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# HEALTH ECONOMICS IN PUBLIC HEALTH



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# CCDR
## CANADA COMMUNICABLE DISEASE REPORT


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CANADA COMMUNICABLE DISEASE REPORT

# HEALTH ECONOMICS IN PUBLIC HEALTH

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# Cost-effectiveness of respiratory syncytial virus vaccination strategies for older Canadian adults: A multi-model comparison

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## Abstract

**Background:** Two respiratory syncytial virus (RSV) vaccines are currently approved for use in adults aged 60 years and older in Canada.

**Objective:** To conduct a multi-model comparison to explore the impact of alternate model structural and methodological assumptions on the estimated cost-effectiveness of RSV adult vaccination programs.

**Methods:** We compared three static cost-utility models developed by the Public Health Agency of Canada, GSK and Pfizer using a common set of input parameters. Each model evaluated sequential incremental cost-effectiveness ratios in 2023 Canadian dollars per quality-adjusted life year (QALY) for a set of policy alternatives, with vaccine eligibility determined by combinations of age and chronic medical condition (CMC) status. Results were calculated for each vaccine separately for scenarios assuming two or three years of vaccine protection using the health system perspective and a 1.5% annual discount rate.

**Results:** The three cost-utility models were broadly concordant across the scenarios modeled. In all scenarios, focusing on vaccination of people with CMCs was preferred over broader age-based policies. Respiratory syncytial virus vaccination for people with CMCs over the age of 70 years was most commonly identified as the optimal policy when using a cost-effectiveness threshold of $50,000/QALY. When only considering policies based on age criteria, vaccinating people over 80 years was cost-effective at this threshold.

**Conclusion:** A multi-model comparison of Canadian cost-utility models shows that RSV vaccination programs for RSV are likely cost-effective for some groups of older adults in Canada. These findings were consistent across models, despite differences in model structure.



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***Keywords:*** respiratory syncytial virus, vaccination, cost-utility analysis, health economics, modelling

## Introduction

Respiratory syncytial virus (RSV) is a major cause of respiratory infections in Canada, with a large burden of disease occurring in young children and older adults (1). Respiratory syncytial virus was estimated to account for 4.8% of hospitalizations for acute respiratory infections among Canadian adults aged over 50 years between 2012–2015 (2). Hospital mortality rates increased with age and among those with chronic medical conditions (2–4).

With the recent authorization of two vaccines for adults aged over 60 years in Canada, policymakers are evaluating the use of these products in this population, including whether to recommend publicly-funded vaccination programs (5). Economic considerations are one important input to these decision processes.

We recently conducted an analysis of the cost-effectiveness of various vaccination program options for older adults in Canada (6) to inform forthcoming National Advisory Committee on Immunization (NACI) recommendations for the use of RSV vaccines in older adults. This analysis showed that vaccinating older adults may be cost-effective, depending on the program design. In particular, we showed that programs focused on vaccinating people with chronic medical conditions (CMCs) that place them at increased risk of RSV disease are expected to provide better value for money than more general age-based programs.

While model-based economic evaluations can provide useful insights for decision-makers, an exploration of how uncertainty impacts the results is important to avoid making suboptimal decisions. Sensitivity analyses can be performed to test uncertainty due to model inputs and parameter assumptions. Although changes to assumptions about model structure can be assessed in scenario analyses, such analyses may be challenging. Multi-model comparison studies can be used to address uncertainty due to model structure and methodology (7,8), and are recommended in the NACI guidelines for economic evaluations (9). By comparing results across independently developed economic models with standardized input parameters, researchers can assess the extent to which model-derived results are robust to differences in model mathematical formulation and methodological choices, allowing for higher confidence when evaluating this evidence.

We conducted a multi-model comparison of three economic cost-utility models to assess the robustness of findings regarding the cost-effectiveness of RSV vaccination program options in older adults in Canada to variation in model assumptions and structure.

# Methods

## Model selection

The multi-model comparison was conducted to support NACI and was part of an economic evidence package considered during the development of recommendations for the use of RSV vaccines in Canadian adults. In addition to the Public Health Agency of Canada (PHAC)-developed model (6), we restricted our focus to models from manufacturers with a product approved for use in Canadian adults aged over 60 years for the 2024–2025 RSV season (Arexvy [GSK] and Abrysvo [Pfizer]). Both GSK and Pfizer provided their models, which were constructed in Microsoft Excel (10). Model reparameterization and re-analyses were conducted by our team.

## Health economic framework

We evaluated all models in a population of 100,000 Canadian adults over the age of 50 years. Although the current RSV vaccines were authorized for use in the population aged 60 years and older at the time of the analysis, we included some vaccination strategies that considered a lower age limit of 50 years, given that a lower age indication is currently under review (11). The population was distributed by age group (12) and stratified as higher risk or average risk based on the presence or absence of any CMCs placing them at increased risk of RSV disease (13). Model-estimated outcomes of interest included the number of RSV-attributable outpatient healthcare provider visits, emergency department visits, hospitalizations, deaths and adverse events following immunization, quality-adjusted life year (QALY) losses, vaccination costs and healthcare costs. We computed expected vaccination costs, RSV-attributable medical costs and QALY losses for a range of possible vaccination programs. We evaluated the impact of vaccination programs using either Arexvy or Abrysvo, for a policy time horizon of two to three years, depending on the assumed duration of vaccine protection. All models began in September of the first year to cover the expected start of the typical RSV season (prior to the SARS-CoV-2 pandemic), with vaccination occurring at the start of the first season. Lifetime QALY losses were computed in the case of RSV mortality. All costs and QALY losses were discounted at a rate of 1.5% per annum (9). Costs and QALYs were used to compute sequential incremental cost-effectiveness ratios (ICERs) for all policy options under consideration. We only considered the health system perspective in this analysis.

## Model overviews and standardization

Each cost-utility model had unique features that required us to adapt input assumptions to be directly comparable, as described below. An overview of important characteristics of the PHAC, GSK and Pfizer models is also provided in **Table 1**.

## Public Health Agency of Canada model

The PHAC model is a static individual-based model with five age groups and two risk strata and includes the following RSV outcomes: outpatient healthcare provider visits, emergency department visits, hospitalization without intensive care unit (ICU), hospitalization with ICU and death (6). Hospitalizations without ICU and hospitalizations with ICU were collapsed to simplify hospitalization for comparability with other models. Adverse events following immunization are assumed to result in a proportion of all immunizations given. The model includes lifetime QALY losses for RSV mortality and uses a fixed policy time horizon of three years.

## Pfizer model

The Pfizer model is a static cohort model with five age groups and two or three risk strata. The model structure has been previously described (14) and the model inputs were adapted for the Canadian context. Because there are fewer age groups in this model than in the policy alternatives considered (described below) we merged some age groups, using population-weighted averages where input assumptions differed between merged age groups.

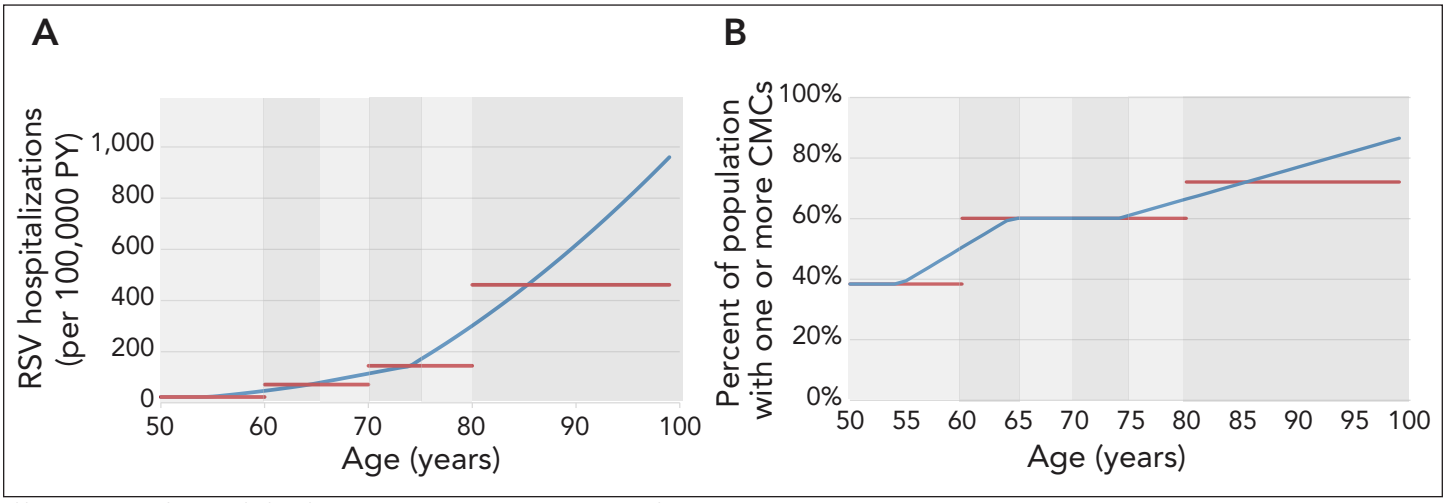
**Table 1: Overview of models included in the multi-model comparison**

| Model attribute | PHAC | GSK | Pfizer |
|---|---|---|---|
| Dynamics | Static | Static | Static |
| Aggregation | Individual | Cohort | Cohort |
| Age groups (years) | 50–59, 60–64, 65–69, 70–74, 70–74, 75–79, 80 and older | 50–59, 60–64, 65–69, 70–74, 75–79, 80 and older | 18–49[a], 50–59, 60–69, 70–79, 80 and older |
| Risk strata | Two strata representing people with and without chronic medical conditions | Strata not explicitly modeled. Average and high risk adults were modeled as separate cohorts | Two or three risk strata, with option to allow people to move to higher risk strata as they age |
| RSV-related outcomes | Outpatient healthcare provider visit, ED visit, hospitalization, ICU | RSV-URTD (outpatient healthcare provider or ED visit), RSV-LRTD (hospitalization) | Non-medically attended, outpatient visit, ED visit, hospitalization |
| Seasonality | Monthly distribution of yearly cases | "Seasonality factor" multiplying expected monthly cases | Monthly distribution of yearly cases |
| VE | Separate VEs for hospitalization and outpatient visit. Waning over 36 months modelled using a cubic polynomial regression model | Separate VEs for RSV-URTD and RSV-LRTD. First month efficacy reduced by half. Linear waning between months 1–7, 7–18, 18 and over | Four VE curves for hospitalization, ED visit, outpatient healthcare provider visit, and non-medically attended RSV. Linear waning between months 0–3, 3–6, 6–12, 12–18, 18–24, 24–36 |
| AEFI | Local and systemic | Local and systemic | Not modelled |
| Vaccination timing | September and October 2024 | October 1, 2024 | September and October 2024 |
| Time horizon | Three years. Third-year VE in two-year scenario is assumed to be zero | Any integer | Any integer, but lifetime horizon must be used to capture QALY losses due to RSV mortality |

Abbreviations: AEFI, adverse events following immunization; ED, emergency department; ICU, intensive care unit; LRTD, lower respiratory tract disease; PHAC, Public Health Agency of Canada; QALY, quality-adjusted life year; RSV, respiratory syncytial virus; URTD, upper respiratory tract disease; VE, vaccine effectiveness
[a] Not included in results, but cannot be removed from model

The model includes costs and QALY losses for non-medically attended cases, outpatient visits, emergency department visits, hospitalizations and death. We excluded costs and QALY losses associated with non-medically attended cases for consistency with the PHAC model. Adverse events following immunization are not explicitly considered in this model. We added the expected cost of treating these adverse events following immunization ($0.67 per vaccinated person) in the vaccine administration cost but were unable to incorporate expected QALY losses. Although the model has a user-specified time horizon, a lifetime model horizon is necessary to fully count QALY losses due to RSV mortality. Finally, unlike the other models, the Pfizer model assumes that age-specific parameter inputs are piecewise linear between age groups in one-year increments, as illustrated in **Figure 1**.

**Figure 1: Comparison of Pfizer piecewise linearity[a] and Public Health Agency of Canada/GSK uniform[a] assumptions for age-varying data[b]**




Abbreviations: CMC, chronic medical condition; PY, person-years; RSV, respiratory syncytial virus
[a] Pfizer piecewise linearity data are shown in blue and Public Health Agency of Canada/GSK uniform are shown in red
[b] Results are shown for A) incidence of RSV-associated hospitalizations per 100,000 person-years and B) prevalence of chronic medical conditions

## GSK model

The GSK model is a static cohort model with up to seven age groups. The model structure has been previously described (14,15) and the model parameters were adapted for the Canadian population. All people in each age group are assumed to be the lowest age; therefore, we staggered age groups to start at the mid-point of desired ranges so that age groups had the same average age and life years lost in the case of RSV mortality. The model does not model risk strata explicitly, but by treating high and low risk people as separate cohorts we achieved the same effect. As in other models, lifetime QALY losses are considered for RSV mortality, but a policy time horizon of two or three years may be selected by the user.

Rather than modelling vaccine effectiveness (VE) as protecting directly against healthcare system use outcomes such as outpatient visits and hospitalization, the original model assumes that all RSV acute respiratory infections (RSV-ARI) lead to either upper respiratory tract disease (RSV-URTD) or lower respiratory tract disease (RSV-LRTD). Differing levels of healthcare resource use are then assumed, depending on whether a person has RSV-URTD or RSV-LRTD. We made a change to this formulation by modelling RSV-LRTD as equivalent to RSV requiring hospitalization, and RSV-URTD as resulting in either outpatient healthcare provider or emergency department visits, with probabilities proportional to the age- and risk-stratified number of cases of each outcome estimated in the PHAC model.

Vaccination in the GSK model confers two levels of protection: against RSV-LRTD and against all RSV-ARI. In the original model VE against RSV-ARI and RSV-LRTD were based on clinical trial results and VE for RSV-URTD was calculated based on the other two VE inputs. For this analysis, we computed RSV-ARI waning profiles for each age-risk stratum such that the resulting VE against RSV-URTD matched the assumptions of VE against outpatient and emergency department visits in the other models.

## Input parameters

Common input parameters were based on those used in the PHAC cost-utility analysis, which preferentially used Canadian data when available, and otherwise used data from other jurisdictions or expert opinion (6). A full description of input parameters used is published separately (6), and the values used in the current analysis are provided in **Table A1** (see **Appendix**) for reference. Some key parameters are described below.

Age-specific proportions of people with one or more CMCs were based on Canadian prevalence estimates of chronic obstructive pulmonary disease, obesity (self-reported body mass index greater than or equal to 30 kg/m$^3$), high blood pressure, cancer, heart disease and suffering from the effects of a stroke, diabetes or dementia (13). Vaccine coverage was assumed to follow influenza vaccine uptake (16). Vaccination costs included administration costs and the public Canadian list price of $230 per dose for both vaccines. Vaccine effectiveness against RSV requiring outpatient medical attendance or hospitalization was assumed to be equal to published VE against mild and severe RSV infections, and to wane over a two or three year period, with the three-year period estimates based on extrapolation from existing data, which were limited to two RSV seasons at the time of the analysis (17–19). Age-specific incidence of RSV-associated hospitalization was estimated based on results from Canadian studies (2), with an assumed case under-detection factor of 1.5-fold (4). Respiratory syncytial virus infections were assumed to be seasonal, with most cases occurring in January to March (20). Where necessary, due to model structural assumptions, we adapted input parameters to have equivalent effects across models but did not modify the underlying logic of any model.

## Model comparisons

As described above, we modelled the use of the Abrysvo (Pfizer) or Arexvy (GSK) vaccines separately under the assumption of either two or three years duration of protection following vaccination, with VE assumed to wane over the specified time period. In addition to no vaccination, we evaluated 19 policy alternatives using different combinations of age and comorbidity eligibility requirements under each scenario (6):

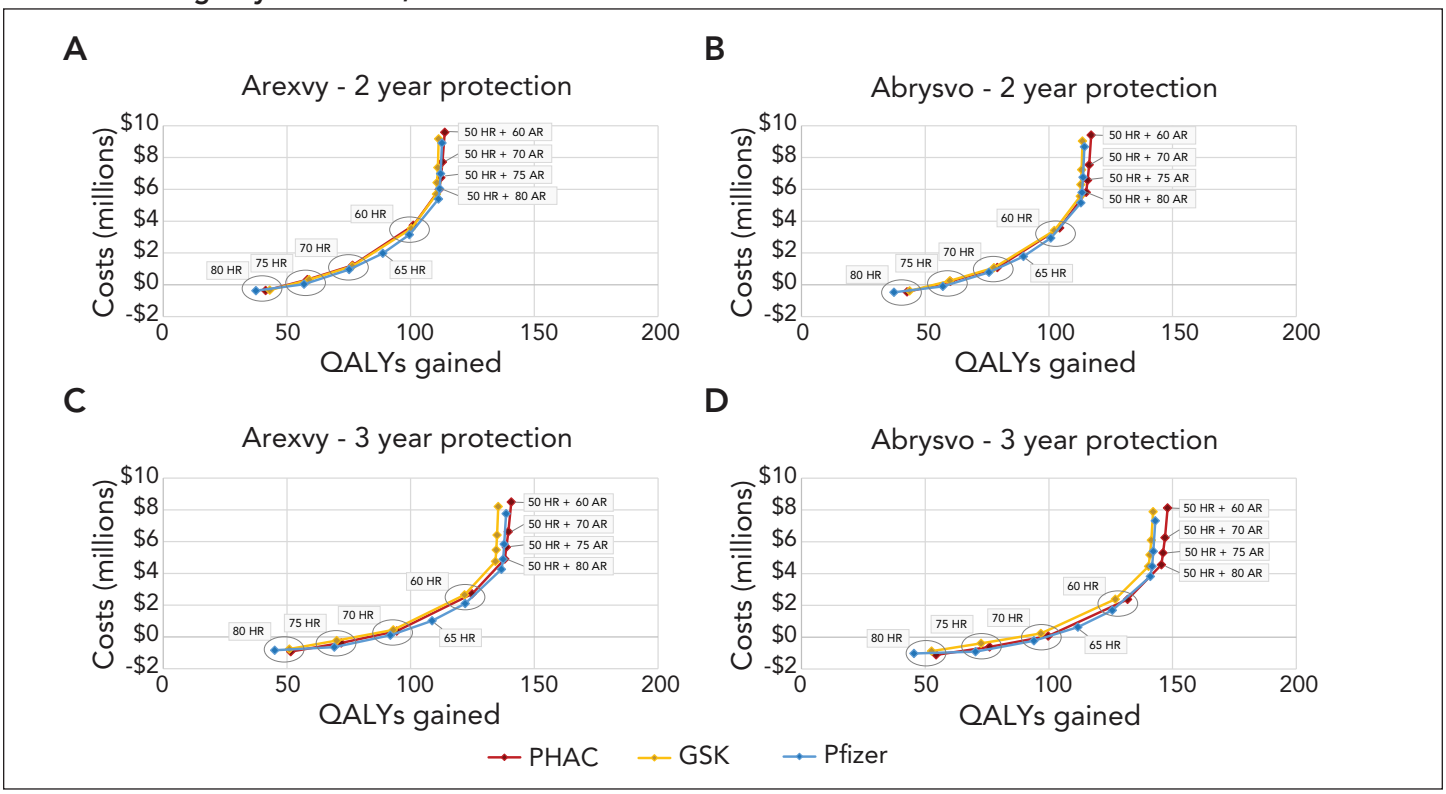
- Age-based policies: all adults older than 60, 65, 70, 75 or 80 years of age were considered eligible
- Medical risk-based policies: all adults older than 60, 65, 70, 75 or 80 years of age who also had one or more CMCs were considered eligible
- Age- and medical risk-based policies: all adults over a general age threshold, plus adults with CMCs over a range of lower age thresholds (50 or 60 years) were considered eligible

While all three models used a lifetime horizon for QALY losses due to RSV mortality, each has differing policy time horizons for evaluating the impact of vaccination programs. As VE is assumed to be finite (i.e., a maximum of three years considered in this analysis), these differing horizons did not impact comparisons of incremental cost-effectiveness ratios. In graphical comparisons of cost-effectiveness frontiers, we used net program costs and effects relative to no vaccination to account for differences in model time horizons.

# Results

A comparison of the cost-effectiveness frontiers for the three models using VE assumptions for Abrysvo (Pfizer) and Arexvy (GSK) in the two-year and three-year waning scenarios is shown in **Figure 2**. The three models were broadly concordant across the four scenarios. The PHAC and GSK models identified the same policy alternatives as potentially cost-effective, with the optimal policy dependent on the cost-effectiveness threshold. The Pfizer model had similar results overall, but identified an

**Figure 2: Potentially cost-effective respiratory syncytial virus vaccination strategies, generated using outputs from Public Health Agency of Canada, GSK and Pfizer models[a]**




Abbreviations: Abrysvo, respiratory syncytial virus vaccine manufactured by Pfizer; AR, average risk; Arexvy, respiratory syncytial virus vaccine manufactured by GSK; HR; high risk; PHAC, Public Health Agency of Canada; QALY, quality-adjusted life year; VE, vaccine effectiveness

[a] Results are shown for the following scenarios: A) Arexvy VE data with waning protection over 2 years, B) Abrysvo VE data with waning over 2 years, C) Arexvy VE data with waning protection over 3 years and D) Abrysvo VE data with waning over 3 years. Labels indicate the vaccination strategy. For clarity, only strategies that were on the cost-effectiveness frontier are shown. All other strategies were dominated or excluded by extended dominance and were not cost-effective options, regardless of the cost-effectiveness threshold used. Incremental cost-effectiveness ratios for the non-dominated strategies are provided in Tables 2 and 3. As described in the methods, costs and QALYs gained are shown relative to no vaccination to allow for a comparison across models

additional policy, vaccination for higher-risk people over the age of 65 years, as a potentially cost-effective option. This policy was consistently subject to extended dominance (i.e., not cost-effective at any cost-effectiveness threshold) using the PHAC and GSK models. For all models, all of the policies identified as potentially cost-effective were either risk-based or age- and risk-based; age-based strategies were never identified as cost-effective options. We found that a policy of vaccinating higher-risk people aged 80 years and older dominated a policy of no vaccination across all models using either vaccine's assumed VE.

## Two-year vaccine protection scenarios

Sequential ICERs for all policies that were not dominated or extendedly dominated in the two-year vaccine protection scenario are shown in **Table 2**. Compared to vaccination of higher-risk people aged 80 years and older, the PHAC and GSK models estimated sequential ICERs between $38,029/QALY and $41,325/QALY for a policy of vaccinating higher-risk people over the age of 75 years, while the Pfizer model had ICERs of approximately $20,000/QALY. With the exception of the Pfizer model parameterized with Arexvy VE estimates, all sequential ICERs for the higher-risk adults aged 70 years and older policy were less than the commonly used $50,000/QALY cost-effectiveness threshold when compared to vaccination of higher-risk adults aged 75 years and older; the sequential ICER for the Pfizer model using Arexvy VE estimates was only slightly above this threshold at $50,388/QALY. The Pfizer model was the only model to estimate that a policy of vaccinating higher-risk people over the age of 65 years could potentially be a cost-effective option, with sequential ICERs of $71,933/QALY to $75,457/QALY compared to a policy for higher-risk adults aged 70 years and older. For all models, sequential ICERs for a policy of vaccinating all higher-risk people over the age of 60 years were approximately $100,000/QALY compared to vaccination of higher-risk adults aged 70 (PHAC and GSK models) or 65 (Pfizer model) years and older. Above this threshold, the next most cost-effective policies were all those vaccinating higher-risk people over the age of 50 years and progressively lower age groups of people without CMCs. Strictly age-based policies were never identified as cost-effective options, regardless of the model used.

