination site pain	9 (32%)
Vaccination site nodule	6 (21%)
Vaccination site swelling	6 (21%)
Vaccination site warmth	6 (21%)
Erythema	<5
Pruritus	<5
Urticaria	<5
Vaccination site induration	<5
Rash	<5
Unknown route of administration	
Vaccination site pain	13 (54%)
Vaccination site erythema	10 (42%)
Vaccination site swelling	8 (33%)
Vaccination site mass	5 (21%)
Pruritus	<5
Rash	<5
Vaccination site nodule	<5
Vaccination site pruritus	<5
Erythema	<5
Vaccination site cellulitis	<5

Abbreviations: AEFI, adverse event following immunization; CAEFISS, Canadian Adverse Events Following Immunization Surveillance System
[a] Note that each report represents one person and may contain information on more than one AEFI
[b] For cells with small counts (n<5), the exact number and proportion is supressed due to potential personal identifiers. Proportions are calculated using total number of reports for each route of administration

Table 3: Reporting rates per 100,000 doses administered for the 10 most frequently reported adverse events following immunization after Imvamune vaccine administration from CAEFISS in Canada, May 24, 2022–December 11, 2022

AEFI[a]	Number of events	Reporting rate (95% CI)
Vaccination site pain	22	18.4 (11.5–27.8)
Vaccination site erythema	20	16.7 (10.2–25.8)
Vaccination site swelling	15	12.5 (7.0–20.6)
Vaccination site mass	9	7.5 (3.4–14.3)
Vaccination site nodule	9	7.5 (3.4–14.3)
Pruritus	8	6.7 (2.9–13.2)
Vaccination site warmth	8	6.7 (2.9–13.2)
Erythema	6	5.0 (1.8–10.9)
Rash	6	5.0 (1.8–10.9)
Vaccination site cellulitis	5	4.2 (1.4–9.7)

Abbreviations: AEFI, adverse event following immunization; CI, confidence interval; CAEFISS, Canadian Adverse Events Following Immunization Surveillance System
[a] Note that each report represents one person and may contain information on more than one AEFI

The majority of AEFIs reported were local reactions associated with the vaccination site. Notably, vaccine site pain was the most reported, with 18.4 reports per 100,000 doses administered (**Table 3**). There were no reports of anaphylaxis.

All serious reports required hospitalizations and no deaths were reported. Medical case review did not confirm an association between the AEFIs reported and the vaccination or deemed this association as unclassifiable.

Serious AEFI reports included events such as cerebrovascular events, superficial vein thrombosis, and injection site reactions.

Discussion

As of this report, monitoring of AEFIs following Imvamune administration has not identified any new or unexpected safety concerns in the Canadian adult population. The predominance of vaccine site reactions following injection aligns closely with what has been observed in clinical studies and with expected reactions listed on the product monograph (10). Furthermore, reporting rates of the most reported AEFIs are comparable to those reported in the United States as part of the mpox outbreak vaccination campaign (17).

Over the seven-month study period, national spontaneously reported data do not suggest any unexpected concerns regarding the number and nature of serious adverse event reports. With respect to other events of special interest, such as myocarditis, there were no reports of such events in Canada. However, given myocarditis was observed in the United States following vaccination with Jynneos at a rate of 1.53 and 2.99 per million doses after dose 1 and dose 2, respectively (17), it is unlikely that such rare adverse events would be observed given the limited use of this vaccine in Canada.

During the Imvamune vaccination campaign, NACI recommended a dose sparing strategy of intradermal injection for immunocompetent adults when given as a second dose, instead of using the standard subcutaneous injection method (11). Based on the data available in CAEFISS, there is no evidence to conclude that the route of vaccine administration may have had a notable impact on the rate of AEFI occurrence. Indeed, the top 10 commonly reported adverse events were similar between vaccinations administered subcutaneously and those where the route of vaccine administration was unknown. Furthermore, reporting from the United States suggests that the adverse events reported were not different between the two routes of administration (17).

Limitations

The results of this investigation are subject to limitations of the CAEFISS reporting system, which include the potential for under-reporting, missing information in submitted reports (which, at times, led to an inability to confirm the diagnosis as reported), and different reporting practices between reporting jurisdictions. In addition, data on the number of doses that may have been administered to the recipient, as well as on the route by which the vaccine was administered (intradermal vs subcutaneous) were missing in a significant number of AEFI reports. This limited our ability to conduct route-specific rate calculations and relative risk comparisons. Finally, the occurrence of an AEFI report does not necessarily confirm that the AEFI meets standard diagnostic criteria or that a causal link exists between the administration of a vaccine and the occurrence of the reported adverse event.

Conclusion

In conclusion, as of this report, monitoring of AEFIs following Imvamune did not reveal any unexpected safety concerns in the Canadian adult population. The adverse events observed during the analysis period align well with published data and serious events were rare. Post-marketing Imvamune safety surveillance studies are limited, and this article adds to the knowledge base of Imvamune outside of clinical trials. The Public Health Agency of Canada will continue to monitor AEFI reports as they are submitted to the CAEFISS reporting system.

Authors' statement

CW — Writing–original draft
YX — Validating, writing–review & editing
AW — Writing–review & editing
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SO-C — Supervision, writing–review & editing

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