## Three-year vaccine protection scenarios

Sequential ICERs for all policies that were not dominated or extendedly dominated for a scenario assuming that vaccine protection extends through a third season are provided in **Table 3**. Incremental cost-effectiveness ratios for these scenarios were predictably lower than their equivalents in the two-year scenarios, owing to longer assumed duration of vaccine

**Table 2: Sequential incremental cost-effectiveness ratios ($/quality-adjusted life year) for respiratory syncytial virus vaccination strategies identified as potentially cost-effective, assuming that vaccine protection wanes within two years[a,b]**

| Policy | Arexvy | | | Abrysvo | | |
|---|---|---|---|---|---|---|
| | PHAC | GSK | Pfizer | PHAC | GSK | Pfizer |
| 80 years of age and older at HR | - | - | - | - | - | - |
| 75 years of age and older at HR | $40,660 | $41,325 | $21,219 | $38,029 | $39,199 | $18,682 |
| 70 years of age and older at HR | $49,502 | $48,068 | $50,388 | $46,157 | $45,591 | $47,309 |
| 65 years of age and older at HR | Extended dominated | | $75,457 | Extended dominated | | $71,933 |
| 60 years of age and older at HR | $102,356 | $99,485 | $108,641 | $98,583 | $96,188 | $104,544 |
| 80 years of age and older at AR and 50 years of age and older at HR | $214,052 | $212,578 | $189,414 | $209,131 | $206,540 | $182,774 |
| 75 years of age and older at AR and 50 years of age and older at HR | $1,317,114 | $2,865,566 | $1,329,263 | $1,421,826 | $2,784,588 | $1,265,781 |
| 70 years of age and older at AR and 50 years of age and older at HR | $1,421,897 | $3,391,567 | $2,829,476 | $1,519,503 | $3,298,674 | $2,703,549 |
| 60 years of age and older at AR and 50 years of age and older at HR | $2,013,359 | $5,059,381 | $3,449,849 | $2,235,963 | $4,920,460 | $3,286,184 |

Abbreviations: Abrysvo, respiratory syncytial virus vaccine manufactured by Pfizer; AR, average risk; Arexvy, respiratory syncytial virus vaccine manufactured by GSK; HR, high risk; PHAC, Public Health Agency of Canada; -, not applicable

[a] Only strategies that were not dominated or subject to extended dominance are listed. For this analysis, the incremental cost-effectiveness ratio is calculated relative to the strategy in the preceding row

[b] Results are shown for each model and using data for either the Arexvy or Abrysvo vaccines

**Table 3: Sequential incremental cost-effectiveness ratios ($/quality-adjusted life year) for vaccination strategies identified as potentially cost-effective, assuming that vaccine protection wanes within three years[a,b]**

| Policy | Arexvy | | | Abrysvo | | |
|---|---|---|---|---|---|---|
| | PHAC | GSK | Pfizer | PHAC | GSK | Pfizer |
| 80 years of age and older at HR | - | - | - | - | - | - |
| 75 years of age and older at HR | $26,834 | $27,801 | $8,269 | $23,169 | $24,695 | $4,745 |
| 70 years of age and older at HR | $32,907 | $29,320 | $32,736 | $28,814 | $25,727 | $28,557 |
| 65 years of age and older at HR | Extended dominated | | $53,647 | Extended dominated | | $48,856 |
| 60 years of age and older at HR | $77,338 | $76,430 | $81,335 | $71,776 | $71,513 | $75,674 |
| 80 years of age and older at AR and 50 years of age and older at HR | $165,771 | $169,258 | $147,249 | $158,601 | $153,336 | $138,356 |
| 75 years of age and older at AR and 50 years of age and older at HR | $1,090,178 | $2,350,773 | $975,340 | $1,135,141 | $1,461,416 | $905,774 |
| 70 years of age and older at AR and 50 years of age and older at HR | $1,219,926 | $2,534,807 | $2,132,683 | $1,290,424 | $1,560,714 | $1,984,098 |
| 60 years of age and older at AR and 50 years of age and older at HR | $1,588,568 | $4,112,609 | $2,577,733 | $1,717,449 | $2,547,744 | $2,394,941 |

Abbreviations: Abrysvo, respiratory syncytial virus vaccine manufactured by Pfizer; AR, average risk; Arexvy, respiratory syncytial virus vaccine manufactured by GSK; HR, high risk; PHAC, Public Health Agency of Canada; -, not applicable

[a] Only strategies that were not dominated or subject to extended dominance are listed. Note that for the results in this table, the incremental cost-effectiveness ratio is calculated relative to the strategy in the preceding row

[b] Results are shown for each model and using data for either the Arexvy or Abrysvo vaccines

protection. Sequential ICERs for a policy of vaccinating higher-risk people over the age of 70 years were between $25,727/QALY and $32,907/QALY compared to vaccination of higher-risk adults over the age of 80 years. As with the two-year vaccine protection scenario, only the Pfizer model identified vaccinating higher-risk people over the age of 65 years as a cost-effective option, with sequential ICERs of $48,856/QALY to $53,647/QALY compared to a policy for higher-risk adults aged 70 years and older. Vaccinating higher-risk people over the age of 60 years resulted in ICERs between $71,513/QALY and $81,335/QALY compared to vaccination for higher-risk adults aged 70 (PHAC and GSK models) or 65 years and older (Pfizer). At higher cost-effectiveness thresholds, as with the two-year vaccine protection scenarios, age- and risk-based policies that included vaccinating higher-risk people over the age of 50 years and progressively lower age groups of average risk people were identified as cost-effective options. Age-based policies were never cost-effective when compared with these other policy options.

## Age-based policies

Though age-based policies were never identified as cost-effective when considered alongside risk- or age- and risk-based options, these may be preferred by some decision-makers based on other considerations, such as potentially reduced complexity of program delivery. We therefore performed a sub-analysis of the two-year vaccine protection scenarios, restricted to only age-based policies (**Table 4**). Sequential ICERs for a policy of vaccinating all people over the age of 80 years were between $3,161/QALY and $6,194/QALY compared to no vaccination. Policies including younger people were unlikely to be considered cost-effective at a $50,000/QALY cost-effectiveness threshold; the PHAC and GSK models estimated ICERs between $78,637/QALY and $85,805/QALY for a policy of vaccinating all people over the age of 75 years compared to a policy for all people over the age of 80 years. However, the Pfizer model had ICERs of between $50,090/QALY and $53,205/QALY in this scenario. More expansive age-based policies had progressively higher ICERs and were unlikely to be considered cost-effective at commonly-used thresholds.

# Discussion

Our multi-model comparison of three Canadian cost-utility models has shown that RSV vaccination programs for older adults may be a cost-effective intervention, particularly when these programs are focused on population groups with the highest risk of RSV disease. These findings were broadly concordant across the scenarios considered; the policies identified as optimal at commonly used cost-effectiveness thresholds were generally consistent. Additionally, estimated ICERs did not differ greatly between the two vaccines considered.

Using harmonized model input parameters, all models consistently identified policies based on medical risk as optimal compared to policies based only on age. One difference across the models related to the identification of a policy of vaccinating higher-risk adults over the age of 65 years as potentially cost-effective only using the Pfizer model. Using the other two models, this policy option was extendedly dominated, as there were alternative policy options that provided better value for money. This difference is likely due to how the models use age-varying data. Although the assumption in the PHAC and GSK models of constant values across each age grouping aligns more closely with source data, the age gradient assumptions used by the Pfizer model may be considered more realistic by some decision-makers.

Although most other published economic evaluations of RSV vaccination in older adults to date have focused on age-based strategies only, the general trends observed in our analysis can be compared with other studies. A systematic review of economic evaluations of RSV vaccines in adults, conducted in the United States and Hong Kong, found that in most studies vaccination programs offered to all adults aged 60 or 65 years and older were unlikely to be cost-effective using a $50,000/QALY threshold, unless there was a substantial reduction in vaccine price (21). As with our analysis, studies that considered multiple age cutoffs for vaccination programs found that ICERs were lower when programs were more restrictive with respect to age eligibility (14,22). A recent Canadian economic evaluation examined policies offering vaccine to residents of long-term care homes alone or alongside age-based vaccination of community dwelling adults (23). This study used a threshold analysis to identify the maximum vaccine price at which vaccination would be cost-effective for a $50,000/QALY threshold and found that higher vaccine prices were acceptable for vaccination strategies restricted to residents of long-term care homes, where the risk of RSV disease is highest. The maximum acceptable vaccine price was reduced as age eligibility for community-dwelling adults was expanded to younger ages (23).

This analysis has some limitations which must be considered when interpreting our results. All models included in our comparison were static models and did not consider indirect effects of vaccination programs. As a result, these models may underestimate the potential cost and QALY savings of these

**Table 4: Sequential incremental cost-effectiveness ratios ($/quality-adjusted life year) comparing only age-based strategies and assuming vaccine protection wanes within two years[a,b]**

| Policy | Arexvy | | | Abrysvo | | |
|---|---|---|---|---|---|---|
| | PHAC | GSK | Pfizer | PHAC | GSK | Pfizer |
| No vaccination | - | - | - | - | - | - |
| 80 years of age and older at AR and HR | $5,391 | $6,194 | $5,883 | $3,261 | $4,838 | $3,161 |
| 75 years of age and older at AR and HR | $82,326 | $85,805 | $53,205 | $78,637 | $82,607 | $50,090 |
| 70 years of age and older at AR and HR | $99,045 | $100,332 | $100,829 | $94,264 | $96,651 | $96,496 |
| 65 years of age and older at AR and HR | Extended dominated | | $136,241 | Extended dominated | | $131,165 |
| 60 years of age and older at AR and HR | $172,061 | $172,531 | $201,336 | $167,226 | $167,515 | $194,749 |

Abbreviations: Abrysvo, respiratory syncytial virus vaccine manufactured by Pfizer; AR, average risk; Arexvy, respiratory syncytial virus vaccine manufactured by GSK; HR, high risk; PHAC, Public Health Agency of Canada; -, not applicable

[a] Incremental cost-effectiveness ratio is calculated relative to the strategy in the preceding row

[b] Results are shown for each model and using data for either the Arexvy or Abrysvo vaccines

programs, leading to the identification of less expansive policy options as optimal. Second, we did not conduct an analysis using the societal perspective and did not consider the possible impact of vaccination for the prevention of non-medically attended RSV disease; our findings may underestimate the benefits of vaccination programs. Finally, we limited our analysis to a small number of scenarios and did not conduct sensitivity analyses. However, given the consistency of our results across the models, the value of further exploration of the impact of parameter uncertainty is likely small for this comparative analysis.

### Conclusion

The multi-model comparison shows that RSV vaccination programs are likely cost-effective for some subgroups of older Canadian adults, particularly those with CMCs that place them at increased risk of RSV disease. These findings are robust to alternate model structural assumptions.

## Authors' statement

MR — Conceptualization, formal analysis, writing–original draft
AES — Conceptualization, writing–review & editing
GBG — Conceptualization, writing–review & editing
ART — Conceptualization, writing–review & editing

### Competing interests

None.

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# Appendix

**Table A1: Model input parameters from Tuite *et al.*, 2024 (6) used in the present analysis**

| Parameter | Base | Range | Reference |
|---|---|---|---|
| **Population distribution (%)** | | | |
| 50–59 years | 31.7 | - | Statistics Canada (12) |
| 60–64 years | 17.5 | - | |
| 65–69 years | 15.8 | - | |
| 70–74 years | 12.8 | - | |
| 75–79 years | 9.9 | - | |
| 80+ years | 12.2 | - | |
| **% of population with one or more CMCs** | | | |
| 50–59 years | 38.4 | - | Statistics Canada (13) |
| 60–79 years | 60.1 | - | |
| 80+ years | 72.1 | - | |
| **Monthly % of annual RSV cases** | | | |
| September | 1.2 | - | Respiratory Virus Detection Surveillance System (average of 9 seasons, 2010–2011 to 2018–2019) (20) |
| October | 1.9 | - | |
| November | 5.5 | - | |
| December | 14.2 | - | |
| January | 17.6 | - | |
| February | 21.1 | - | |
| March | 17.0 | - | |
| April | 11.0 | - | |
| May | 5.6 | - | |
| June | 2.6 | - | |
| July | 1.3 | - | |
| August | 1.1 | - | |
| **Odds ratio for medically-attended outpatient care in adults with one or more CMCs** | | | |
| All ages | 1.1 | - | Shi *et al.*, 2022 (24) |
| **% of patients requiring hospitalization with one or more CMCs** | | | |
| All ages | 98.2 | - | ElSherif *et al.*, 2023 (2) |
| **Under-detection factor for medically-attended RSV in adults** | | | |
| All ages | 1.5 | 1–2 | McLaughlin *et al.*, 2022 (4) |

**Table A1: Model input parameters from Tuite *et al.*, 2024 (6) used in the present analysis (*continued*)**

| Parameter | Base | Range | Reference |
|---|---|---|---|
| **Annual incidence of medically-attended RSV requiring outpatient healthcare provider visit per 100,000 population (unadjusted for under-detection)** | | | |
| 50–59 years | 261.9 | 186.5–337.3 | ElSherif *et al.*, 2023 (2); McLaughlin *et al.*, 2022 (4); Respiratory Virus Detection Surveillance System (20) |
| 60–69 years | 604.1 | 472.8–707.8 | |
| 70–79 years | 780.0 | 625.1–934.1 | |
| 80+ years | 2,487.1 | 2,097.1–2,877.2 | |
| **Annual incidence of medically-attended RSV requiring emergency department visit per 100,000 population (unadjusted for under-detection)** | | | |
| 50–59 years | 16.8 | 12.0–21.6 | ElSherif *et al.*, 2023 (2); McLaughlin *et al.*, 2022 (4); Respiratory Virus Detection Surveillance System (20) |
| 60–69 years | 43.3 | 33.9–50.7 | |
| 70–79 years | 68.5 | 54.9–82.0 | |
| 80+ years | 218.3 | 184.1–252.5 | |
| **Annual incidence of RSV-attributable hospitalization per 100,000 population (unadjusted for under-detection)** | | | |
| 50–59 years | 15.1 | 10.8–19.5 | ElSherif *et al.*, 2023 (2); Respiratory Virus Detection Surveillance System (20) |
| 60–69 years | 47.5 | 37.2–55.7 | |
| 70–79 years | 96.4 | 77.3–115.4 | |
| 80+ years | 307.4 | 259.2–355.6 | |
| **% of patients hospitalized with RSV requiring ICU admission** | | | |
| All ages | 13.7 | 10.2–17.9 | ElSherif *et al.*, 2023 (2) |
| **% of patients with medically attended RSV prescribed an antimicrobial** | | | |
| All ages | 50 | 14–89 | Bernardo *et al.*, 2019 (25); ElSherif *et al.*, 2023 (2) |
| **RSV mortality per hospitalization (%)** | | | |
| 50–64 years | 7.2 | 5.4–9.5 | Chen *et al.*, 2024 (26) |
| 65–74 years | 6.6 | 5.2–8.4 | |
| 75+ years | 10.1 | 9.0–11.3 | |
| **All-cause mortality rate (per year, per 1,000 population)** | | | |
| All ages | Age-specific rates | - | Statistics Canada (27) |
| **Immunization coverage (%), with CMCs** | | | |
| 50–59 years | 58.6 | - | Seasonal Influenza Vaccination Coverage Survey, 2022–2023 (28) |
| 60–64 years | 59.9 | - | |
| 65–69 years | 65.2 | - | |
| 70–79 years | 82.7 | - | |
| 80+ years | 83.4 | - | |
| **Immunization coverage (%), without CMCs** | | | |
| 50–59 years | 36.7 | - | Seasonal Influenza Vaccination Coverage Survey 2022–2023 (28) |
| 60–64 years | 49.4 | - | |
| 65–69 years | 61.1 | - | |
| 70–79 years | 74.9 | - | |
| 80+ years | 74.8 | - | |
| **Vaccine effectiveness (%), Arexvy (GSK)** | | | |
| Outpatient RSV — season 1 (7-month follow-up) | 82.6 | - | Friedland, 2023 (17); Ison *et al.*, 2024 (18); assumption for season 3 |
| Outpatient RSV — season 2 (6-month follow-up) | 56.1 | - | |
| Outpatient RSV — season 3 | 18.7 | - | |
| Hospitalized RSV — season 1 (7-month follow-up) | 94.1 | - | |
| Hospitalized RSV — season 2 (6-month follow-up) | 64.2 | - | |
| Hospitalized RSV — season 3 | 21.4 | - | |

**Table A1: Model input parameters from Tuite *et al.*, 2024 (6) used in the present analysis (*continued*)**

| Parameter | Base | Range | Reference |
|---|---|---|---|
| **Vaccine effectiveness (%), Abrysvo (Pfizer)** | | | |
| Outpatient RSV — season 1 (7-month follow-up) | 65.1 | - | Gurtman, 2023 (19); assumption for season 3 |
| Outpatient RSV — season 2 (4-month follow-up) | 48.9 | - | |
| Outpatient RSV — season 3 | 16.3 | - | |
| Hospitalized RSV — season 1 (7-month follow-up) | 88.9 | - | |
| Hospitalized RSV — season 2 (4-month follow-up) | 78.6 | - | |
| Hospitalized RSV — season 3 | 26.2 | - | |
| **Vaccine wastage rate (%)** | | | |
| All ages | 5 | - | WHO, 2019 (29) |
| **Adverse events following immunization (%)** | | | |
| Severe local adverse event | 0.51 | 0.16–1.84 | Melgar *et al.*, 2023 (30) |
| Severe systemic adverse event | 0.57 | 0.10–2.35 | |
| **Cost of vaccine administration per dose ($)** | | | |
| All ages | 18 | 13–22 | O'Reilly *et al.*, 2017 (31) |
| **Immunization cost per dose ($)** | | | |
| Arexvy (GSK) | 230 | 100–230 | Robertson, 2023 (32) |
| Abrysvo (Pfizer) | 230 | 100–230 | |
| **Attributable costs per person hospitalized with RSV ($)** | | | |
| Hospitalization (6 months) | 32,228 | 31,622–32,836 | Mac *et al.*, 2023 (3) |
| Hospitalization, dying in hospital | 27,534 | 22,027–33,041[a] | |
| **Costs per person with RSV treated in the outpatient setting ($)** | | | |
| Healthcare provider visit | 62 | 48–82 | Sander *et al.*, 2010 (33); CIHI (34); Alliance for Healthier Communities (35) |
| ED visit | 340 | 302–509 | |
| **Direct medical costs for severe local adverse event following vaccination ($)** | | | |
| <65 years | 62 | 48–82 | Sander *et al.*, 2010 (33); CIHI (34); Lee *et al.*, 2009 (36) |
| 65+ years | 63 | 49–83 | |
| **Direct medical costs for severe systemic adverse event following vaccination ($)** | | | |
| <65 years | 62 | 48–82 | Sander *et al.*, 2010 (33); CIHI (34); Lee *et al.*, 2009 (36) |
| 65+ years | 66 | 51–87 | |
| **Transportation costs ($)** | | | |
| Cost of travel to inpatient care | 417 | 210–623 | NACI (37) |
| **Background health utility** | | | |
| 50–59 years | 0.848 | - | Yan *et al.*, 2023 (38) |
| 60–64 years | 0.839 | - | |
| 65–74 years | 0.867 | - | |
| 75+ years | 0.861 | - | |
| **QALY loss, outpatient, with or without ED visit** | | | |
| All ages | 0.0056 | 0.0037–0.0075 | Herring *et al.*, 2022 (39); Mao *et al.*, 2022 (40); Zeevat *et al.*, 2022 (41); Meijboom *et al.*, 2013 (42) |
| **QALY loss, hospitalization** | | | |
| All ages | 0.020 | 0.017–0.030 | Herring *et al.*, 2022 (39); Mao *et al.*, 2022 (40); Zeevat *et al.*, 2022 (41); Meijboom *et al.*, 2013 (42) |

**Table A1: Model input parameters from Tuite *et al.*, 2024 (6) used in the present analysis (*continued*)**

| Parameter | Base | Range | Reference |
|---|---|---|---|
| **QALY loss, death** | | | |
| 50–59 years | 20.26 | - | Yan *et al.*, 2023 (38); Statistics Canada (27,43) |
| 60–64 years | 16.74 | - | |
| 65–69 years | 14.29 | - | |
| 70–74 years | 11.75 | - | |
| 75–79 years | 9.38 | - | |
| 80+ years | 5.84 | - | |
| **QALY loss, adverse event following vaccination** | | | |
| Serious local adverse event | 0.0003 | 0.0002–0.0004 | Prosser, 2023 (44); assumption |
| Serious systemic adverse event | 0.0004 | 0.0003–0.0005 | |

Abbreviations: CIHI, Canadian Institute for Health Information; CMC, chronic medical condition; ED, emergency department; ICU, intensive care unit; NACI, National Advisory Committee on Immunization; QALY, quality-adjusted life year; RSV, respiratory syncytial virus; WHO, World Health Organization; -, not applicable
[a] Range defined as ±20% of the base value

# Comparison of 13-, 15- and 20-valent pneumococcal conjugate vaccines in the paediatric Canadian population: A cost-utility analysis

Alison E Simmons[1,2], Gebremedhin B Gebretekle[1], Robert Pless[1], Aleksandra Wierzbowski[1], Matthew Tunis[1], Ashleigh R Tuite[1,2]*

## Abstract

**Background:** Two pneumococcal conjugate vaccines, covering 15 and 20 *Streptococcus pneumoniae* serotypes (Pneu-C-15 and Pneu-C-20, respectively), were recently approved for use in the Canadian paediatric population.

**Objective:** To assess the cost-effectiveness of Pneu-C-15 and Pneu-C-20 in unvaccinated infants initiating routine pneumococcal vaccination, compared to the currently used 13-valent conjugate vaccine (Pneu-C-13).

**Methods:** A static cohort model was used to estimate sequential incremental cost-effectiveness ratios (ICERs in 2022 Canadian dollars per quality-adjusted life year [QALY]) of Pneu-C-13, Pneu-C-15 and Pneu-C-20 in the paediatric population starting their primary series. Costs and outcomes were calculated over a 10-year time horizon at the program level and a lifetime time horizon at the individual level and discounted at a rate of 1.5% per year. We explored the impact of uncertainties in model parameters and assumptions in scenario and sensitivity analyses.

**Results:** Routine use of Pneu-C-20 and, to a lesser extent, Pneu-C-15 is projected to reduce pneumococcal disease burden, compared to Pneu-C-13. Based on product cost assumptions, sequential ICERs for Pneu-C-15 and Pneu-C-20 were $58,800 and $135,200 per QALY gained from the health system perspective and $18,272 and $93,416 per QALY gained from the societal perspective, excluding indirect effects. A reduction in serotype-attributable disease due to indirect vaccine effects of 5% or greater resulted in ICERs below $30,000 per QALY gained for Pneu-C-15 and Pneu-C-20, with the optimal strategy determined by the magnitude and time to reach a reduction in pneumococcal disease.

**Conclusion:** Both Pneu-C-15 and Pneu-C-20 are expected to increase QALYs in Canadian children compared to Pneu-C-13 and may be cost-effective interventions.



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## Introduction

Pneumococcal disease (PD), caused by *Streptococcus pneumoniae*, causes significant global morbidity and mortality, particularly in children, older adults and people with immunocompromising conditions. Although *S. pneumoniae* frequently colonizes the human nasopharynx without causing illness, it can cause severe invasive (e.g., meningitis and bacteremia) and, more commonly, non-invasive (e.g., pneumococcal community acquired pneumonia [pCAP] and acute otitis media [AOM]) disease (1). More than 100 distinct capsular types, or serotypes, of *S. pneumoniae* have been identified, but the majority of invasive pneumococcal disease (IPD) cases are attributed to a subset of these serotypes (2,3).

Infectious disease modelling is often used to support pneumococcal vaccine decisions due to complex serotype dynamics observed over years under previous vaccination schedules. In the early 2000s, the first pneumococcal conjugate vaccines (Pneu-C-7 and Pneu-C-10) were authorized for use in Canada and were provided in publicly funded immunization programs. In 2009, Pneu-C-13 vaccine received approval and in 2010, Canada's National Advisory Committee on Immunization (NACI) recommended that healthy children receive 2+1 doses of Pneu-C-13 at two, four and 12–15 months of age or 3+1 doses of Pneu-C-13 at two, four, six and 12–18 months of age (4). The Pneu-C-13 vaccine consists of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F. Two pneumococcal conjugate vaccines, covering 15 and 20 *S. pneumoniae* serotypes, were authorized by Health Canada for use in paediatric populations on July 8, 2022 (Pneu-C-15) and July 21, 2023 (Pneu-C-20). The Pneu-C-15 vaccine includes Pneu-C-13 serotypes as well as serotypes 22F and 33F, and Pneu-C-20 includes Pneu-C-13 serotypes as well as serotypes 8, 10A, 11A, 12F, 15B, 22F and 33F (5,6).

Following the introduction of Pneu-C-13, the incidence of IPD caused by the 13 *S. pneumoniae* serotypes included in the vaccine decreased across all age groups (7–9); however, overall IPD incidence remained relatively unchanged across all age groups due to *S. pneumoniae* serotype replacement as well as persistence of some Pneu-C-13 serotypes (10,11). Between 2016 and 2020, a significant increase in IPD caused by serotypes 19F and 11A was observed among children younger than five years old in Canada (12). Serotype 19F is included in Pneu-C-13, Pneu-C-15 and Pneu-C-20, and serotype 11A is included only in Pneu-C-20.

Given the broader serotype coverage provided by Pneu-C-15 and Pneu-C-20, we conducted a model-based economic evaluation to assess the cost-effectiveness of their use in the Canadian paediatric population compared to the current standard of care.

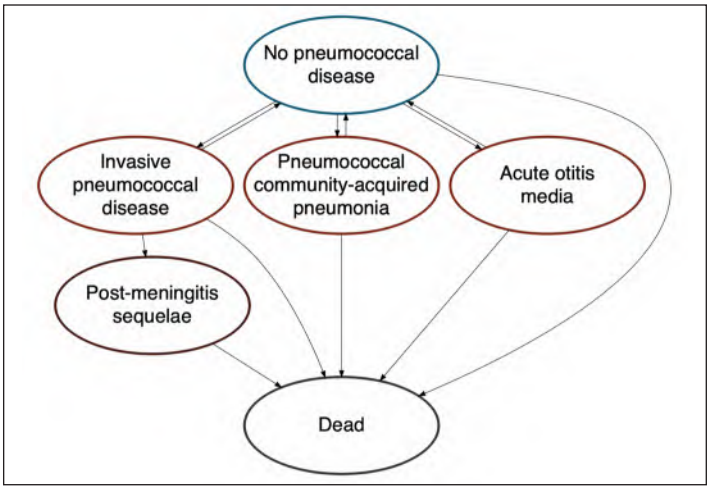
# Methods

We developed a static Markov cohort model to quantify the health impact of three paediatric pneumococcal vaccination strategies in previously unvaccinated infants. We compared 2+1 doses of Pneu-C-13 (current policy), Pneu-C-15 and Pneu-C-20. *Streptococcus pneumoniae*-associated health outcomes from the cohort model were used to inform a cost-utility analysis. Outcomes included the incidence of IPD, non-invasive pCAP and AOM, hospitalizations, deaths, costs, quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs). At the time of the analysis, NACI had not yet published recommendations for the use of Pneu-C-15 and Pneu-C-20 in the paediatric population. This economic analysis was conducted to support the development of NACI's recommendations and additional details of the economic evidence considered are available online (13).

## Model structure

Our model followed a multi-age, open population cohort over 10 years. Birth and death rates within the cohort were informed by Canadian population projections (14–16). Individuals were free of PD at model entry, but could develop IPD, pCAP and AOM over their lifetime (**Figure 1**, **Table 1**). A subset of individuals with IPD developed post-meningitis sequelae. We assumed IPD was treated in an inpatient setting, pCAP was treated in an inpatient or outpatient setting and AOM was treated in an outpatient setting. Incidence, costs and health consequences of AOM were restricted to individuals younger than 10 years of age (17).

**Figure 1: Pneumococcal disease model health states[a,b]**




[a] Vaccinated and unvaccinated people experienced the same health states, with risk modified based on vaccination status, type of vaccine received and time since vaccination
[b] Post-meningitis sequelae include auditory and neurologic sequelae

**Table 1: Epidemiologic parameters**

| Parameter | Base | Range | Reference(s) |
|---|---|---|---|
| **IPD incidence (per 100,000 population)** | | | |
| Younger than 2 years | 14.5 | - | CNDSS, 2019; ICS program, 2019 (18) |
| 2–4 years | 10.2 | - | |
| 5–17 years | 2.1 | - | |
| 18–49 years | 5.2 | - | |
| 50–64 years | 13.6 | - | |
| 65 years and older | 23.8 | - | |
| **CAP incidence (per 100,000 population)** | | | |
| Younger than 5 years | 4,991.1 | - | Nasreen *et al.*, 2022 (19) |
| 5–17 years | 1,249.0 | - | |
| 18–39 years | 815.9 | - | |
| 40–64 years | 1,529.9 | - | |
| 65–74 years | 3,095.7 | - | |
| 75–84 years | 5,398.1 | - | |
| 85 years and older | 10,122.7 | - | |

**Table 1: Epidemiologic parameters (*continued*)**

| Parameter | Base | Range | Reference(s) |
|---|---|---|---|
| **AOM incidence (per 100,000 population)** | | | |
| Younger than 5 years | 25,467.6 | - | Nasreen *et al.*, 2022 (19) |
| 5–17 years | 7,225.9 | - | |
| 18–39 years | 2,204.4 | - | |
| 40–64 years | 2,058.6 | - | |
| 65–74 years | 1,954.7 | - | |
| 75–84 years | 1,857.4 | - | |
| 85 years and older | 1,621.4 | - | |
| **Relative risk of PD in higher incidence setting** | | | |
| Younger than 2 years | 6.8 | - | CNDSS, 2019; ICS program, 2015–2019 (18) |
| 2–4 years | 0.9 | - | |
| 5–17 years | 3.9 | - | |
| 18–49 years | 2.1 | - | |
| 50–64 years | 2.1 | - | |
| 65 years and older | 2.4 | - | |
| **Proportion of patients with CAP attributed to *S. pneumoniae* (%)** | | | |
| Younger than 1 year | 6.0 | 5.1–9.1 | King, 2023; LeBlanc *et al.*, 2022; Pneumonia Etiology Research for Child Health (PERCH) Study Group, 2019 (20–22) |
| 1–15 years | 12.0 | 10.1–18.2 | |
| 16–49 years | 19.5 | 17.3–21.7 | |
| 50–64 years | 19.0 | 17.3–20.7 | |
| 65 years and older | 11.2 | 10.4–12.1 | |
| **Proportion of patients with AOM attributed to *S. pneumoniae* (%)** | | | |
| Younger than 18 years | 17 | 14–22 | Kim *et al.*, 2017; King, 2023 (20,23) |
| **Proportion of patients with pCAP managed in inpatient setting (%)** | | | |
| Younger than 65 years | 4.6 | 2.2–9.3 | O'Reilly *et al.*, 2023 (24) |
| 65 years and older | 12.3 | 7.9–18.6 | |
| **Proportion of patients with IPD with meningitis (%)** | | | |
| Younger than 1 year | 16.9 | 13.3–21.1 | Morrow *et al.*, 2007 (17) |
| 1–4 years | 4.6 | 3.0–6.8 | |
| 5–9 years | 8.7 | 4.1–15.9 | |
| 10–19 years | 8.5 | 5.1–13.3 | |
| 20–64 years | 5.1 | 3.9–6.4 | |
| 65 years and older | 3.1 | 2.2–4.1 | |
| **Proportion of patients with meningitis with long-term post-meningitis sequelae (%)** | | | |
| Neurologic sequelae | 12.2 | 5.3–19.1 | Jit, 2010 (25) |
| Hearing loss | 8.2 | 4.5–11.9 | |
| **Proportion of patients with AOM with ear tube placement (%)** | | | |
| Younger than 10 years | 6 | 4–12 | Canadian Institute for Health Information, 2020; Chuck *et al.*, 2010; Nasreen *et al.*, 2022; Assumption (19,26,27) |
| **IPD case fatality (%)** | | | |
| Younger than 1 year | 11.8 | 11.2–12.3 | Wijayasri *et al.*, 2019 (7) |
| 1–4 years | 1.6 | 0.8–2.7 | |
| 5–49 years | 5.7 | 4.9–6.7 | |
| 50–64 years | 10.9 | 9.9–12 | |
| 65 years and older | 17.2 | 16.2–18.3 | |

**Table 1: Epidemiologic parameters (*continued*)**

| Parameter | Base | Range | Reference(s) |
|---|---|---|---|
| **pCAP (inpatient) case fatality (%)** | | | |
| Younger than 10 years | 1.0 | 0.3–3.1 | LeBlanc *et al.*, 2022; Morrow *et al.*, 2007; Assumption (17,22) |
| 10–15 years | 1.6 | 0.6–4.3 | |
| 16–49 years | 3.8 | 1.7–7.0 | |
| 50–64 years | 4.8 | 2.7–7.1 | |
| 65 years and older | 9.9 | 7.7–12.3 | |
| **Vaccine-type serotype distribution (%), younger than 2 years** | | | |
| ST3 | 8 | - | National Microbiology Laboratory, 2019 (18) |
| Pneu-C-13/non-ST3 | 9 | - | |
| Pneu-C-15/non-Pneu-C-13 | 21 | - | |
| Pneu-C-20/non-Pneu-C-15 | 19 | - | |
| NVT | 43 | - | |
| **Vaccine-type serotype distribution (%), 2–4 years** | | | |
| ST3 | 11 | - | National Microbiology Laboratory, 2019 (18) |
| Pneu-C-13/non-ST3 | 16 | - | |
| Pneu-C-15/non-Pneu-C-13 | 16 | - | |
| Pneu-C-20/non-Pneu-C-15 | 23 | - | |
| NVT | 33 | - | |
| **Vaccine-type serotype distribution (%), 5–17 years** | | | |
| ST3 | 8 | - | National Microbiology Laboratory, 2019 (18) |
| Pneu-C-13/non-ST3 | 23 | - | |
| Pneu-C-15/non-Pneu-C-13 | 20 | - | |
| Pneu-C-20/non-Pneu-C-15 | 14 | - | |
| NVT | 35 | - | |
| **Vaccine-type serotype distribution (%), 18–49 years** | | | |
| ST3 | 10 | - | National Microbiology Laboratory, 2019 (18) |
| Pneu-C-13/non-ST3 | 32 | - | |
| Pneu-C-15/non-Pneu-C-13 | 11 | - | |
| Pneu-C-20/non-Pneu-C-15 | 21 | - | |
| NVT | 26 | - | |
| **Vaccine-type serotype distribution (%), 50–64 years** | | | |
| ST3 | 12 | - | National Microbiology Laboratory, 2019 (18) |
| Pneu-C-13/non-ST3 | 32 | - | |
| Pneu-C-15/non-Pneu-C-13 | 11 | - | |
| Pneu-C-20/non-Pneu-C-15 | 21 | - | |
| NVT | 26 | - | |

**Table 1: Epidemiologic parameters (*continued*)**

| Parameter | Base | Range | Reference(s) |
|---|---|---|---|
| **Vaccine-type serotype distribution (%), 65 years and older** | | | |
| ST3 | 13 | - | National Microbiology Laboratory, 2019 (18) |
| Pneu-C-13/non-ST3 | 16 | - | |
| Pneu-C-15/non-Pneu-C-13 | 15 | - | |
| Pneu-C-20/non-Pneu-C-15 | 14 | - | |
| NVT | 42 | - | |

Abbreviations: AOM, acute otitis media; CAP, community acquired pneumonia; CNDSS, Canadian Notifiable Disease System; ICS, International Circumpolar Surveillance; IPD, invasive pneumococcal disease; NVT, non-vaccine type; pCAP, pneumococcal community acquired pneumonia; PD, pneumococcal disease; Pneu-C, pneumococcal conjugate vaccine; ST3, serotype 3; -, not applicable

Upon model entry, a proportion of each birth cohort was vaccinated at two, four and 12 months of age, based on estimated Pneu-C-13 vaccination coverage (**Table 2**) (28). Vaccination was assumed to reduce the risk of PD caused by the serotypes included in the vaccine. We assumed vaccine effectiveness (VE) for Pneu-C-15 and Pneu-C-20 was equivalent to VE for Pneu-C-13. All vaccines had a lower VE against serotype 3 compared to the other vaccine serotypes. In the model, vaccine-derived protection began after the second dose and waned over 15 years (29). The base case model did not include indirect effects of vaccination including herd immunity and serotype replacement.

## Cost-utility analysis

We used the outputs from our model to inform a cost-utility analysis of the three vaccination strategies over a 10-year programmatic time horizon. A lifetime time horizon was used at the individual level (i.e., all long-term consequences of PD accrued over an individual's lifetime were included). The assumed cost per dose in our base case was $71.50 for Pneu-C-13, $78.10 for Pneu-C-15 and $90.10 for Pneu-C-20 (**Table 3**). An unpublished analysis conducted by the Public Health Agency of Canada found that Canadian negotiated vaccine prices across all vaccine programs are typically 30%–50% of United States contract prices; we applied a 40% discount rate to the United States' Centers for Disease Control and Prevention public vaccine prices to estimate the cost per dose in our base case (34). Costs and utilities were derived preferentially from Canadian surveillance data and published studies, and by assumption (Table 3, **Table 4**). We applied a discount rate of 1.5% to QALYs and costs, with costs inflated to 2022 Canadian dollars (35). Probabilistic model estimates were based on 10,000 simulations. For each model simulation, parameters were drawn from distributions and results were calculated for each scenario; summary results across the 10,000 simulations were computed. Values with ranges provided in Tables 1–4 indicate model parameters that were sampled probabilistically to capture uncertainty (i.e., sampled from beta distributions for probabilities and utilities and gamma distributions for costs). The model was constructed in R and parameters specifying distributions (shape and scale for gamma distributions and shape1 and shape2 for beta distributions) were estimated using the specified means and ranges (36,37). We conducted our analyses from both the health system and societal perspectives. In addition to including health outcome and health system costs, the latter also incorporates costs not paid by the publicly funded health system (e.g., direct out-of-pocket costs, productivity loss) (38).

**Table 2: Vaccination parameters**

| Parameter | Base | Range | Reference(s) |
|---|---|---|---|
| **Vaccination coverage (%)** | | | |
| 2 doses | 87 | - | Assumption[a] |
| 2+1 doses | 84.5 | - | Childhood National Immunization Coverage Survey (cNICS), 2022 (28) |
| **Pneu-C effectiveness of 2+1 doses (%)** | | | |
| VT-IPD | 85 | 67–96 | Farrar *et al.*, 2022; Prasad *et al.*, 2023; Assumption (29,30) |
| ST3-IPD | 33 | 10–66 | Farrar *et al.*, 2022; Prasad *et al.*, 2023; Assumption (29,30) |
| VT-pCAP | 64 | 50–72 | Prasad *et al.*, 2023; Stoecker, 2023; Assumption (based on adult data for relative VE for IPD vs. pCAP) (29,31) |
| ST3-pCAP | 25 | 19–28 | Assumption (based on IPD) |
| VT-AOM | 54 | 40–64 | Eskola, 2001 (32) |
| ST3-AOM | 21 | 15–25 | Assumption (based on IPD) |
| **Pneu-C effectiveness of 2 doses** | | | |
| % of VE achieved with first 2 doses of series | 75 | 60–90 | Andrews *et al.*, 2014; Assumption (33) |
| **Duration of protection** | | | |
| Pneu-C | 15 years: stable for 5 years, linear decline to 0 over 10 years | - | Prasad *et al.*, 2023 (29) |

Abbreviations: IPD, invasive pneumococcal disease; pCAP, pneumococcal community acquired pneumonia; Pneu-C, pneumococcal conjugate vaccine; ST3-AOM, serotype 3 acute otitis media; ST3-IPD, serotype 3 invasive pneumococcal disease; ST3-pCAP, serotype 3 pneumococcal community acquired pneumonia; VE, vaccine effectiveness; VT-AOM, vaccine-type acute otitis media; VT-IPD, vaccine-type invasive pneumococcal disease; VT-pCAP, vaccine-type pneumococcal community acquired pneumonia; -, not applicable

[a] Based on diphtheria, tetanus and acellular pertussis (DTaP) coverage at 3 months (1 or more doses) and 12 months (3 or more doses) (28)

**Table 3: Direct and indirect cost parameters**

| Parameter | Base ($) | Range ($) | Reference(s) |
|---|---|---|---|
| **Cost per dose of vaccine** | | | |
| Vaccine administration | 16.77 | 12.58–20.96 | O'Reilly *et al.*, 2017 (39) |
| Pneu-C-13 | 71.5 | - | Centers for Disease Control and Prevention; Assumption (34) |
| Pneu-C-15 | 78.1 (9.2% higher than Pneu-C-13) | 72.2–87.9 (1%–23% higher than Pneu-C-13) | |
| Pneu-C-20 | 90.1 (26.1% higher than Pneu-C-13) | 78.6–107.2 (10%–50% higher than Pneu-C-13) | |
| **Cost per patient with IPD** | | | |
| Younger than 5 years | 20,468 | 17,422–23,755 | Discharge Abstract Database, 2015–2019 (40–43) |
| 5–17 years | 14,717 | 12,510–17,100 | |
| 18–49 years | 28,812 | 26,559–31,155 | |
| 50–64 years | 29,146 | 27,363–30,984 | |
| 65–74 years | 28,955 | 26,727–31,271 | |
| 75 years and older | 21,501 | 20,001–23,054 | |
| **Cost per patient with pCAP managed in inpatient setting** | | | |
| Younger than 18 years | 7,345 | 7,189–7,545 | O'Reilly *et al.*, 2023 (24) |
| 18–64 years | 14,185 | 13,708–14,686 | |
| 65 years and older | 14,179 | 13,931–14,433 | |
| **Cost per patient with pCAP managed in outpatient setting** | | | |
| Younger than 18 years | 450 | 438–461 | O'Reilly *et al.*, 2023 (24) |
| 18–64 years | 1,187 | 1,154–1,221 | |
| 65 years and older | 3,343 | 3,283–3,400 | |
| **Cost per AOM case, excluding ear tube placement** | | | |
| Younger than 2 years | 260 | 258–301 | Gaboury *et al.*, 2010; Assumption (44) |
| 2–9 years | 178 | 148–207 | |
| Cost of surgery for ear tube placement | 1,790 | 1,340–2,240[a] | Canadian Institute for Health Information, 2020 (26) |
| **Cost of care for patients with post-meningitis sequelae (per year)** | | | |
| Annual cost of care for those with auditory sequelae | 2,783.3 | 2,087.5–3,479.2[a] | Christensen *et al.*, 2014 (45) |
| Annual cost of care for those with neurologic sequelae | 9,262.4 | 6,946.8–11,578.0[a] | |
| **Out-of-pocket costs** | | | |
| Medication, younger than 65 years | 18.1 | 13.6–22.6 | American Academy of Pediatrics, 2021; Metlay *et al.*, 2019; Ontario Ministry of Health, 2022; Patented Medicine Prices Review Board Canada, 2019–2020 (46–49) |
| Transportation to inpatient care | 139 | 29–333 | Canada Revenue Agency, 2022; Colbert, 2020; Discharge Abstract Database, 2015–2019 (40–43,50,51) |
| Transportation to outpatient care | 3.7 | 2.8–4.6[a] | Canada Revenue Agency, 2022; Pong and Pitblado, 2005 (51,52) |
| **Relative increase of direct costs in higher cost setting** | | | |
| Inpatient case | 1.8 | - | NACI (53) |
| Outpatient case | 1.2 | - | |
| Travel for outpatient case | 33 | - | |
| **Workdays lost (16 years and older)** | | | |
| Inpatient IPD or pCAP | 15 | 9–29 | Pasquale *et al.*, 2019 (54) |
| Outpatient pCAP | 5.4 | 1.8–6.3 | |

**Table 3: Direct and indirect cost parameters (*continued*)**

| Parameter | Base ($) | Range ($) | Reference(s) |
|---|---|---|---|
| **Reduction in employment in patients with post-meningitis sequelae (%)** | | | |
| Auditory sequelae | 25 | 15–35 | Bizier *et al.*, 2016; Jiang *et al.*, 2012 (55,56) |
| Neurologic sequelae | 98 | 75–100 | Jiang *et al.*, 2012; Assumption (56) |
| **Caregiver workdays lost, IPD** | | | |
| Younger than 5 years | 11.2 | 9.4–13.0 | Discharge Abstract Database, 2015–2019 (40–43) |
| 5–15 years | 9.9 | 7.8–12.0 | |
| 16 years and older | 5.4 | 1.5–10.8 | Wyrwich *et al.*, 2015 (57) |
| **Caregiver workdays lost, inpatient pCAP** | | | |
| Younger than 5 years | 4.2 | 4.2–4.3 | Discharge Abstract Database, 2015–2019 (40–43) |
| 5–15 years | 5.0 | 7.8–12.0 | |
| 16 years and older | 5.4 | 1.5–10.8 | Wyrwich *et al.*, 2015 (57) |
| **Caregiver work days lost, outpatient pCAP** | | | |
| Younger than 16 years | 5.4 | 1.8–6.3 | Pasquale *et al.*, 2019; Assumption (54) |
| 16 years and older | 1.1 | 1.0–1.2 | Dubé *et al.*, 2011 (58) |
| **Caregiver work days lost, AOM** | | | |
| AOM | 1.3 | 0.8–1.7 | Barber *et al.*, 2014; Dubé *et al.*, 2011 (58,59) |
| Ear tube placement | 2.1 | - | Petit *et al.*, 2003 (60) |
| **Caregiver work days lost, sequelae** | | | |
| Auditory sequelae (annual) | 0 | - | Assumption |
| Neurologic sequelae (annual) | 190 | 146–240[a] | Ganapathy *et al.*, 2015 (61) |
| **Caregiver work days lost, vaccination** | | | |
| Visit healthcare provider for vaccination | 0.5 | - | Assumption |
| **Average employment income ($)** | | | |
| Age 16 years and older | Age-specific values | - | Statistics Canada (62) |
| Caregiver | 58,811 | - | |
| **Labour force participation (%)** | | | |
| Age 16 years and older | Age-specific values | - | Statistics Canada (63) |
| Caregiver (age 25–54 years) | 87 | - | |

Abbreviations: AOM, acute otitis media; IPD, invasive pneumococcal disease; NACI, National Advisory Committee on Immunization; pCAP, pneumococcal community acquired pneumonia; Pneu-C, pneumococcal conjugate vaccine; -, not applicable
[a] Range defined as ±25% of the base value

**Table 4: Health utilities and utility decrements**

| Parameter | Base | Range | Reference(s) |
|---|---|---|---|
| **Background health utility** | | | |
| Younger than 6 years | 0.97 | 0.96–0.98 | Molina *et al.*, 2023; Assumption (64) |
| 6–11 years | 0.95 | 0.94–0.96 | Molina *et al.*, 2023 (64) |
| 12–17 years | 0.89 | 0.87–0.91 | Yan *et al.*, 2023 (65) |
| 18–24 years | 0.879 | 0.863–0.895 | |
| 25–34 years | 0.881 | 0.864–0.898 | |
| 35–44 years | 0.878 | 0.863–0.893 | |
| 45–54 years | 0.855 | 0.838–0.872 | |
| 55–64 years | 0.839 | 0.822–0.856 | |
| 65–74 years | 0.867 | 0.849–0.885 | |
| 75 years and older | 0.861 | 0.835–0.887 | |

**Table 4: Health utilities and utility decrements (*continued*)**

| Parameter | Base | Range | Reference(s) |
|---|---|---|---|
| **IPD utility decrement** | | | |
| Younger than 19 years | 0.028 | 0.0165–0.0308 | Tang *et al.*, 2022; Assumption (66) |
| 19–64 years | 0.0533 | 0.0425–0.0547 | |
| 65 years and older | 0.0745 | 0.0001–0.0745 | |
| **Outpatient pCAP utility decrement** | | | |
| Younger than 19 years | 0.0004 | 0.0001–0.0329 | Tang *et al.*, 2022 (66) |
| 19–64 years | 0.0094 | 0.0001–0.0205 | |
| 65 years and older | 0.0586 | 0.0271–0.0659 | |
| **Inpatient pCAP utility decrement** | | | |
| Younger than 19 years | 0.0105 | 0.001–0.0155 | Tang *et al.*, 2022; Assumption (66) |
| 19–64 years | 0.0396 | 0.0001–0.168 | |
| 65 years and older | 0.1154 | 0.0068–0.29 | |
| **AOM utility decrement** | | | |
| Younger than 10 years | 0.0016 | 0–0.1461 | Tang *et al.*, 2022 (66) |
| **Auditory sequelae utility decrement (per year)** | | | |
| Younger than 19 years | 0.2137 | 0.07–0.72 | Tang *et al.*, 2022 (66) |
| 19 years and older | 0.365 | 0.273–0.418 | Tang *et al.*, 2022; Assumption (66) |
| **Neurologic sequelae utility decrement (per year)** | | | |
| Younger than 19 years | 0.2456 | 0.16–0.49 | Tang *et al.*, 2022 (66) |
| 19 years and older | 0.5278 | 0.22–0.783 | Tang *et al.*, 2022; Assumption (66) |

Abbreviations: AOM, acute otitis media; IPD, invasive pneumococcal disease; pCAP, pneumococcal community acquired pneumonia; Pneu-C, pneumococcal conjugate vaccine

To compare the three vaccination strategies, we conducted a sequential cost-effectiveness analysis (38). In short, the three vaccination strategies were ordered from lowest to highest cost. Incremental costs and QALYs gained were compared between a given strategy and the next less costly strategy. A vaccination strategy was considered dominated if at least one other vaccination strategy was expected to result in additional QALYs gained at a lower cost.

## Scenario and sensitivity analyses

We conducted a scenario analysis to estimate the potential impact of vaccine-derived indirect effects on ICERs by including an exponential decline in PD incidence caused by Pneu-C-15 specific serotypes (i.e., 22F and 33F) and Pneu-C-20 specific serotypes (i.e., 8, 10A, 11A, 12F, 15B, 22F and 33F) across all age groups. We included an exponential decline ranging from 0%–50%, with effects beginning one year after the vaccination program was implemented and taking five to 10 years to reach maximum effect.

We also evaluated the cost-effectiveness of the three vaccination strategies in a higher cost, higher PD incidence setting such as that observed in the circumpolar region (18,67). Age-specific relative risks were calculated by comparing IPD incidence in Yukon, Northwest Territories and Nunavut to all of Canada (including the territories) (18). A relative measure of the increased cost associated with medical care in Yukon, Northwest Territories and Nunavut compared to all of Canada was extracted from an economic analysis of pneumococcal vaccines in older adults (53). We applied these multipliers to *S. pneumoniae*-attributed health outcomes and relevant costs in our base case analysis.

In addition to a probabilistic sensitivity analysis, we conducted deterministic sensitivity analyses to examine the robustness of the base case findings to our assumptions. First, we examined the impact of varying key model parameters in our base case in a one-way sensitivity analysis. Parameters were varied across a range of values (Tables 1–4). Second, given the uncertainty of the prices of Pneu-C-15 and Pneu-C-20, we conducted a two-way sensitivity analysis. We varied the incremental price of Pneu-C-15 and Pneu-C-20 to be up to 50% higher than the assumed price of Pneu-C-13. Third, we lowered the incidence of pCAP and AOM in our model, reflective of data from British Columbia (19); data from Ontario informed our base case analysis. Fourth, we lowered the number of AOM cases projected to be prevented by replacing Pneu-C-13 with Pneu-C-15 or Pneu-C-20. This reflects the lower AOM incidence attributed Pneu-C-15 and Pneu-C-20 vaccine serotypes in the United States (68).

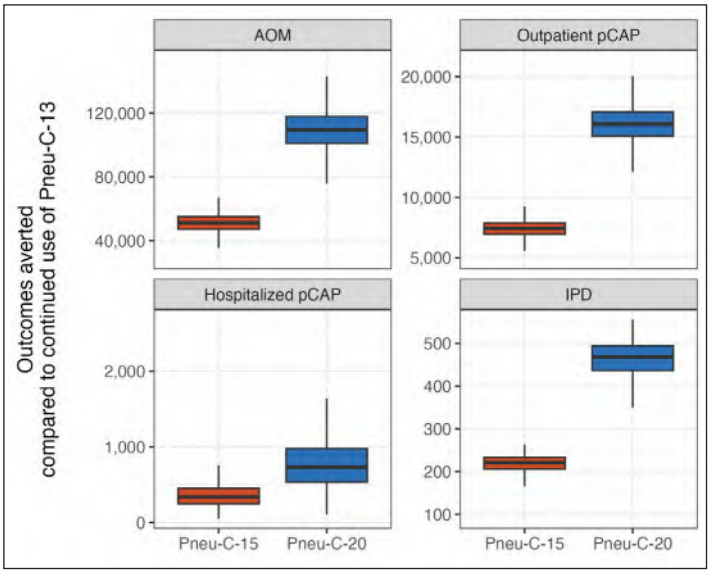
Although Canada does not have a set cost-effectiveness threshold, we used two common thresholds, $30,000 per QALY and $60,000 per QALY, in our scenario and sensitivity analyses for illustrative purposes (69,70).

Our study follows the Professional Society for Health Economics and Outcomes Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) 2022.

## Results

The use of Pneu-C-15 and Pneu-C-20 averted additional *S. pneumoniae*-attributable health outcomes over 10 years compared to the continued use of Pneu-C-13 (**Figure 2**). On average, Pneu-C-15 averted an additional 221 (interquartile range [IQR]: 206–233) IPD cases, 337 (IQR: 533–976) hospitalized pCAP cases, 7,428 (IQR: 6,965–7,885) outpatient pCAP cases and 51,143 (IQR: 47,184–55,089) AOM cases in the Canadian population compared to the continued use of Pneu-C-13 in our base case. The Pneu-C-20 vaccine averted an additional 468 (IQR: 436–494) IPD cases, 730 (IQR: 533–976) hospitalized pCAP cases, 16,084 (IQR: 15,082–17,071) outpatient pCAP cases and 109,527 (IQR: 101,054–117,926) AOM cases compared Pneu-C-13.

**Figure 2: Outcomes averted in all age groups compared to continued use of Pneu-C-13 over 10 years in the base case scenario[a]**




Abbreviations: AOM, acute otitis media; IPD, invasive pneumococcal disease; pCAP, pneumococcal community acquired pneumonia; Pneu-C, pneumococcal conjugate vaccine
[a] Results are shown for 10,000 model simulations

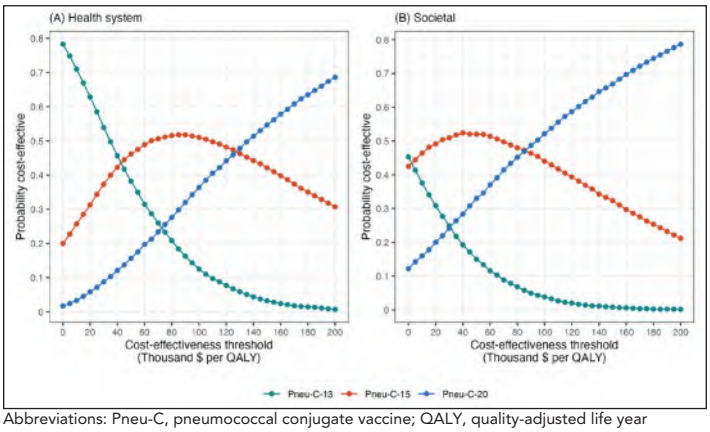
From the health system perspective, replacing Pneu-C-13 with Pneu-C-15 is expected to save an average of 497 QALYs and cost an additional $30 million over 10 years (**Table 5**). Replacing Pneu-C-13 with Pneu-C-20 is expected to save an average of 1,039 QALYs and cost an additional $103 million over ten years. From the societal perspective, Pneu-C-15 is expected to cost an additional $9 million and Pneu-C-20 is expected to cost an additional $60 million over 10 years compared to the continued use of Pneu-C-13. From the health system perspective, Pneu-C-15 is most likely to be the optimal strategy at cost-effectiveness threshold ranges of $43,000 to $127,000 per QALY (**Figure 3**). Above $127,000 per QALY, Pneu-C-20 is most likely to be the optimal strategy. From the societal perspective, Pneu-C-15 is most likely to be the optimal strategy at cost-effectiveness threshold ranges of $3,000 to $86,000 per QALY, and Pneu-C-20 is most likely to be the optimal strategy at thresholds above $86,000 per QALY.

**Table 5: Mean quality-adjusted life years lost, cost and incremental cost-effectiveness ratios for the base case scenario, in the absence of indirect effects**

| Strategy | Effect (QALYs lost) | Cost ($, millions) | Sequential ICER ($/QALY) |
|---|---|---|---|
| **Health system perspective** | | | |
| Pneu-C-13 | 229,769 | 4,945 | - |
| Pneu-C-15 | 229,272 | 4,975 | 58,823 |
| Pneu-C-20 | 228,730 | 5,048 | 135,289 |
| **Societal perspective** | | | |
| Pneu-C-13 | 229,769 | 432,243 | - |
| Pneu-C-15 | 229,272 | 432,252 | 18,272 |
| Pneu-C-20 | 228,730 | 432,303 | 93,416 |

Abbreviations: ICER, incremental cost-effectiveness ratio; Pneu-C, pneumococcal conjugate vaccine; QALY, quality-adjusted life year; -, not applicable

**Figure 3: Percent of simulations for which each vaccination strategy was the optimal strategy for a given cost-effectiveness threshold in the base case from the health system and societal perspectives, in the absence of indirect effects**

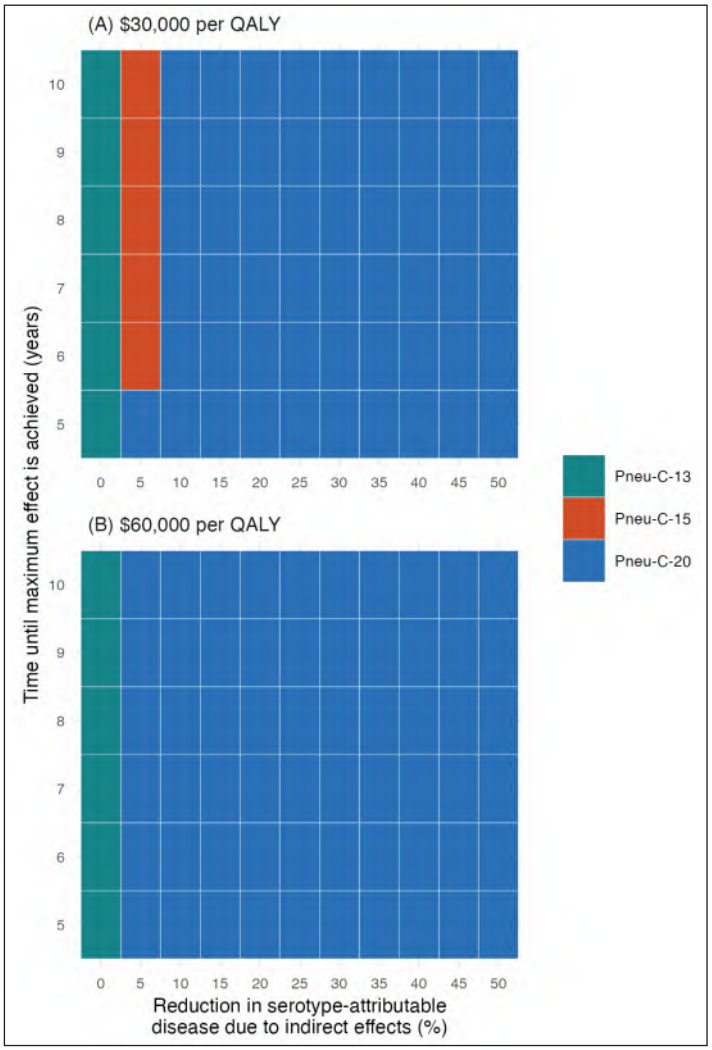



Abbreviations: Pneu-C, pneumococcal conjugate vaccine; QALY, quality-adjusted life year

The inclusion of indirect effects leads to lower ICERs because of the resulting reduction in PD among population members who did not receive the vaccine (**Figure 4**). At a cost-effectiveness threshold of $30,000 per QALY, a 5% reduction in PD caused by the additional serotypes contained in Pneu-C-15 over a six-year period would result in Pneu-C-15 being the optimal strategy. At a cost-effectiveness threshold of $30,000 per QALY, a 10% or greater percent decrease in PD over a five-year period caused by the additional serotypes contained in Pneu-C-20 results in Pneu-C-20 being the preferred strategy. From the societal perspective, even smaller indirect effects would result in Pneu-C-15 or Pneu-C-20 being the optimal strategy.

In a higher cost and higher PD incidence setting, on average, Pneu-C-15 averted an additional 925 (IQR: 859–979) IPD cases, 1,116 (IQR: 855–1,545) hospitalized pCAP cases, 25,638 (IQR: 24,055–27,254) outpatient pCAP cases and 190,760 (IQR: 175,466–205,884) AOM cases on

**Figure 4: Impact of a reduction in serotype-attributable disease due to indirect vaccine effects on the optimal vaccination strategy at $30,000 and $60,000 per QALY from a health system perspective[a]**

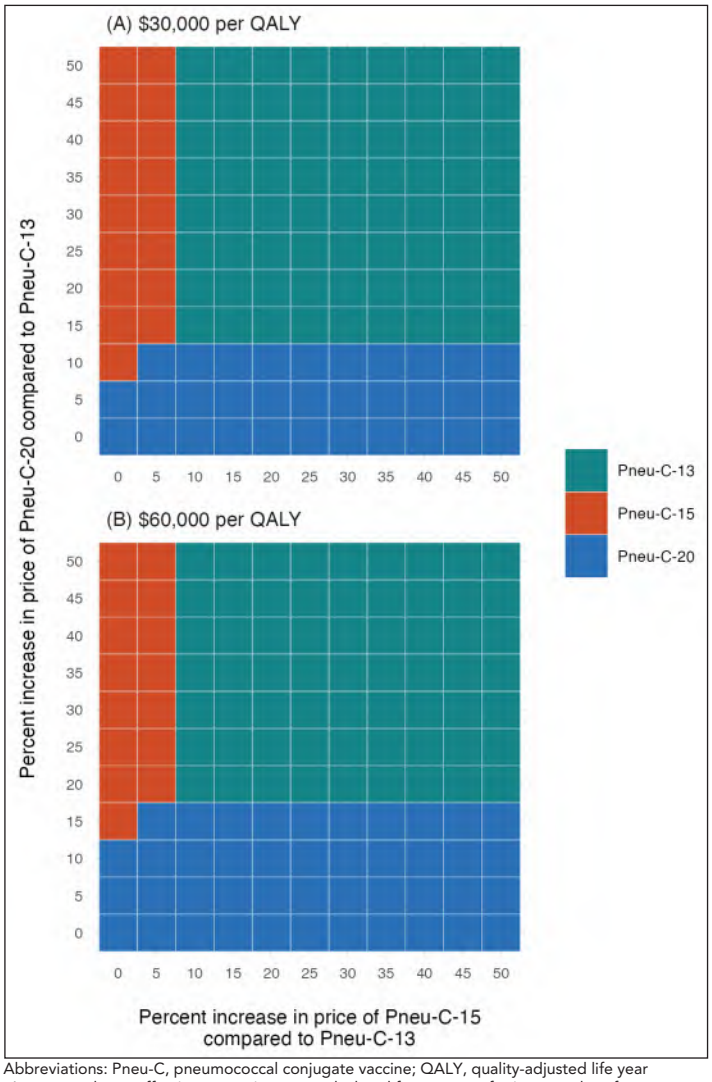



Abbreviations: Pneu-C, pneumococcal conjugate vaccine; QALY, quality-adjusted life year
[a] Results are a function of the percent reduction in serotype-attributable disease due to indirect effects and the time until the maximum effect is achieved

average over 10 years compared to the continued use of Pneu-C-13 (**Appendix, Figure A1**). The Pneu-C-20 vaccine averted an additional 1,808 (IQR: 1,680–1,914) IPD cases, 2,294 (IQR: 1,683–3,039) hospitalized pCAP cases, 50,446 (IQR: 47,333–53,624) outpatient pCAP cases and 373,543 (IQR: 343,610–403,099) AOM cases compared Pneu-C-13. The Pneu-C-20 vaccine dominates (i.e., is less costly and more effective than) Pneu-C-13 and Pneu-C-15 from the both the health system and societal perspectives (Appendix, **Table A1**). The Pneu-C-20 vaccine is dominant, with lower costs and fewer QALYs lost than the current strategy (i.e., Pneu-C-13) and Pneu-C-15.

Our base case conclusions relied on several assumptions that we examined in sensitivity analyses. In our one-way sensitivity analysis of model parameters, vaccine price was the most influential parameter (not shown). When the relative vaccine prices of Pneu-C-15 and Pneu-C-20 compared to Pneu-C-13 were increased compared to their base case values, Pneu-C-13 remained the strategy with the lowest ICER (**Figure 5**). At a $30,000 per QALY threshold, Pneu-C-15 was the optimal strategy when the relative price increase of Pneu-C-15 was 5% or less than the price of Pneu-C-13. The Pneu-C-20 vaccine was the optimal strategy when the relative price increase of Pneu-C-20 was 10% or less than the price of Pneu-C-13. At a $60,000 per QALY threshold, Pneu-C-15 or Pneu-C-20 was the optimal strategy if the relative price increases for Pneu-C-15 or Pneu-C-20 were 5% or 15% or less than the price of Pneu-C-13, respectively. A lower incidence of pCAP and AOM led to sequential ICERs of over $100,000 per QALY for Pneu-C-15 and over $200,000 per QALY for Pneu-C-20. Additionally, an AOM serotype distribution more similar to the United States, which differs from the serotype distribution of IPD in Canada, results in sequential ICERs of over $100,000 per QALY for Pneu-C-15 and Pneu-C-20.

**Figure 5: Sensitivity analysis of vaccine costs[a,b]**




Abbreviations: Pneu-C, pneumococcal conjugate vaccine; QALY, quality-adjusted life year
[a] Incremental cost-effectiveness ratios were calculated for a range of prices per dose for Pneu-C-15 and Pneu-C-20, ranging from 0%–50% higher than the price of Pneu-C-13
[b] The optimal strategy was identified for cost-effectiveness thresholds of $30,000 and $60,000 per QALY from the health system perspective

## Discussion

We conducted an economic evaluation to estimate the health impact and cost-effectiveness of replacing Pneu-C-13 with Pneu-C-15 or with Pneu-C-20 for routine use in the paediatric population in Canada. Our base case results found that both Pneu-C-15 and Pneu-C-20 prevented additional cases of IPD, pCAP and AOM compared to the continued use of Pneu-C-13. In our base case, Pneu-C-15 would require a threshold of $58,823 per QALY from the health system perspective and $18,272 per QALY from the societal perspective to be considered cost effective. The Pneu-C-20 vaccine would require a threshold of $135,289 per QALY from the health system perspective and $93,416 per QALY from the societal perspective to be considered cost effective. In contrast, with the inclusion of moderate indirect vaccine effects (e.g., a reduction of 5% or greater in serotype-attributable PD), both Pneu-C-15 and Pneu-C-20 could be considered cost effective at thresholds under $30,000 per QALY from the health system and societal perspectives. In a higher cost and higher PD incidence setting, Pneu-C-20 dominates the other vaccination strategies.

A recent comparative analysis of three cost-utility models conducted in the United States compared Pneu-C-20 to either Pneu-C-15 or Pneu-C-13 using a 3+1 schedule in children younger than two years of age (71). It showed similar trends as our analysis, with Pneu-C-20 expected to result in the largest gain in health outcomes compared to the other vaccines. From the societal perspective, results varied across the three included models, with ICERs for Pneu-C-20 ranging from dominant to $162,700 per QALY compared to Pneu-C-15. The models included in this analysis were all static but differed in structure, analytic time horizon, assumptions about indirect protection effects and key parameters, further highlighting the sensitivity of these model-based economic evaluation results to model assumptions and input parameters (13).

The estimated cost-effectiveness of the different conjugate vaccines was driven, in part, by the presence or absence of indirect effects. After the introduction of Pneu-C-13 in paediatric populations, IPD incidence caused by the serotypes in the vaccine decreased in all age groups (7,8), but overall IPD incidence in the population did not substantially decrease (10). In several countries including Canada, the introduction of pneumococcal conjugate vaccines (i.e., Pneu-C-7, Pneu-C-10 and Pneu-C-13) resulted in increases in the incidence of IPD caused by serotypes not included in the vaccines across all ages (72,73). In our base case analysis, we conservatively did not include indirect effects, given the uncertainty of herd immunity effects and serotype replacement. In our scenario analysis, we modelled indirect effects as a decline in pneumococcal disease in the broader population not receiving the higher valency conjugate vaccines.

Uncertainty about vaccine price in the Canadian context adds complexity to the interpretation of our results, given how influential the prices of Pneu-C-15 and Pneu-C-20 were on the estimated ICERs. In sensitivity analysis, we showed that at lower incremental prices compared to the price per dose of Pneu-C-13, both higher valency vaccines can be cost-effective options. Our analysis provides an indication of the prices at which either vaccine may become the optimal strategy based on commonly used thresholds.

### Limitations

Because we used a static model, our approach did not fully capture the transmission dynamics associated with herd immunity effects and serotype replacement. Future economic evaluations of pneumococcal conjugate vaccination should consider using dynamic models to inform cost-utility analyses to better capture these effects (74).

Additionally, our economic evaluation focused on children beginning their pneumococcal vaccination series. We did not assess the cost-effectiveness of the three strategies among children who were mid-way through their vaccine series, and we did not assess the impact of a potential catch-up program. Our estimates of the incidence of PD included children at both low and high risk of PD. We did not identify the optimal vaccination strategy independently among children at higher risk for PD outside of a higher cost setting.

### Conclusion

Our study provides evidence of the impact Pneu-C-15 and Pneu-C-20 could have on reducing the burden of PD in Canada compared to the continued use of Pneu-C-13. Although ICERs were relatively high in the base case analysis, at lower vaccine prices and/or in the presence of indirect effects in the broader population following vaccine introduction, both vaccines have the potential to improve health in a cost-effective manner.

## Authors' statement

AS — Conceptualization, formal analysis, writing–original draft
GG — Conceptualization, formal analysis, writing–review & editing
RP — Conceptualization, writing–review & editing
AW — Conceptualization, writing–review & editing
MT — Conceptualization, writing–review & editing
AT — Conceptualization, analysis, modelling, writing–review & editing, supervision

### Competing interests

None.

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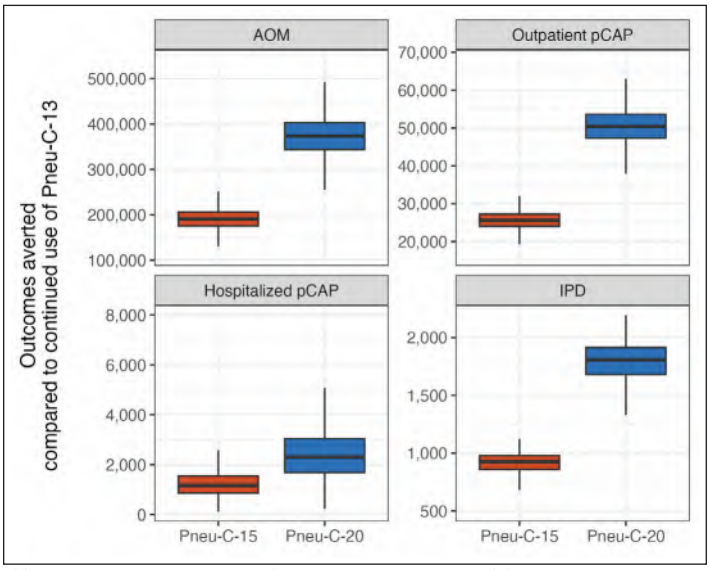
# Appendix

**Figure A1: Outcomes averted in all age groups compared to continued use of Pneu-C-13 over 10 years in the higher cost and higher pneumococcal disease incidence scenario[a]**




Abbreviations: AOM, acute otitis media; IPD, invasive pneumococcal disease; pCAP, pneumococcal community acquired pneumonia; Pneu-C, pneumococcal conjugate vaccine
[a] Results are shown for 10,000 model simulations

**Table A1: Mean quality-adjusted life years lost, cost, and incremental cost-effectiveness ratios for the higher cost and higher pneumococcal disease incidence scenario, in the absence of indirect effects**

| Strategy | Effect (QALYs lost) | Cost ($, millions) | Sequential ICER ($/QALY) |
|---|---|---|---|
| **Health system perspective** | | | |
| Pneu-C-20 | 15,794 | 541,539 | - |
| Pneu-C-15 | 15,819 | 543,513 | Dominated by Pneu-C-20 |
| Pneu-C-13 | 15,897 | 545,613 | Dominated by Pneu-C-20 |
| **Societal perspective** | | | |
| Pneu-C-20 | 541,539 | 445,465 | - |
| Pneu-C-15 | 543,513 | 455,579 | Dominated by Pneu-C-20 |
| Pneu-C-13 | 545,613 | 445,760 | Dominated by Pneu-C-20 |

Abbreviations: ICER, incremental cost-effectiveness ratio; Pneu-C, pneumococcal conjugate vaccine; QALY, quality-adjusted life year; -, not applicable

# Cost effectiveness of a 21-valent pneumococcal conjugate vaccine in adults: A systematic review of economic evaluations

Alison E Simmons[1,2]*, Raphael Ximenes[1], Gebremedhin B Gebretekle[1], Marina I Salvadori[1,3], Eva Wong[1], Ashleigh R Tuite[1,2]

## Abstract

**Background:** In July 2024, Health Canada authorized a 21-valent pneumococcal conjugate vaccine (Pneu-C-21) for use in adults.

**Objective:** To conduct a systematic review of the cost-effectiveness of Pneu-C-21 for preventing pneumococcal disease in adults.

**Methods:** We conducted a systematic search of the literature and National Immunization Technical Advisory Groups' websites on July 3, 2024. We included economic evaluations that assessed Pneu-C-21 as a vaccination strategy among adults aged 18 years and older. Costs were adjusted to 2023 Canadian dollars.

**Results:** We identified 10 studies in our search, five of which were summarized in our review. No economic evaluations were conducted in Canada. All economic evaluations used static cohort models and incorporated indirect effects from paediatric pneumococcal conjugate vaccination in primary or sensitivity analyses. Although incremental cost-effectiveness ratios were heterogeneous across included economic evaluations, overall, they qualitatively identified the same vaccination strategies as optimal within the given age and risk groups. Pneu-C-21 is likely to be cost-effective in adults aged 65 years and older and adults under the age of 65 years with specific high risk conditions.

**Conclusion:** Pneu-C-21 is likely to be cost-effective in adults within specific age and risk groups. The applicability of the included economic evaluations to adults living in Canada is limited because the serotype-specific incidence of pneumococcal disease and the impact of indirect effects from pediatric vaccination varies by region and over time.

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***Keywords:*** 21-valent pneumococcal conjugate vaccine, pneumococcal disease, vaccination, cost-utility analysis, health economics



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## Introduction

The bacterium *Streptococcus pneumoniae* is a significant cause of morbidity and mortality in Canada and worldwide (1). Of over 100 known serotypes of *S. pneumoniae* (2), 15 cause the majority of disease in Canada (1). The upper respiratory tracts of between 20%–60% of children and approximately 10% of healthy adults are colonized with *S. pneumoniae* (3). In rare cases, there is infection of a normally sterile site (e.g., blood, meninges), causing invasive pneumococcal disease (IPD).

There are a number of pneumococcal vaccines authorized for use in Canada, including the 15- and 20-valent pneumococcal conjugate vaccines (Pneu-C-15 and Pneu-C-20, respectively)

and the 23-valent pneumococcal polysaccharide vaccine (Pneu-P-23) (4), that aim to protect vaccine recipients from severe disease caused by 15-, 20- or 23-valent *S. pneumoniae* serotypes. Canada's National Advisory Committee on Immunization (NACI) currently recommends the use of Pneu-C-20 in adults at high risk of IPD, including adults aged 65 years and older and adults under 65 years of age with medical or social risk factors.

In July 2024, Health Canada approved a 21-valent pneumococcal conjugate vaccine (Pneu-C-21) for use in individuals aged 18 years and older (5). One month prior, in June 2024, the United States Advisory Committee on Immunization Practices recommended Pneu-C-21 as an option for adults aged 19 years and older who were recommended to receive Pneu-C-15 or Pneu-C-20 (6). Pneu-C-21 contains 10 unique non-cross-reactive serotypes (9N, 15A, 16F, 17F, 20A, 23A, 23B, 24F, 31 and 35B) compared to Pneu-C-20, and Pneu-C-20 contains nine unique serotypes not included in Pneu-C-21 (1, 4, 5, 6B, 9V, 14, 18C, 19F and 23F). Using established methodology to assess the benefit of Pneu-C-21 in public health programs (7), NACI sought to update recommendations on the use of pneumococcal vaccines in adults as part of its mandate. Economic evidence was determined to be a necessary component to inform the development of the vaccine guidance.

In support of NACI's workplan (8), Canada's Drug Agency (CDA; formerly Canadian Agency for Drugs and Technologies in Health) conducted a systematic review on the cost-effectiveness of pneumococcal conjugate vaccines in adults at high risk for pneumococcal disease (PD) aged 18 to 64 years (9). The systematic review generally found that Pneu-C-13, alone or in combination with Pneu-P-23, and Pneu-C-20 may be cost-effective compared to no vaccination at a threshold of $50,000/quality-adjusted life year (QALY) gained in populations at higher risk of IPD (9). Pneu-C-15 used in combination with Pneu-P-23 was unlikely to be cost effective at commonly used thresholds in high-risk adults. None of the included economic evaluations included Pneu-C-21 as an intervention or comparator.

The CDA systematic review focused on the question of whether pneumococcal conjugate vaccines are a cost-effective intervention in adults less than 65 years of age at risk for PD. We conducted a separate systematic review to address the policy question of whether Pneu-C-21 is cost-effective for preventing PD in adults aged 18 years and older. The aim of this review was to identify any more recently published studies and include all adults, including those aged 65 years and older.

## Methods

Our systematic review was informed by NACI's Guidelines for Systematic Reviews on Economic Evaluations of Vaccination Programs (10). We conducted a literature search of EBM Reviews; Cochrane Central Register of Controlled Trials, EconLit, Embase, International Pharmaceutical Abstracts, Ovid MEDLINE and Scopus. In addition, we searched the websites of National Immunization Technical Advisory Groups, including the Joint Committee on Immunisation (United Kingdom), the Advisory Committee on Immunization Practices (ACIP; United States), Standing Committee on Immunization (Germany) and Australian Technical Advisory Group on Immunisation (Australia). Our search was limited to literature published in English and French from 2019 onward. The search strategy was developed in consultation with and validated by a librarian at the Health Canada Library. It is available directly from the authors as Supplemental material (see **Appendix** for more information). The search was completed on July 3, 2024.

Full texts were identified, retrieved and screened against our inclusion criteria by two reviewers (**Table 1**). Our inclusion criteria ensured included studies were full economic evaluations with Pneu-C-21 as the intervention. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (11) that details this process was developed.

**Table 1: Policy question and inclusion criteria**

| Inclusion criteria | Description |
|---|---|
| Population | Adults aged 18 years and older |
| Intervention | 21-valent pneumococcal conjugate vaccine (Pneu-C-21; V116) |
| Comparators | Any (i.e., placebo, no intervention, other pneumococcal vaccines) |
| Outcomes | QALYs, DALYs, incremental costs, incremental cost-effectiveness ratios (cost per QALY gained or incremental cost per event or event avoided), net monetary benefit, net health benefit |
| Study designs | Full economic evaluations (e.g., cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses)[a] |

Abbreviations: DALY, disability-adjusted life years; Pneu-C-21, 21-valent pneumococcal conjugate vaccine; QALY, quality-adjusted life year
[a] Studies with only abstracts available were excluded

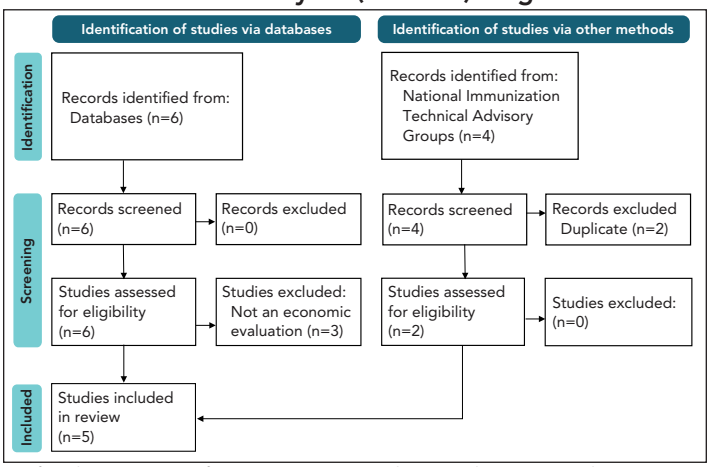
We extracted study characteristics, methods, findings and funding sources from evaluations that met our inclusion criteria. To ensure our findings were informative for NACI's decision-making, we focused our review on health outcomes and costs for vaccination strategies that were under consideration (i.e., currently recommended strategies as comparators) (Appendix, Table S1). Costs were converted to 2023 Canadian dollars (CAD) using the Organisation for Economic and Co-operation and Development (OECD) purchasing parity rates (12) and the Bank of Canada's inflation calculator (13). Our main outcome of interest was the incremental cost-effectiveness ratio (ICER). When comparators from a study were not aligned with NACI's policy questions, we calculated ICERs using the relevant comparator based on the costs and QALYs provided in the published study. Included economic evaluations were critically appraised by one reviewer using the Joanna Briggs Institute Critical Appraisal

Checklist for Economic Evaluations (JBI Checklist) (14). To complement the JBI Checklist, we also appraised included studies against three questions from World Health Organization for standardization of economic evaluations of immunization programmes (10,15). To assess the generalizability of the included studies (i.e., JBI Checklist item 11: "Are the results generalizable to the setting of interest in the review?"), we considered guidance from Heyland *et al.* (16).

## Results

Ten publications were identified in our search and five were included in our systematic review (**Figure 1**). Three economic evaluations were included from the peer-reviewed literature (17–19). Results from three economic evaluations were summarized and presented to ACIP (20), including a model by Altawalbeh *et al.* (17) that was also identified in the peer-reviewed literature. For clarity, the models summarised to ACIP are referred to by the names of the model authors (i.e., Altawalbeh *et al.*, 2024 (17); Owusu-Edusei *et al.*, 2024 (21); Stoecker, 2024 (22)). One of the evaluations presented to ACIP was an industry-funded model by Merck (21).

**Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram[a]**



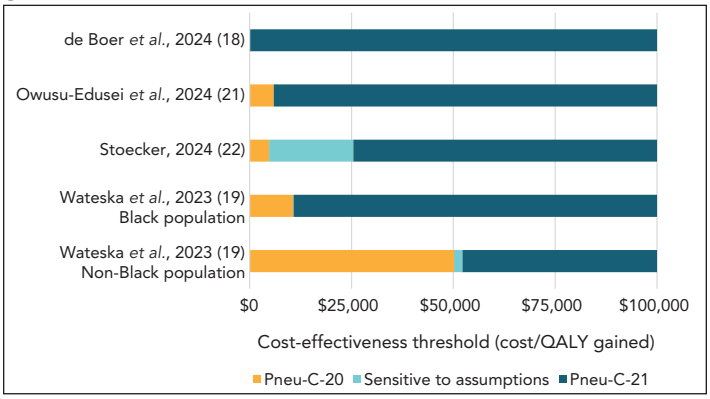

[a] Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (11) detailing the search and screening process used to select included economic evaluations on the use of a 21-valent pneumococcal conjugate vaccine (Pneu-C-21) in adults

All five economic evaluations used static cohort models to inform their cost-utility analyses (**Table 2**). Four evaluations were conducted in the United States (17,19,21,22) and one was conducted in the Netherlands (18). Three economic evaluations were conducted from the societal perspective (18,21,22), one was conducted from the health system perspective (19) and one included findings from both the societal and health system perspectives (17). The four studies conducted in the United States used a 3% discount rate (17,19,21,22) and de Boer *et al.* used a 4% discount rate for costs and a 1.5% discount rate for QALYs (18). The three peer-reviewed studies met nine out of 11 of the JBI Checklist criteria and were high quality (**Table 3**). The two models only presented at ACIP met between three and six of the 11 JBI Checklist criteria. Only one study (18) thoroughly discussed the strengths and weaknesses of their model in relation to pneumococcal transmission dynamics.

Each of the included economic evaluations assumed different age-specific serotype distributions of PD cases. However, serotypes included in Pneu-C-21 caused more IPD cases than serotypes included in Pneu-C-20 in all of the economic evaluations (Appendix, Figure S1). Detailed assumptions on the assumed impact of paediatric pneumococcal conjugate vaccination on PD in adults due to indirect effects are shown in Appendix, Table S2. Each economic evaluation included indirect effects from pediatric vaccination in primary (18,22) or sensitivity analyses (17,19,21).

Four of the economic evaluations included vaccinating all individuals aged 65 years with Pneu-C-20 as a comparator (Appendix, Table S3). Pneu-C-21 was the optimal vaccination strategy at a cost-effectiveness threshold of $50,000/QALY gained in this population, when compared to Pneu-C-20, in the majority of included studies (**Figure 2**). In the analysis by de Boer *et al.* (18), Pneu-C-20 was dominated by Pneu-C-21, meaning that Pneu-C-21 was both less costly and more effective than Pneu-C-20. Incremental cost-effectiveness ratios ranged from $4,793/QALY gained (22) to $52,265/QALY gained (19) when comparing Pneu-C-21 to Pneu-C-20 in the other economic evaluations (Figure 2; Appendix, Table S3).

**Figure 2: Preferred pneumococcal vaccination strategy in adults aged 65 years at cost-effectiveness thresholds ranging from $0/QALY gained to $100,000/QALY gained**




Abbreviations: Pneu-C-20, 20-valent pneumococcal conjugate vaccine; Pneu-C-21, 21-valent pneumococcal conjugate vaccine; QALY, quality-adjusted life years

Two of the included economic evaluations compared the cost-effectiveness of vaccinating adults aged 50 years with Pneu-C-21 compared to no vaccination (Appendix, Table S3). Altawalbeh *et al.* (17) compared vaccinating Black and non-Black adults at the age of 50 years with Pneu-C-21 to no vaccination. In contrast, Stoecker (22) compared a strategy of vaccinating adults at the ages of 50 years and 65 years with Pneu-C-21 to a strategy

**Table 2: Summary of included economic evaluations**

| Economic evaluations | Altawalbeh *et al.*, 2024 (17) | de Boer *et al.*, 2024 (18) | Owusu-Edusei *et al.*, 2024 (21) | Stoecker, 2024 (22) | Wateska *et al.*, 2023 (19) |
|---|---|---|---|---|---|
| Country | United States | Netherlands | United States | United States | United States |
| Perspective | Health system and societal | Societal | Societal | Societal | Health system |
| Modelling approach | Static cohort model | Static cohort model | Static cohort model | Static multi-cohort model | Static cohort model |
| Inclusion of indirect effects/serotype replacement from pediatric vaccination | Indirect effects only | Indirect effects and serotype replacement | Indirect effects only | Indirect effects only | Indirect effects only |
| Time horizon | Lifetime | 15 years | 100 years | Varies | Lifetime |
| Discount rate | 3% | 4% for costs and 1.5% for QALYs | Assumed 3% | 3% | 3% |
| Study population | Adults aged ≥50 years and older and high risk adults younger than 50 years; stratified by race | Adults aged 60 years and older | Adults aged 19 years and older | Adults aged 19 years and older | Adults aged 65 years and older; stratified by race |
| Comparators | Pneu-C-20, Pneu-C-15+Pneu-P-23, no vaccination | Pneu-C-20, Pneu-C-15+Pneu-P-23, Pneu-C-15, no vaccination | Pneu-C-20 | Pneu-C-20 | Pneu-C-20, Pneu-C-15+Pneu-P-23, no vaccination |
| Price per dose | 2019 USD<br>Pneu-C-21: $333.00<br>Pneu-C-20: $249.00<br>Pneu-C-15: $216.09<br>Pneu-P-23: $117.08 | 2021 EUR<br>Pneu-C-21: €82.17<br>Pneu-C-20: €82.17<br>Pneu-C-15: €74.73<br>Pneu-P-23: €25.94 | 2023 USD<br>Pneu-C-21: $287<br>Pneu-C-20: $261 | 2023 USD<br>Pneu-C-21: $319.43<br>Pneu-C-20: $288.66 | 2019 USD<br>Pneu-C-21: $333.00<br>Pneu-C-20: $249.00<br>Pneu-C-15: $216.09<br>Pneu-P-23: $117.08 |
| Price per dose (2023 CAD)[a] | Pneu-C-21: $466<br>Pneu-C-20: $349<br>Pneu-C-15: $303<br>Pneu-P-23: $164 | Pneu-C-21: $148<br>Pneu-C-20: $148<br>Pneu-C-15: $135<br>Pneu-P-23: $47 | Pneu-C-21: $333<br>Pneu-C-20: $303 | Pneu-C-21: $371<br>Pneu-C-20: $335 | Pneu-C-21: $466<br>Pneu-C-20: $349<br>Pneu-C-15: $303<br>Pneu-P-23: $164 |
| Funding | National Institute of Allergy and Infectious Diseases | Netherlands Ministry of Health, Welfare and Sport | Merck industry model | None listed | None listed |

Abbreviations: CAD, Canadian dollar; EUR, Euro; Pneu-C-15, 15-valent pneumococcal conjugate vaccine; Pneu-C-20, 20-valent pneumococcal conjugate vaccine; Pneu-C-21, 21-valent pneumococcal conjugate vaccine; Pneu-C-23, 23-valent pneumococcal polysaccharide vaccine; QALY, quality-adjusted life years; USD, United States dollar

[a] Costs were converted to 2023 CAD using the Organisation for Economic and Co-operation and Development (OECD) purchasing parity rates (12) and Bank of Canada's inflation calculator (consumer price index)

**Table 3: Quality appraisal[a] of included economic evaluations (14,15)**

| Study (reference) | Joanna Briggs Institute checklist | | | | | | | | | | | WHO checklist | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 |
| Altawalbeh *et al.*, 2024 (17) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Unclear | Unclear |
| de Boer *et al.*, 2024 (18) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Yes | Unclear |
| Owusu-Edusei *et al.*, 2024 (21)[b] | Yes | Yes | Unclear | Unclear | Unclear | Unclear | Unclear | Yes | Unclear | No | No | Unclear | Unclear | Unclear |
| Stoecker, 2024 (22)[b] | Yes | Yes | Unclear | Yes | Unclear | Unclear | Yes | Yes | Yes | No | No | Unclear | Unclear | Unclear |
| Wateska *et al.*, 2023 (19) | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | No | No | Yes | Unclear | Unclear |

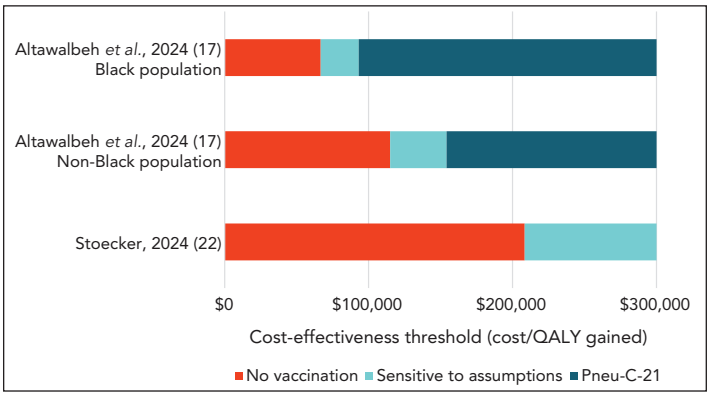
Abbreviation: WHO, World Health Organization

[a] Questions: 1) Is there a well-defined question?; 2) Is there a comprehensive description of alternatives?; 3) Are all important and relative costs and outcomes for each alternative identified?; 4) Has clinical effectiveness been established?; 5) Are costs and outcomes measured accurately?; 6) Are costs and outcomes valued credibly?; 7) Are costs and outcomes adjusted for differential timing?; 8) Is there an incremental analysis of costs and consequences?; 9) Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?; 10) Do study results include all issues of concern to users?; 11) Are the results generalizable to the setting of interest in the review?; 12) Are the model structure and implicit or explicit assumptions clearly described?; 13) Is the model type (static, dynamic or stochastic) clearly stated and justified in light of likely changes to the force of infection and the role of chance in the transmission process? Have the model's strengths and weaknesses been discussed?; 14) Has the model been validated? If so, has it been validated in as many facets of validation as possible?

[b] Study methods and findings were extracted from slides presented to the American Committee on Immunization Practices (ACIP) and limited details were available

of vaccinating adults at only the age of 65 years with Pneu-C-21, effectively comparing Pneu-C-21 at the age of 50 years to no vaccination in a population receiving Pneu-C-21 at the age of 65 years. Incremental cost-effectiveness ratios ranged from $66,706/QALY gained to $313,121/QALY gained (17,22), with the former reflecting the cost-effectiveness of vaccinating Black population members (**Figure 3**).

**Figure 3: Preferred pneumococcal vaccination strategy in adults aged 50 years at cost-effectiveness thresholds ranging from $0/QALY gained to $300,000/QALY gained**




Abbreviations: Pneu-C-21, 21-valent pneumococcal conjugate vaccine; QALY, quality-adjusted life years

One economic evaluation compared the cost-effectiveness of vaccinating adults younger than 50 years of age at high risk of PD (Appendix, Table S3). In a cohort of adults aged 42 years living with immunocompromising conditions, including HIV, cancer, organ transplants and dialysis, Pneu-C-20 was dominated by Pneu-C-21 (22).

Catch-up vaccination was examined by Owusu-Edusei *et al.* (21) and Stoecker (22) in a range of age and risk groups (Appendix, Table S3). A catch-up dose of Pneu-C-21 between one and five years after a dose of Pneu-C-20 was never cost-effective at commonly used thresholds, with ICERs ranging from $239,128/QALY gained (22) to $594,229/QALY gained (21).

## Discussion

Our review identified five economic evaluations that assessed the cost-effectiveness of using Pneu-C-21 in adults. Three economic evaluations were summarized from the peer-reviewed literature (17–19) and two were summarized from ACIP presentations (21,22). In economic evaluations that included the strategy of vaccinating adults aged 65 years and older with Pneu-C-21 compared to Pneu-C-20, ICERs were around or below $50,000/QALY gained (18,19,21,22). A strategy of vaccinating adults aged 50 to 64 years with Pneu-C-21 compared to no vaccination had ICERs over $65,000/QALY gained, with the highest estimate being over $300,000/QALY gained (17,22). In adults younger than 50 years of age, a strategy with Pneu-C-21 dominated Pneu-C-20 in adults with immunocompromising conditions, but no vaccination dominated Pneu-C-21 in a strategy of vaccinating all adults (regardless of the presence of a chronic medical or immunocompromising condition) (22). Incremental cost-effectiveness ratios for a catch-up dose of Pneu-C-21 after vaccination with Pneu-C-20 were over $230,000/QALY gained (21,22). In the two studies that presented race-stratified results (17,19), ICERs were lower in the Black population compared to the non-Black population, primarily due to a higher risk of PD.

Although none of the included economic evaluations were conducted in Canada, they all employed cost-utility models, with health outcomes expressed as QALYs, which aligns with NACI's guidelines for economic evaluations (23). Vaccine prices used in the economic evaluations conducted in the United States are higher than vaccine prices expected in Canada. An analysis commissioned by the United States Department of Health and Human Services and conducted by the RAND Corporation found that drug prices in Canada were, on average, 56% lower than those in the United States (24). Findings were especially sensitive to vaccine price assumptions when the comparator was no vaccination. In Canada, the recommended discount rate of future (i.e., beyond one year) costs and QALYs is 1.5% (23); with the exception of the discount rate of QALYs used by de Boer *et al.* (18), discount rates were greater than recommended by NACI's guidelines (17–19,21,22). Altawalbeh *et al.* (17) was the only economic evaluation to present results from both the health system and societal perspective. The model by Owusu-Edusei *et al.* (21) is an industry-led model by Merck, the manufacturer of Pneu-C-21 (5). Finally, many of the vaccination strategies included in the economic evaluations were not relevant to current vaccine recommendations for adults living in Canada.

### Limitations

The results of the included economic evaluations were sensitive to key assumptions. First, the incidence of PD caused by vaccine-type and non-vaccine-type serotypes differs by region and over time, and the impact of the COVID-19 pandemic on PD dynamics is still unknown (19). Because higher valency pneumococcal conjugate vaccines for children are new, assumptions of the potential impact of indirect effects from pediatric vaccination with Pneu-C-15 or Pneu-C-20 were necessary (18,20,22). In a multi-model comparison, Leidner (20) identified the presence of indirect effects from pediatric vaccination, the PD case fatality rate, the prevalence and severity of long-term post-PD disability, productivity losses and vaccine price as key assumptions and parameters that impacted model findings. Altawalbeh *et al.* (17) and Wateska *et al.* (19) highlighted uncertainties surrounding vaccine price and vaccine effectiveness.

Additional limitations include the difficulty of assessing the quality of the economic evaluations presented to ACIP (because only presentation materials were available), the use of static models and assumptions regarding serotype replacement. To

date, pneumococcal conjugate vaccines have been effective against *S. pneumoniae* colonization and their use has resulted in indirect (herd) effects. Dynamic transmission models are better equipped to capture the population level impact of pneumococcal conjugate vaccination strategies (25). Finally, with the exception of the model by de Boer *et al.* (18), none of the models included serotype replacement (17,19,21,22). Following the introduction of Pneu-C-13 in the routine pediatric vaccination schedule in Canada, serotype replacement resulted in a rise in IPD caused by the serotypes not included in the vaccine (26,27).

### Conclusion

Our systematic review of economic evaluations assessing the cost-effectiveness of Pneu-C-21 in adults to support guidance on its use in adults living in Canada adults suggests that it may be a cost-effective intervention compared to current recommendations in some populations. However, to best understand the potential cost-effectiveness of the use of Pneu-C-21 in adults living in Canada, a *de novo* economic evaluation that better reflects the Canadian context is required.

## Authors' statement

AS — Conceptualization, formal analysis, writing–original draft
RX — Conceptualization, writing–review & editing
GG — Conceptualization, writing–review & editing
MS — Conceptualization, writing–review & editing
EW — Conceptualization, writing–review & editing
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### Competing interests

None.

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## Appendix

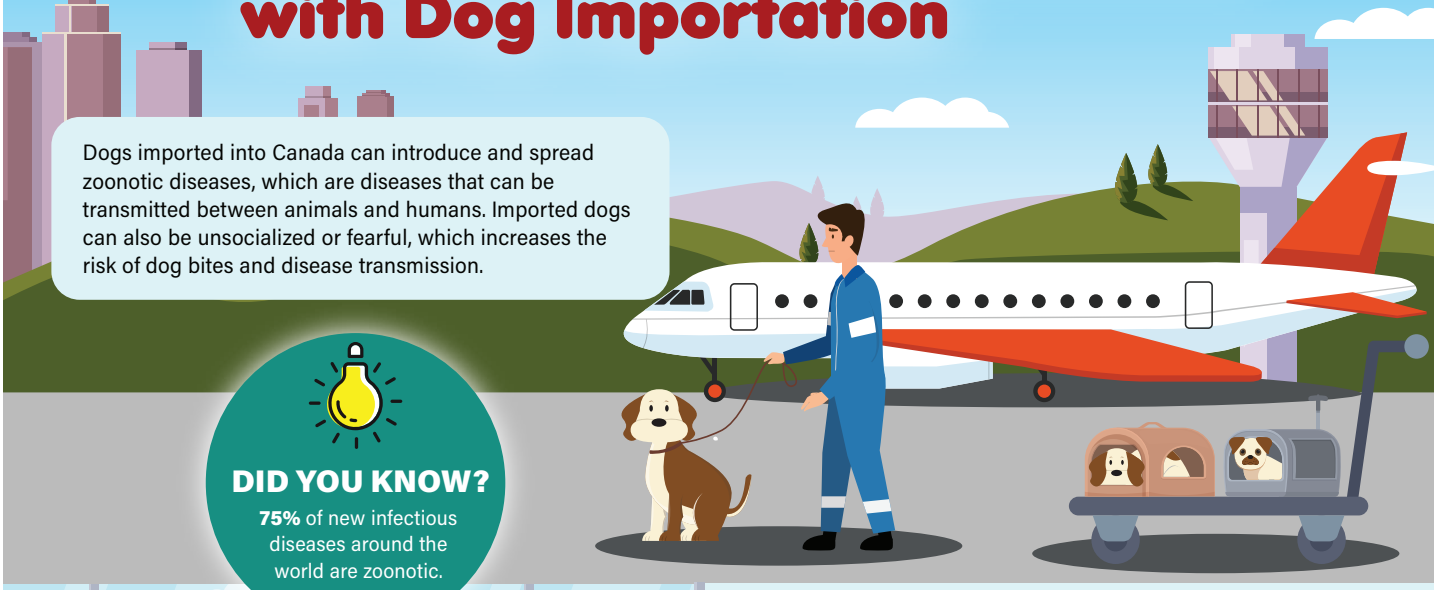
Additional data is available upon request to the author: alison.simmons@mail.utoronto.ca

EBM Reviews: Cochrane Central Register of Controlled Trials
EBM Reviews: EconLit
EBM Reviews: Embase
EBM Reviews: International Pharmaceutical Abstracts
EBM Reviews: Ovid MEDLINE(R) ALL
EBM Reviews: SCOPUS

Table S1: Current pneumococcal vaccination strategies for adults in Canada
Figure S1: Assumed age-specific pneumococcal serotype distributions in included economic evaluations
Table S2: Summary of assumptions relating to indirect effects and serotype replacement from pediatric pneumococcal conjugate vaccination in included economic evaluations
Table S3: Incremental cost-effectiveness ratios (ICERs) from selected strategies

# Public Health Risks Associated with Dog Importation

Dogs imported into Canada can introduce and spread zoonotic diseases, which are diseases that can be transmitted between animals and humans. Imported dogs can also be unsocialized or fearful, which increases the risk of dog bites and disease transmission.



**DID YOU KNOW?**

**75%** of new infectious diseases around the world are zoonotic.

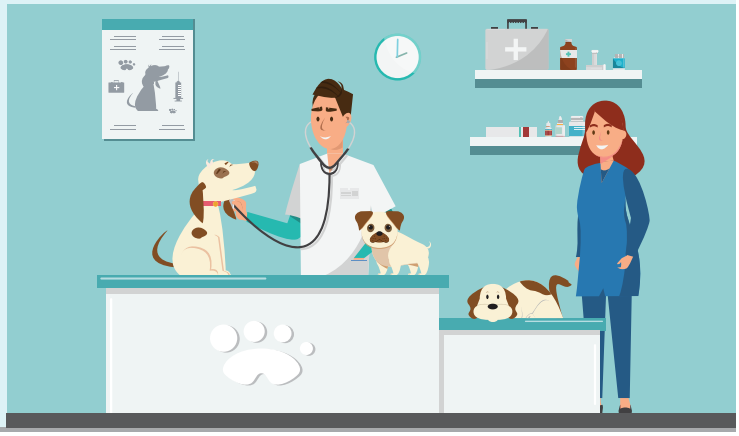

## Dogs are great companions and dog ownership has many benefits, but some of the public health risks from imported dogs include:

1. **Zoonotic diseases**
   - viruses (e.g. rabies)
   - bacteria (e.g. *Brucella* spp.)
   - parasites (e.g. *Echinococcus* spp.)
2. **Dog bites**

One of the zoonotic disease risks associated with dog importation is dog rabies. Importing dog rabies is a serious public health threat to people as rabies can be deadly, if not treated before symptoms begin. Rabies kills thousands of people around the world every year and dog rabies is responsible for 99% of these deaths. Canada has wildlife **rabies** but it does **NOT** have dog rabies, which circulates in dogs in other countries.

## How can you help keep dog rabies and other zoonotic diseases out of Canada?

- **Choose local.** Many local rescue dogs need homes. If you want a specific breed, find a local, reputable breeder you can trust.
- **Understand the rules.** Visit the Canadian Food Inspection Agency's website to learn more.
- **Ask your veterinarian** about zoonotic disease risks. If you import a dog, ask if you should **RE-VACCINATE, RE-TEST & RE-TREAT** your dog. Vaccines, tests and treatments from other countries may not be as reliable as those in Canada, so they may need to be repeated.
- **Quarantine** your imported dog from other animals and vulnerable people (i.e., young children, elderly, immuno-compromised) for 2–4 weeks after they've arrived.



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

Canada

OUTBREAK REPORT

# Summary of the mpox outbreak in Canada, April 28–December 31, 2022

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## Abstract

**Background:** Mpox is an infectious disease caused by the monkeypox virus (MPXV), closely related to the virus that causes smallpox. In May 2022, cases of mpox were reported in previously non-endemic countries including Canada.

**Objective:** To summarize the epidemiology of the mpox outbreak in Canada, as well as key public health response activities, between April and December 2022.

**Methods:** The Public Health Agency of Canada (PHAC) worked closely with local, provincial and territorial public health authorities to develop national case investigation and reporting tools, including national case definitions for confirmed and probable mpox cases. Based on de-identified case data submitted to PHAC, patterns and trends were examined, including the distribution of cases by sociodemographic, clinical and transmission factors.

**Results:** Overall, 1,474 mpox cases (1,396 confirmed, 78 probable) were reported to PHAC. All reported cases were associated with MPXV clade IIb. Mpox disproportionately affected gay, bisexual and other men who have sex with men (80.0%) and those between 20–49 years of age (86.0%). Available data suggests that the most likely mode of disease acquisition was through sexual contact, with limited evidence on other possible modes of transmission. Some cases were hospitalized (3.0%); however, there were no mpox-related deaths in Canada.

**Conclusion:** Rapid coordination and surveillance activities supported the timely implementation of tailored interventions, including the procurement and distribution of vaccines. These actions, coupled with vaccination uptake and behavioural changes, contributed to reducing transmission and health impacts of mpox on the Canadian population.



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***Keywords:*** mpox, communicable diseases, zoonoses, orthopoxvirus, disease outbreaks, men who have sex with men

## Introduction

Mpox (formerly monkeypox) is a viral infectious disease caused by the monkeypox virus (MPXV), which is a species within the *Orthopoxvirus* genus. First discovered in non-human primates in 1958, human cases of this disease experience symptoms akin to those of smallpox but with a much lower case fatality rate (1). From the 1970s to the early 2000s, the epidemiological range of MPXV remained mostly limited to central and western Africa, given the proximity to its wildlife reservoir, including rodents and other small mammals (1). The occasional detection of cases outside the traditional endemic range of MPXV was mainly due to travel and exportation of reservoir animals (2–6). However, increased transmission among humans has been observed in the last two decades, likely relating to changes at the human-environment interface causing increased zoonotic spillovers; reduction in cross-protection from the smallpox vaccine following the end of global vaccination programs; and genetic evolution of MPXV (7).

On May 16, 2022, the United Kingdom reported a cluster of mpox cases among gay, bisexual and other men who have sex with men (GBMSM), without a history of travel to an endemic area (8). In Canada, the city of Montréal in Québec investigated the first cases of mpox between May 8–13, 2022 (9), and this cluster of cases was then confirmed by the Public Health Agency of Canada's (PHAC) National Microbiology Laboratory on May 19, 2022 (10). The Public Health Agency of Canada conducted a preliminary risk assessment, escalated its Health Portfolio Operations Centre to a Level 2 (Increased Vigilance and Readiness) on May 21, 2022, and activated an Incident Management System to respond to the emergence of mpox and support the coordination of the outbreak investigation and response activities across the country, in collaboration with local, provincial and territorial (LPT) public health authorities. We conducted a descriptive analysis of mpox cases reported in Canada between April and December 2022, and examined differences in sociodemographic, clinical and transmission characteristics between GBMSM and non-GBMSM subgroups.

# Methods

## Case definitions, data collection and investigation

Following the initial reporting of mpox cases in Canada, PHAC collaborated closely with affected local and provincial public health units and interim guidance issued by the World Health Organization (11) to develop national case definitions (see **Table 1**) (12) and investigation tools (13). This work relied on epidemiological and clinical observations made by public health units in the affected regions, as well as data shared by international partners. This rapid knowledge exchange from affected regions informed the development and harmonization of standardized tools for public health investigations across the country. Local, provincial and territorial public health authorities conducted case investigations and data were shared with PHAC on a weekly basis. Through case investigations, LPT public health authorities collected information on demographics, symptoms and clinical manifestations, as well as information on relevant risk factors, including recent sexual and travel history. Local, provincial and territorial public health authorities conducted their own molecular testing to screen or confirm cases whenever possible and were supported by National Microbiology Laboratory for confirmatory testing and genomic sequencing, as needed.

## Interventions

The Public Health Agency of Canada coordinated various responses to the 2022 mpox outbreak in Canada. A critical component of PHAC's response was the rapid deployment of medical countermeasures from existing stockpiles, primarily Imvamune® (Modified Vaccinia Ankara Bavarian Nordic), a vaccine originally approved for immunization against smallpox. The expansion of the vaccine's indication to include immunization against all orthopoxviruses for adults considered at high risk for exposure had been granted by Health Canada in 2020, which allowed the rapid implementation of a vaccination program in response to the mpox outbreak. Local, provincial and territorial public health authorities initially offered one dose of the two-dose vaccine schedule to eligible individuals to strategically leverage the limited vaccine supply and maximize vaccination uptake. Following early recommendations issued by the Québec Immunization Committee, Montréal Public Health in Québec initiated the first post-exposure prophylaxis vaccination

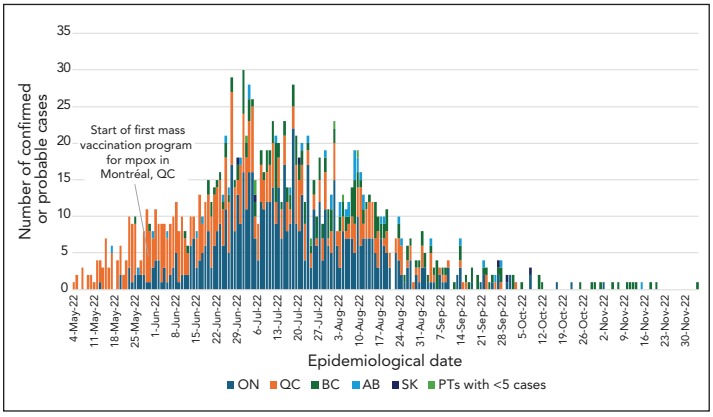
**Table 1: National mpox case classifications in Canada, 2022**

| Case classification | Definition |
|---|---|
| Confirmed | A person who is laboratory-confirmed for monkeypox virus by detection of unique sequences of viral DNA either by real-time polymerase chain reaction and/or sequencing |
| Probable | A person of any age who presents with an unexplained[a] acute rash or lesion(s)[b]<br>AND<br>Has one or more of the following:<br>• An epidemiological link[c] to a probable or confirmed mpox case in the 21 days before symptom onset, OR<br>• Reported travel history to or place of residence in a location where mpox is reported[d] in the 21 days before symptom onset |
| Suspected | A person of any age who presents with one or more of the following:<br>• An unexplained[a] acute rash[b] AND has at least one of the following signs or symptoms:<br>◦ Headache<br>◦ Acute onset of fever (higher than 38.5°C)<br>◦ Lymphadenopathy (swollen lymph nodes)<br>◦ Myalgia (muscle and body aches)<br>◦ Back pain<br>◦ Asthenia (profound weakness)<br>• An unexplained[a] acute genital, perianal or oral lesion(s) |

[a] Other common causes of acute rash can include varicella zoster, herpes zoster, measles, herpes simplex, syphilis, chancroid, lymphogranuloma venereum and hand-foot-and-mouth disease
[b] Acute rash: mpox illness includes a progressively developing rash that usually starts on the face and then spreads elsewhere on the body. The rash can affect the mucous membranes in the mouth, tongue and genitalia. The rash can also affect the palms of hands and soles of the feet. The rash can last for two to four weeks and progresses through the following stages: macules, papules, vesicles, pustules and scabs. Note: It is not necessary to obtain negative laboratory results for listed infectious causes of rash in order to classify a case as suspected
[c] An epidemiological link can be: face-to-face exposure, including health workers without appropriate personal protective equipment (PPE); direct physical contact, including sexual contact; or contact with contaminated materials, such as clothing or bedding
[d] Reported travel history includes regional, national or international travel in the 21 days before symptom onset to any area where mpox may be reported

program for mpox on May 30, 2022, which was later expanded to include pre-exposure prophylaxis on June 14, 2022 (9). The National Advisory Committee on Immunization recommended the use of Imvamune for prophylaxis in the context of mpox outbreaks in Canada on June 8, 2022 (14), which supported the rapid implementation of vaccination programs against mpox in all other jurisdictions. The Public Health Agency of Canada continued to procure additional Imvamune vaccine doses to support program expansion of vaccination activities in all jurisdictions; worked closely with LPTs to establish harmonized, national guidance for health professionals (13) as well as case and contact management (15); issued travel health advisories; and disseminated tailored risk communication through official, press and social media platforms. The Public Health Agency of Canada's activation was de-escalated to normal operations on December 15, 2022, following a sustained reduction in mpox case reports across Canada.

**Figure 1: Distribution of confirmed or probable mpox cases in Canada by earliest date and province/territory, April–December 2022**




Abbreviations: AB, Alberta; BC, British Columbia; ON, Ontario; PTs, provinces/territories in Canada; QC, Québec; SK, Saskatchewan

## Data analyses

People with a confirmed or probable mpox infection with illness onset between April 28, 2022, and December 31, 2022, were included for the analysis. An epidemic curve was developed to visually summarize aggregate case numbers over time by epidemiological date, which was defined as the earliest available date from the following hierarchy: date of symptom onset, date of specimen collection for laboratory testing and date reported to the local public health unit. Descriptive statistics were computed to summarize case patterns by sociodemographic, clinical and transmission characteristics. Additionally, differences were examined across GBMSM and non-GBMSM subgroups. Statistically significant differences in case patterns between GBMSM and non-GBMSM were determined based on a t-test for continuous variables and a chi-square or Fisher's exact test for categorical variables. Given the low number of probable cases, confirmed and probable mpox cases were examined together for all analyses. Information on sexual behaviours was not directly collected through case report forms but was derived based on available data from the following variables: sex, gender and gender(s) of sexual partner(s) in the 21 days before the date of symptom onset. Epidemiological link refers to a known case's contact with another possible or known case or contact with contaminated material. Data are presented as counts and percentages (%). All analyses were conducted in R statistical software (16,17).

# Results

A total of 1,474 mpox cases were reported to PHAC in 2022 (1,396 confirmed; 78 probable). The first two cases of mpox were confirmed on May 19, 2022, with the first reported case having a symptom onset date of April 28, 2022. Based on available information from laboratory testing and genomic sequencing, all mpox cases reported in 2022 were associated with MPXV clade IIb. As shown in **Figure 1**, there was a steady increase in cases, which included two peaks in the summer of 2022.

The majority of cases were reported in Ontario, Québec and British Columbia, accounting for 96% of all cases (**Table 2**). No cases were reported in Prince Edward Island, Nunavut and the Northwest Territories. There was a notable decrease in cases starting in August 2022, and by October 2022, cases were more sporadic.

Available data on sex and gender was as follows: 99.0% (n=757/767) of cases were of male sex (Table 2) and 98.0% (n=1,296/1,322) identified as men. Based on available information on sex, gender and gender(s) of sexual partner(s), 80.3% (n=1,184/1,474) were grouped as GBMSM, 3.1% (n=46/1,474) as non-GBMSM and information regarding the gender(s) of sexual partner(s) was unknown for 16.6% (n=244/1,474). The majority of cases were between 20–49 years old (86.1%, n=1,269/1,474), with a mean age of 37 years. There were no significant differences in the distribution of cases by age group between the GBMSM and non-GBMSM groups (**Table 3**). Nearly one-third of cases with available data (30.8%, n=299/972) reported living with HIV; a significantly higher proportion of people reported living with HIV in the GBMSM group (31.0%, n=246/793) compared to the non-GBMSM group (13.2%, n=5/38). Additionally, 7.0% (n=48/244) of cases for whom we have no information on the gender(s) of sexual partner(s) reported living with HIV. A diagnosis of a concurrent sexually transmitted or blood-borne infection was reported among 22.2% (n=209/941) of cases with information available, with 22.7% (n=173/763) in the GBMSM group and 20.6% (n=7/34) in the non-GBMSM group.

Among the GBMSM group, sexual contact was the most likely mode of acquisition for 97.1% (n=642/661) of cases, and 57.9% (n=162/280) of cases were epidemiologically linked. Among the non-GBMSM group with available data, sexual contact was the most likely mode of acquisition for 80.0% (n=16/20) of cases, whilst 50.0% (n=3/6) had a known epidemiological link.

**Table 2: Summary of mpox cases reported in Canada, 2022**

| Characteristic | n (%) | Unknown, n (%) |
|---|---|---|
| Total cases | 1,474 (100%) | N/A |
| Confirmed | 1,396 (94.7%) | |
| Probable | 78 (5.3%) | |
| **Sex** | | |
| Male | 757 (98.7%) | 707 (48.0%) |
| Female | 9 (1.2%) | |
| **Gender** | | |
| Woman | 11 (0.8%) | 152 (10.3%) |
| Man | 1,296 (98.0%) | |
| Transgender | 4 (0.3%) | |
| Non-binary | 3 (0.2%) | |
| Other | 7 (0.5%) | |
| **Sexual orientation** | | |
| GBMSM | 1,184 (80.3%) | 244 (16.6%) |
| Non-GBMSM | 46 (3.1%) | |
| **Province** | | |
| Ontario | 700 (47.5%) | 0 (0.0%) |
| Québec | 525 (35.6%) | |
| British Columbia | 193 (13.1%) | |
| Alberta | 43 (2.9%) | |
| Saskatchewan | 6 (0.4%) | |
| Newfoundland and Labrador | 2 (0.1%) | |
| Yukon | 2 (0.1%) | |
| Manitoba | 1 (0.1%) | |
| New Brunswick | 1 (0.1%) | |
| Nova Scotia | 1 (0.1%) | |

Abbreviations: GBMSM, gay, bisexual and other men who have sex with men; non-GBMSM, all other sexual identities and behaviours, including those for whom we have no information on sex/gender and gender(s) of sexual partner(s); N/A, not applicable

The majority of cases provided information on recent travel history during the 21 days before symptom onset (84.8%, n=1,250/1,474), with 22.1% (n=276/1,250) reporting travel outside their province of residence. Among those with travel outside their province of residence, 37.7% (n=104/276) reported international travel, 36.6% (n=101/276) reported domestic travel and 5.1% (n=14/276) reported both international and domestic travel.

Of all cases with information available, 45.2% (n=307/679) reported receiving a vaccination for one or more of the following: previous smallpox vaccination unrelated to the current outbreak; pre-exposure prophylaxis for the current outbreak; or post-exposure prophylaxis for the current outbreak. The proportion of people who received a vaccination was significantly higher among GBMSM (47.4%, n=276/582) compared to the non-GBMSM group (11.8%, n=2/17), reflecting vaccination eligibility criteria, which were based on the epidemiology within the context of the outbreak in Canada.

The five most common symptoms reported among cases with available data were rash/lesions (89.1%, n=1,245/1,398), fever (76.2%, n=744/977), chills (75.2%, n=394/524), lymphadenopathy (73.2%, n=706/964) and fatigue/exhaustion (73.0%, n=699/958). There were no significant differences in common symptom presentation between the GBMSM and non-GBMSM groups. The most common site for a rash was the anogenital/perianal area (75.0%, n=483/1,474). A significantly higher proportion of cases in the non-GBMSM group reported a rash on their limbs (60.0%, n=12/20) and feet (25.0%, n=5/20) compared to the GBMSM group (35.9% and 9.4%, respectively). Among those with information on the number of lesions, the majority of cases reported two to nine lesions (57.5%, n=126/219).

**Table 3: Frequency and percent distribution of people with a confirmed or probable diagnosis of mpox by select demographic and clinical factors across subgroups[a]**

| Case characteristics | Overall (N=1,474) | GBMSM (n=1,184) | Non-GBMSM (n=46) | *p*-value |
|---|---|---|---|---|
| | n (%) | | | |
| **Age group (in years)** | | | | |
| <15 | 2 (0.1%) | N/A | N/A | 0.281[b] |
| 15–19 | 8 (0.5%) | 6 (0.5%) | 0 (0.0%) | |
| 20–29 | 345 (23.4%) | 271 (22.9%) | 19 (41.3%) | |
| 30–39 | 579 (39.3%) | 475 (40.1%) | 12 (26.1%) | |
| 40–49 | 345 (23.4%) | 276 (23.3%) | 9 (19.6%) | |
| 50–59 | 136 (9.2%) | 111 (9.4%) | 3 (6.5%) | |
| 60–69 | 53 (3.6%) | 41 (3.5%) | 3 (6.5%) | |
| ≥70 | 5 (0.3%) | 0 (0.0%) | 0 (0.0%) | |
| **Hospitalized** | | | | |
| Yes | 46 (3.4%) | 35 (3.1%) | 2 (4.3%) | 0.651[c] |
| No | 1,319 (96.6%) | 1,106 (96.9%) | 44 (95.7%) | |

**Table 3: Frequency and percent distribution of people with a confirmed or probable diagnosis of mpox by select demographic and clinical factors across subgroups[a] (*continued*)**

| Case characteristics | Overall (N=1,474) | GBMSM (n=1,184) | Non-GBMSM (n=46) | *p*-value |
|---|---|---|---|---|
| | n (%) | | | |
| **Admitted to an ICU** | | | | |
| Yes | 3 (1.1%) | 3 (1.2%) | 0 (0.0%) | 1.000[c] |
| No | 277 (98.9%) | 244 (98.8%) | 14 (100%) | |
| **HIV status** | | | | |
| Positive | 299 (30.8%) | 246 (31.0%) | 5 (13.2%) | 0.019[a] |
| Negative | 673 (69.2%) | 547 (69.0%) | 33 (86.8%) | |
| **Concurrent STBBI** | | | | |
| Yes | 209 (22.2%) | 173 (22.7%) | 7 (20.6%) | 0.776 |
| No | 731 (77.8%) | 590 (77.3%) | 27 (79.4%) | |
| **Received vaccination** | | | | |
| Yes | 307 (45.2%) | 276 (47.4%) | 2 (11.8%) | 0.004[a] |
| No | 372 (54.8%) | 306 (52.6%) | 15 (88.2%) | |
| **Most common symptoms reported** | | | | |
| Rash/lesion | 1,245 (89.1%) | 1,061 (91.5%) | 41 (89.1%) | 0.588[c] |
| Fever | 744 (76.2%) | 634 (75.5%) | 24 (85.7%) | 0.213 |
| Chills | 394 (75.2%) | 331 (74.7%) | 14 (82.4%) | 0.580[c] |
| Lymphadenopathy | 706 (73.2%) | 610 (73.3%) | 21 (65.6%) | 0.336 |
| Fatigue/exhaustion | 699 (73.0%) | 597 (72.0%) | 23 (79.3%) | 0.388 |
| **Site of lesion** | | | | |
| Anogenital | 483 (75.0%) | 424 (76.4%) | 14 (70.0%) | 0.592[c] |
| Face | 197 (30.6%) | 172 (31.0%) | 7 (35.0%) | 0.704 |
| Tongue/mouth/lip | 89 (13.8%) | 78 (14.1%) | 4 (20.0%) | 0.510[c] |
| Limbs | 237 (36.8%) | 199 (35.9%) | 12 (60.0%) | 0.028[a] |
| Hand | 153 (23.8%) | 126 (22.7%) | 6 (30.0%) | 0.425[c] |
| Feet | 67 (10.4%) | 52 (9.4%) | 5 (25.0%) | 0.039[a,b] |
| Torso | 186 (28.9%) | 161 (29.0%) | 8 (40.0%) | 0.289 |
| **Number of lesions** | | | | |
| ≤1 | 33 (15.1%) | 28 (15.0%) | 1 (16.7%) | 0.868[b] |
| 2–9 | 126 (57.5%) | 110 (58.8%) | 3 (50.0%) | |
| 10–49 | 53 (24.2%) | 45 (24.1%) | 2 (33.3%) | |
| 50–99 | 5 (2.28%) | 3 (1.6%) | 0 (0.0%) | |
| ≥100 | 2 (0.9%) | 1 (0.5%) | 0 (0.0%) | |
| **Common exposures and likely mode of acquisition** | | | | |
| Contact with a possible or known case/ contaminated material | 191 (59.1%) | 162 (57.9%) | 3 (50.0%) | 0.700[b] |
| Person-to-person transmission via sexual contact | 717 (96.2%) | 642 (97.1%) | 16 (80.0%) | 0.003[a,b] |
| Travel history in the 21 days prior to symptom onset | 276 (22.1%) | 241 (22.1%) | 8 (17.8%) | 0.489 |

Abbreviations: GBMSM, gay, bisexual and other men who have sex with men; ICU, intensive care unit; non-GBMSM, all other sexual identities and behaviours, including those for whom we have no information on sex/gender and gender(s) of sexual partner(s); N/A, not applicable; STBBI, sexually transmitted and blood-borne infection

[a] Statistically significant ($p<0.05$) difference between GBMSM and non-GBMSM mpox cases. The *p*-value was determined based on a $\chi^2$ test of homogeneity at $\alpha=0.05$

[b] The *p*-value determined based on an independent t-test to compare mean age (in years) between GBMSM and non-GBMSM mpox cases

[c] The *p*-value determined based on Fisher's exact test instead of a $\chi^2$ test, given expected cell values are less than five

Of all cases for whom information was available, 3.4% (n=46/1,365) were hospitalized, and 1.0% (n=3/300) were admitted to an intensive care unit. Among the GBMSM group, 3.1% of cases (n=35/1,141) were hospitalized, and 4.3% (n=2/46) of non-GBMSM cases were hospitalized; no statistically significant difference in hospitalization between GBMSM and non-GBMSM groups was observed.

## Discussion

This paper describes the epidemiology of the multi-jurisdictional mpox outbreak in Canada between April and December 2022. The 2022 mpox outbreak in Canada predominantly affected GBMSM in large metropolitan cities (Toronto, Montréal and Vancouver) and sexual contact was the likely route of transmission for most cases (9,18,19). Similar to other affected countries during the 2022 global mpox outbreak (20), initial transmission within high-contact sexual networks likely drove the rapid increase in cases in June 2022. Across both the GBMSM and non-GBMSM groups, the most common symptoms were rash/lesions, fever, chills, lymphadenopathy and fatigue/exhaustion. A higher proportion of cases among GBMSM were living with HIV, compared to non-GBMSM, which is similar to findings from the 2022 global mpox outbreak (20). However, there was no statistically significant difference in hospitalization status between the two groups, and the majority of overall cases did not require hospitalization, suggesting low disease severity within the Canadian context. No mpox-related deaths were reported in Canada throughout the outbreak.

Our data also show that the non-GBMSM group had a relatively lower percentage of cases associated with sexual transmission than the GBMSM group. Additionally, presentation of a rash on limbs and feet were significantly more common among non-GBMSM compared to GBMSM, which may suggest variable sites of inoculation and lesion patterns by subgroup. A global case series examining transmission in women and non-binary individuals across 15 countries during the 2022 mpox outbreak reported that acquisition through close household and occupational contacts were more common among this group, compared to sexual contact (21). In Canada, there were no reported cases of occupational transmission and a limited number of cases among household contacts, including children younger than 15 years. Given the limited number of non-GBMSM cases in Canada, it is difficult to draw conclusions about other possible modes of transmission.

The outbreak was contained using multi-level approaches with efforts across various levels of government, relying heavily on existing liaisons with local public health units that were most affected by the outbreak, as well as community engagement and advocacy. At the federal level, PHAC: 1) activated an Incident Management System aimed at coordinating and responding to the emerging mpox outbreak, 2) conducted risk assessments to evaluate the domestic situation, 3) recommended actions grounded in evidence and 4) coordinated national meetings to share data and information, collaborate on products and disseminate best practices to respond effectively to the outbreak. At the local and provincial/territorial level, successful strategies included mass pre-exposure prophylaxis vaccination clinics, case and contact management, guidance to health care providers and use of antivirals for clinically severe cases (9). Local, provincial and territorial public health authorities engaged with community organizations (e.g., Gay Men's Sexual Health Alliance in Ontario) to help mobilize affected communities with mpox-related knowledge (e.g., signs and symptoms, mpox vaccination, testing resources, safer sex messaging, etc.) and encourage testing in the presence of compatible symptoms through social media and popular dating applications.

While targeted vaccination played an important role in curbing the mpox outbreak (22,23), evidence from mathematical models calibrated to both Canadian case and vaccination data from 2022 highlighted the importance of changes to sexual practices as a major driver in decreasing transmission and the duration of the outbreak (24).

Sporadic detection of mpox cases continue to occur globally with small, localized increases in activity occurring in many jurisdictions, including Canada, since 2022 (25,26). It is, therefore, important that jurisdictions continue their surveillance efforts for mpox to ensure early detection of a resurgence in cases, including new outbreaks linked to different MPXV lineages, and to continue to offer vaccination against mpox for those who are eligible to minimize transmission and severity of disease (22,23). Mpox is a notifiable disease in most provinces and territories across Canada, and in August 2024, it became a nationally notifiable disease, which facilitates ongoing surveillance work. Public Health Agency of Canada, along with federal/LPT partners, are continuing to collaborate and conduct surveillance activities, including laboratory-based and wastewater surveillance of MPXV (27).

### Limitations

Due to the complexity of rapidly establishing enhanced surveillance to characterize an emerging infection, there are several considerations regarding the quality and consistency of reported data. First, the development of the national case report form was iterative, with initial cases potentially missing some information that was later prioritized (e.g., expanded data capture for gender). Second, due to the diversity of public health systems across LPTs, some information could not be collected or was incomplete. While a history of vaccination against mpox may have mitigated the extent and severity of the overall clinical presentation of cases (23), a high level of missing data for vaccination history (54%) in the national mpox dataset precluded an assessment of this variable in this report. Some data, such as risk factors and likely source of acquisition, were also self-reported, which could have been impacted by recall bias as

well as stigma. Lastly, it is likely that the number of mpox cases reported is an underestimate of the true burden of disease as those with mild symptoms who did not seek health care would not have been tested for MPXV.

### Conclusion

The patterns and characteristics of the mpox outbreak in Canada were similar to other countries implicated in the 2022 global mpox outbreak, whereby GBMSM were disproportionately impacted. Changes in sexual practices and uptake of vaccinations helped to rapidly reduce transmission of mpox during the 2022 outbreak in Canada. Alongside partners, PHAC will continue to vigilantly monitor for cases and use evidence-informed practices to support the timely implementation of public health interventions to reduce transmission.

## Authors' statement

MB — Conceptualization, investigation, methodology, formal analysis, data interpretation, writing–original draft, writing–review & editing
JV — Conceptualization, investigation, methodology, formal analysis, data interpretation, writing–original draft, writing–review & editing
MP — Investigation, methodology, data interpretation, writing–original draft, writing–review & editing
GB — Investigation, methodology, data interpretation, writing–review & editing
GC — Investigation, methodology, data interpretation, writing–review & editing
JK — Investigation, methodology, data interpretation, writing–review & editing
MS — Investigation, methodology, data interpretation, writing–review & editing
KT — Investigation, methodology, data interpretation, writing–review & editing
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### Competing interests

None.

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# Differences in sensationalism in international news media reporting of COVID-19: An exploratory analysis using the Global Public Health Intelligence Network (GPHIN) system

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## Abstract

**Background:** The Global Public Health Intelligence Network (GPHIN) is an event-based surveillance platform that collects thousands of pieces of open-source information, including international news media, across multiple languages on a daily basis. Analysts have observed that news media reporting in some languages tended to use more sensational wording to describe major health events. There has been minimal research exploring potential differences in sensationalism in international news media reporting to confirm these observations.

**Objective:** This exploratory study assessed the differences in the level of sensationalism in early international news media reporting of COVID-19 through a mixed-methods analysis.

**Methods:** Relevant news media articles received in GPHIN seven days following the Public Health Emergency of International Concern declaration of COVID-19 by the World Health Organization were extracted for screening and analysis. An adapted tool was used to measure the sensationalism of pandemic-related health news. Deductive thematic analysis was conducted to examine themes of sensationalism. Differences in prevalence of sensationalism in news media reporting by language and country/territory of publication were assessed. Sentiment analysis assessed the sentiment and emotional tone of the news media articles.

**Results:** Of 951 news articles that met the eligibility criteria, 155 contained sensationalism. There were significant differences between languages (French, Russian and Spanish) and various domains of sensationalism. This study also found a more negative emotional tone in news media articles with sensationalism.

**Conclusion:** This exploratory study showed that language has the potential to impact the perception of health events using more sensationalized language.

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## Introduction

On January 7, 2020, Chinese authorities identified a novel coronavirus temporarily named "2019-nCoV" (1), which rapidly spread around the world. The World Health Organization (WHO) declared a public health emergency of international concern (PHEIC) on January 30, 2020. Due to the global spread of the virus, which came to be known as COVID-19, WHO characterized the outbreak as a pandemic on March 11, 2020 (1).

This pandemic was the first public health event of its kind with constant media coverage (2), becoming a political battleground, with leaders debating over public policy and medical interpretations (2). The pandemic also highlighted multiple social, cultural and economic issues arising from the media's constant dissemination of information (3). Verified, official information, based on best information available at the time, was complicated by inaccurate claims amplified on various news media platforms, which proved to be almost as much of a threat to global public health as the virus itself (4).

Technological advancements and online news media create opportunities to keep people informed, connected and safe (4). However, it can also create the opportunity for sensationalizing issues by presenting news as more extraordinary, interesting or relevant than is objectively warranted, which can undermine global responses and jeopardize measures to control major public health events (4).

During global disasters such as pandemics, crisis communication is crucial to dispel fears and uncertainties and unify individuals worldwide against public health threats (5). Sensational communication, however, can result in negative personal and economic consequences (5). For new or emerging diseases, particularly when there is limited available information from official sources, sensational reporting may influence the risk assessment and response to the event implemented by decision-makers, as well as the perception of the risk of the event by the public (6,7).

The Global Public Health Intelligence Network (GPHIN) is an all-hazards event-based surveillance system that is operated by the Public Health Agency of Canada (PHAC) (8). The system was developed by the Government of Canada in collaboration with the WHO for use by non-governmental agencies and organizations, as well as government authorities who conduct public health surveillance (9). To identify potential public health threats, GPHIN collects and assesses thousands of pieces of open-source information on a daily basis through artificial intelligence algorithms (i.e., machine learning, natural language processing). Although GPHIN monitors a diverse array of open sources, most of the information is currently sourced from news media (i.e., news media in the context of this study refers to mass media that focus on delivering news in text format via the Internet to the public) (8). The information is then curated by a multicultural team of analysts, covering 10 languages (Arabic, Chinese [Simplified], Chinese [Traditional], English, Farsi, French, Hindi, Portuguese, Russian and Spanish).

Given their linguistic and cultural diversity, GPHIN analysts add a language and cultural perspective to the interpretation of international reporting that may otherwise be misinterpreted or misunderstood if only machine-translated English or only a Canadian cultural lens is used. Over time, GPHIN analysts have observed that news media from various languages tended to use more exaggerated or hyperbolical expressions/terms to describe new or emerging diseases.

There has been minimal research exploring potential differences in sensationalism in international news media reporting of major health events to confirm these observations and presents a knowledge/research gap. To address this gap, this exploratory study assessed the differences in the level of sensationalism in early international news media reporting of COVID-19 through a mixed-methods analysis.

## Methods

Relevant news media articles received in the GPHIN system in the first seven days following the declaration of the COVID-19 PHEIC on January 30, 2020, were identified and extracted (**Table 1**). The time restriction of the first seven days was chosen to observe the initial reaction of news media following the COVID-19 PHEIC declaration, so there is a shared baseline for the globally relevant health event. Articles in Arabic, Chinese (Simplified and Traditional), English, Farsi, French, Portuguese, Russian and Spanish were reviewed (the Hindi language was not yet implemented into the GPHIN system at the time of the study). Reports from non-news media sources, including official sources such as the WHO, European Centre for Disease Prevention and Control, and United States Centers for Disease Control and Prevention were excluded.

An adapted version a tool by Hoffman *et al*. (10) was piloted to measure the sensationalism of pandemic-related health news was used to assess five domains of sensationalism as described in **Table 2**. For this study, a binary "Yes/No" response was used for the tool, instead of the five-point Likert-like scale, where "Yes" represented the presence of sensational text and "No" represented the absence of sensational text. This modification was made to avoid the potential subjectivity of assessing the relative degree of sensationalism using the Likert-like scale (where the differences between "not too much," "somewhat" and "fairly" sensationalizing are open to interpretation). An article was deemed to have overall sensationalism if at least one of the domains listed in Table 2 was selected as "Yes."

**Table 1: Global Public Health Intelligence Network system query/search strategy**

| Date | GPHIN system query | Search results (conducted on September 14, 2022) |
|---|---|---|
| Date of PHEIC declaration by the WHO: January 30, 2020<br>Date range of relevant news media articles received in the GPHIN system: January 30–February 6, 2020 | (Title/Text contains (exact match): coronavirus OR Title/Text contains (exact match): corona virus OR Title/Text contains (exact match): 2019-nCoV OR Title/Text contains (exact match): Wuhan pneumonia) AND (Title/Text contains (exact match): PHEIC OR Title/Text contains (exact match): public health emergency of international concern OR Title/Text contains all of the following (comma separated): international, emergency) AND Date received between 2020-01-30 and 2020-02-06[a] | 951 |

Abbreviations: GPHIN, Global Public Health Intelligence Network; PHEIC, public health event of international concern; WHO, World Health Organization
[a] The COVID-19 and SARS-CoV-2 nomenclature were officially introduced by WHO on February 11, 2022, and therefore not included in the query (including them in the query did not change the search results)

**Table 2: Five domains of sensationalism tool[a]**

| Domain | Question |
|---|---|
| Exposing | Does the article attempt to expose certain events? |
| Speculating | Does the article offer a guess or suggest what the future consequences of an issue are likely to be? |
| Generalizing | Does the article make generalizing statements that extrapolate a trend out of an incident or pass a judgement about a whole class of people? |
| Warning | Does the article generate anxiety about an issue or offer suggestions on how to avoid becoming a victim? |
| Extolling | Does the article exaggerate facts as extraordinary, project events as historic, praise individuals for heroic acts, etc.? |

[a] Adapted from reference (10)

An inclusion/exclusion assessment was performed using the criteria in Table 1 by two reviewers, with any disagreements resolved by consensus. The following data was extracted for each article included for analysis: assessment against each of the five domains of sensationalism, overall assessment of sensationalism (Sensationalism=Yes if at least one domain selected and Sensationalism=No if no domains were selected), date of publication, country/territory of news media outlet and original language of publication. Data extraction was performed by one reviewer and validated by a second reviewer.

The title and body of each news media article included for analysis were independently appraised for sensationalism by two reviewers, with any disagreements resolved by consensus. For non-English articles, English analysts reviewed the machine-translated text in English, while GPHIN analysts with expertise in the language of the article performed a secondary review in the original language.

This study used a mixed-method approach for analysis. For the qualitative portion, thematic analysis, a flexible method that enables the identification of patterns of meaning (themes) across data sets by interrogating both semantic and latent meanings (i.e., content, ideas, assumptions) below the surface (11), was used. In this study, deductive thematic analysis was used as themes were identified within each domain. There were 155 news media articles identified as having overall sensationalism and top themes within each domain were recorded.

For the quantitative portion of the study, the analysis of articles with overall sensationalism (Sensationalism=Yes) was performed using Stata IC 15.1. Differences in the prevalence of sensationalism in news media reporting by language were assessed using the chi-square test and Fisher's exact test, depending on whether assumptions were met. Four sentiment analysis methods, AFINN, Bing, Syuzhet and National Research Council packages, were performed to assess the sentiment and emotional tone of news media articles (12). These sentiment analyses were done using algorithms implemented in R programming language (see **Table 3**). Using the Welch two sample t-test function in R, the sentiments were then compared between news media articles with ("Yes") and without ("No") overall sensationalism to determine whether there were statistical differences in the sentiment and tone of describing and reporting on COVID-19. The text analyzed in this analysis was strictly in English or machine-translated English due to R package restrictions.

# Results

## Screening

From the GPHIN system, 951 articles were screened and assessed for eligibility. Of these, 449 were excluded as they did not meet the eligibility criteria. There were 200 English and 302 non-English articles included in the analysis (**Figure 1**). Out of 502 articles, 155 were identified as having overall sensationalism. Sensationalism and news media country/territory of publication was not found to be statistically significant (**Appendix, Table A1**) and, therefore, we could not explore the potential differences between reporting in countries and assess whether it was a potential confounder.

## Qualitative analysis

Common themes observed within news media articles that had overall sensationalism are presented in **Table 4**.

**Table 3: Sentiment analysis methods**

| Method | Summary |
|---|---|
| AFINN | AFINN is a lexicon-based sentiment analysis method. It assigns pre-defined sentiment scores (positive or negative) to individual words in a document.<br>The scores for each word are then aggregated to calculate an overall sentiment score for the document.<br>AFINN typically provides a numeric score for each document, where a higher score indicates a more positive sentiment and a lower score indicates a more negative sentiment. |
| Bing | Bing is another lexicon-based sentiment analysis method. It assigns positive, negative or neutral labels to individual words.<br>Like AFINN, it aggregates the sentiment labels to calculate an overall sentiment score for a document.<br>It is often used for binary sentiment classification (positive or negative). |
| Syuzhet[a] | Syuzhet is a sentiment analysis package in R that relies on sentiment lexicons and dictionaries.<br>It provides a more fine-grained approach, categorizing sentiment into emotions such as joy, anger, sadness and overall sentiment.<br>This method allows for a more nuanced emotional tone analysis and can provide insights into the specific emotions expressed in a document. |
| National Research Council Canada (NRC) | The NRC *Sentiment and Emotion Lexicons* tool is a more advanced approach considering a broader range of emotions and sentiments.<br>It categorizes sentiment into various dimensions: positive, negative, anger, anticipation, disgust, fear, joy, sadness, surprise and trust.<br>This method provides a rich understanding of the emotional content in a document, making it suitable for more detailed sentiment analysis. |

[a] Reference (12)

**Figure 1: Screening of news media related to COVID-19 public health event of international concern on the Global Public Health Intelligence Network system**

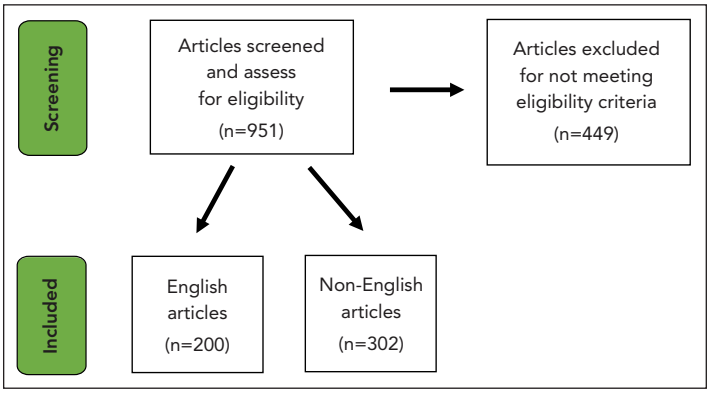


**Table 4: Themes identified within sensationalism domains in COVID-19 news media**

| Domain | Themes identified |
|---|---|
| Exposing | Criticism of China<br>Negative feedback on how the situation is being handled<br>Racism against the Chinese population<br>Deficiencies in government system<br>Sparse information being given from China<br>Foreigners not being taken care of<br>Local infrastructure being overwhelmed<br>Mistrust over China's handling of the situation<br>China semi-quarantine "threat" to the global economy<br>Situation could have been prevented<br>Criticism of the United States<br>Downplaying the virus severity<br>Unnecessary or excessive restrictions on China<br>Promoting panic through closing borders<br>Inappropriately overreacted |
| Speculating | Unknown/grim outcome, unknown consequences<br>Uncertainty looms<br>Impact being difficult to assess<br>Suspicions over the true cause of the virus and spread<br>Future of virus being unpredictable<br>COVID-19 may impact China's economy/global economy (How will tourism/businesses be affected) |
| Generalizing | Discrimination of Chinese individuals and their "cause" of COVID-19<br>COVID being "less dangerous" than influenza/SARS<br>Unnecessary/unjustified panic, not a major problem |
| Warning | Threat of COVID-19 spreading to other countries/worldwide<br>Flu being more of a threat than COVID-19 (therefore, individuals should focus more on flu prevention)<br>Threat of misinformation spreading<br>Potential negative impact on China's economy and moreover, to the global economy<br>Whole world should be "on alert" |
| Extolling | Labelling COVID-19 as a monster/evil/demon/invisible killer<br>Comparing the fight against COVID-19 to war<br>Describing the situation as the end of the world: zombie apocalypse, ghostly city, devastating plague, doomsday predictions, pandemic deadlier than wars<br>The notion of fear "spreading like a virus" |

With each sensationalism domain, five statistically significant themes were observed.

**Exposing domain:** News media in the French language exposed that local healthcare systems were becoming overwhelmed and saturated with patients (13). There was also negative criticism of how China was handling the COVID-19 situation and how they tried to maintain an image to the global community, however the "social pressure was too much" (14).

**Speculating domain:** The French language news media had speculated about what would happen to the local business and economy if COVID-19 spread and shut down countries (15). Articles had also speculated about the true cause of COVID-19 and from where it came (16). They also questioned whether isolation measures ever worked (17). Similarly, news media in the Russian language speculated about whether COVID-19 would do harm to the economy (18).

**Generalizing domain:** Discriminatory undertones were found within new media in the French language. Articles stated that the cause of the situation was due to Chinese citizens and that it was Wuhan's problem rather than a problem for the rest of the world (14,19–21).

**Warning domain:** For the articles with the elements of the warning domain, the focus was broad. Articles in the Spanish language warned about the situation of COVID-19 spreading to other countries and that COVID-19 was spreading much faster than the previous SARS outbreak in 2001 (22–25). Articles further warned readers that the situation in China was completely out of hand and that the issue of COVID-19 was extremely serious (26). There was also a notion that the virus was unstoppable, emphasizing the urgency and anxiety of the situation. A theme of warning, telling readers that they were dealing with a dangerous enemy, was also noted (27–29).

**Extolling domain:** The Russian language was the only language that was statistically significant by the extolling domain. Articles mentioned the "fight against evil" and that "a monster is born" for which "the world is not ready" (30,31).

## Quantitative analysis

**Sensationalism domains and language:** English and Arabic were identified as having the highest number of articles with overall sensationalism (n=62 and n=24, respectively), while Farsi, Russian and Chinese were found to have the lowest number of overall sensationalism (n=1, n=7 and n=7, respectively) (**Figure 2**). The French language was statistically significant for exposing ($p$=0.004), speculating ($p$=0.007) and generalizing ($p$=0.007). The Russian language was statistically significant for speculating ($p$=0.046), generalizing ($p$=0.046), warning ($p$=0.013), extolling ($p$=0.046) and overall sensationalism ($p$=0.004). The Spanish language was statistically significant for warning ($p$=0.034) and overall sensationalism ($p$=0.034).

**Figure 2: News media articles reviewed by language with and without overall sensationalism**


**Sentiment analysis:** To determine whether differences in sentiment were statistically significant for the two groups (Overall Sensationalism=Yes vs. Overall Sensational=No), t-tests were performed using R programming.

- For the AFINN score comparison: t(240)=−3.8309, $p$<0.001
- For the Bing score comparison: t(235)=−4.7292, $p$<0.001
- For the Syuzhet score comparison: t(217)=−2.962, $p$<0.001

The $p$-value obtained from the tests suggested statistical significance in sentiment scores between the two groups. A more negative mean AFINN, Bing and Syuzhet score for the overall sensationalism news article group indicated a difference in the overall sentiment or emotional tone between these groups.

Regarding the National Research Council Canada's (NRC) score for sentiments, the comparison was made to negative, positive and fear sentiments. The scores in the Overall Sensationalism=Yes news group were significantly higher in all three using the t-test to compare.

- The results for NRC-negative comparison: t(239)=5.483, df=239.67, $p$<0.001
- The results for NRC-positive comparison: t(247)=4.5944, $p$<0.001
- The results for NRC-fear comparison: t(254)=5.4729, $p$<0.001

The NRC sentiment scores for negative, positive and fear sentiments were significantly higher in the Overall Sensationalism=Yes news article group. This aligns with the expectation that sensationalism exaggerates emotions, including negative and fearful sentiments. The higher positive scores may be due to sensationalized content trying to elicit strong emotional reactions from readers.

Based on the provided results and analysis, there was a significant difference in sentiment and emotional tone between articles with sensationalism compared with those without sensationalism.

## Discussion

This study has demonstrated that even with machine translation, sensational language can still be understood, and this may have an influence on a reader's perception of a given issue. Themes repeated in news media articles, regardless of language, may also impact and change the reader's perceptions. Sensationalism in news media reporting could have impacted how COVID-19 was perceived after the PHEIC declaration. The analysis of sentiment scores indicated a clear and statistically significant difference in sentiment and emotional tone between sensational and non-sensational articles.

As seen in our study, media may use elements from warning, extolling, speculating and/or exaggerating domains of sensationalism to capture the reader's attention and sway the reader in a particular direction. This could be damaging to a reader as, oftentimes, when reading a news article, they may not be able to do anything to prevent or reduce the issue's risk, which could increase perceived vulnerability, creating anxiety (32). This idea complements further evidence suggesting that the more access one has to information, the more stressful one may become, potentially inducing unnecessary fear and concern (33).

Our study did not look at the effects of the use of sensationalism in social media; however, our findings on traditional news media complement research on both social media and traditional news media and the potential misperception of information regarding COVID-19. A study by Montezari *et al.* highlighted that exposure to COVID-19 news on social media was significantly correlated with increased feelings of anxiety and fear, as well as behavioural changes (32). Ravenelle *et al.* observed that increased media consumption was linked to decreased mental health and a sense of unhealthiness (34). Other research studies have found that even if one has a highly curated social media feed, there is still a possibility for media to contain misconstrued messages and information (35,36). Dechene *et al.* noted that with increasing cumulative exposure to exaggerated information, users are more likely to experience a "reinforcement effect," where familiarity leads to a stronger change and belief of opinion (37).

### Limitations

A limitation of this exploratory study was that the articles included for review were restricted to those picked up through the GPHIN system and therefore may not be representative of all available news media articles available online. Misclassification bias could have occurred when reviewing articles for sensationalism. We note that the analysis performed was only looking at the seven days following the PHEIC; therefore, we were unable to conduct a trend analysis over time to see if there was a change in the language used in the reporting of COVID-19 by the media. Although efforts were made to minimize translation and cultural bias by including language specialists in the sensationalism assessments, there was likely residual language/cultural bias due to the study team living in Canada and working in English/French. The validity of the pilot tool used in this exploratory study to assess sensationalism has not yet been established.

### Conclusion/future research

Having ready access to international news media reporting allows individuals to be informed and connected; however, as demonstrated in this study, news media sources may be prone to sensationalism and should be interpreted with caution. The findings of this exploratory study suggest that it would be beneficial for tools to be developed that can help analysts and users of event-based surveillance systems flag potentially sensational articles so that the information could be appropriately assessed and used to inform decision-making. Such tools do not currently exist, although there are similar tools (e.g., websites such as mediabiasfactcheck.com) that provide information on political standpoints and the trustworthiness of news media sources. Additional research is needed to refine and validate tools for assessing sensationalism in news media and other media, as well as to examine the topic across different health events and time periods to identify broader trends.

## Authors' statement

JP — Supervision, conceptualization, data extraction, formal analysis, writing–original draft, writing–reviewing & editing
TN — Conceptualization, methodology, data extraction, writing–review & editing
AZ — Methodology, data extraction, analysis, writing–review & editing
FT — Writing–review & editing
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### Competing interests

None.

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# Appendix

**Table A1: Proportion of articles by language and country/territory of publication (n=502)**

| Country/territory of publication | Languages | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Arabic n (%) | Chinese n (%) | English n (%) | Farsi n (%) | French n (%) | Portuguese n (%) | Russian n (%) | Spanish n (%) |
| Argentina | - | - | - | - | - | - | - | 3 (6.1) |
| Australia | - | - | 10 (5.0) | - | 3 (6.8) | - | - | - |
| Austria | - | - | - | - | - | 1 (2.2) | - | - |
| Bahrain | 1 (1.4) | - | - | - | - | - | - | - |
| Bangladesh | - | - | 2 (1.0) | - | - | - | - | - |
| Brazil | - | - | 1 (0.5) | - | - | 20 (44.4) | - | - |
| Canada | - | - | 13 (6.5) | - | - | - | - | - |
| Chile | - | - | - | - | - | - | - | 3 (6.1) |
| China | 5 (7.0) | 4 (10.0) | 2 (1.0) | - | 1 (2.2) | - | 2 (3.9) | - |
| Czechia | - | - | - | 1 (50.0) | - | - | - | - |
| Egypt | 11 (15.4) | - | - | - | - | - | - | - |
| France | 7 (9.8) | 2 (5.0) | - | - | 30 (68.1) | - | - | 2 (4.0) |
| Gaza Strip and West Bank | 2 (2.8) | - | - | - | - | - | - | - |
| Germany | 4 (5.6) | 1 (2.5) | 3 (1.5) | - | - | - | - | - |
| Hong Kong | - | 15 (37.5) | - | - | - | - | - | - |
| India | - | - | 11 (5.5) | - | - | - | - | - |
| Indonesia | - | - | 1 (0.5) | - | - | - | - | - |
| Iran | - | - | - | 1 (50.0) | - | - | - | - |
| Iraq | 3 (4.2) | - | - | - | - | - | - | - |
| Ireland | - | - | 3 (1.5) | - | - | - | - | - |
| Jordan | 3 (4.2) | - | - | - | - | - | - | - |
| Kuwait | 4 (5.6) | - | - | - | - | - | - | - |
| Latvia | - | - | - | - | - | - | 1 (1.9) | - |
| Lebanon | 1 (1.4) | - | - | - | - | - | - | - |
| Libya | 1 (1.4) | - | - | - | - | - | - | - |
| Luxembourg | - | - | - | - | 1 (2.2) | - | - | - |
| Malaysia | - | - | 4 (2.0) | - | - | - | - | - |
| Mauritania | - | - | - | - | 1 (2.2) | - | - | - |
| Mauritius | - | - | - | - | 1 (2.2) | - | - | - |
| Mexico | - | - | - | - | - | 1 (2.2) | - | 3 (6.1) |
| Morocco | 1 (1.4) | - | - | - | - | - | - | - |
| Netherlands | - | - | 1 (0.5) | - | - | - | - | - |
| New Zealand | - | - | 1 (0.5) | - | - | - | - | - |
| Oman | 2 (2.8) | - | - | - | - | - | - | - |
| Pakistan | - | - | 4 (2.0) | - | - | - | - | - |
| Peru | - | - | - | - | - | - | - | 4 (8.1) |
| Philippines | - | - | 7 (3.5) | - | - | - | - | - |
| Portugal | - | - | - | - | - | 9 (20.0) | - | - |

**Table A1: Proportion of articles by language and country/territory of publication (n=502) (*continued*)**

| Country/territory of publication | Languages | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Arabic n (%) | Chinese n (%) | English n (%) | Farsi n (%) | French n (%) | Portuguese n (%) | Russian n (%) | Spanish n (%) |
| Qatar | 7 (9.8) | - | 10 (5.0) | - | - | - | - | - |
| Republic of Congo | - | - | 3 (1.5) | - | - | - | - | - |
| Russia | - | - | 2 (1.0) | - | - | - | 37 (72.5) | 4 (8.1) |
| Saudi Arabia | 6 (8.4) | - | - | - | - | - | - | - |
| Singapore | - | 2 (5.0) | 4 (2.0) | - | - | - | - | - |
| South Korea | - | 5 (12.5) | 2 (1.0) | - | - | - | - | - |
| Spain | - | - | 1 (0.5) | - | - | 1 (2.2) | - | 17 (34.6) |
| Switzerland | - | - | - | - | 2 (4.5) | - | - | - |
| Syria | 1 (1.4) | - | - | - | - | - | - | - |
| Taiwan | - | 7 (17.5) | 1 (0.5) | - | - | - | - | - |
| Tunisia | 1 (1.4) | - | - | - | 2 (4.5) | - | - | - |
| Turkey | - | - | 1 (0.5) | - | 1 (2.2) | - | - | - |
| Ukraine | - | - | - | - | - | - | 11 (21.5) | - |
| United Arab Emirates | 4 (5.6) | - | - | - | - | - | - | - |
| United Kingdom | 5 (7.0) | - | 40 (20.0) | - | - | - | - | 2 (4.0) |
| United States | 2 (2.8) | - | 67 (33.5) | - | - | 13 (28.8) | - | 11 (22.4) |
| Unknown | - | 4 (10.0) | 4 (2.0) | - | 2 (4.5) | - | - | - |
| Vietnam | - | - | 2 (1.0) | - | - | - | - | - |
| Total | 71 | 40 | 200 | 2 | 44 | 45 | 51 | 49 |

Abbreviation: -, not applicable

# Infectious syphilis and congenital syphilis in Canada, 2023*

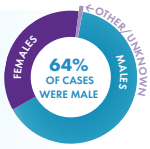
## INFECTIOUS SYPHILIS

**12,135** CASES IN 2023

### MOST IMPACTED POPULATION GROUPS IN 2023

#### BY SEX & GENDER

The rate among **FEMALES** has **TRIPLED** since 2018 – a **MUCH FASTER INCREASE** than among males




#### BY SEXUAL BEHAVIOUR

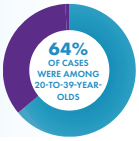
There has been a **FASTER INCREASE** in cases in the **NON-GBMSM POPULATION**, compared to GBMSM, since 2018 (177% increase vs. 2% increase)


#### BY AGE GROUP

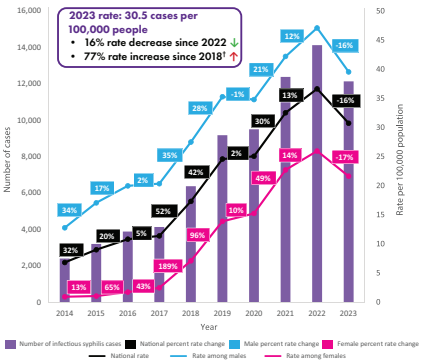
Males aged **30 TO 39** years old had the **HIGHEST RATE** of any age group, male or female, in the population and represented 22% of total cases

**MALES: 25-29-** and **30-39-**year-olds had the **HIGHEST RATES** (49% of male cases)

**FEMALES: 20-24-** and **25-29-**year-olds had the **HIGHEST RATES** (40% of female cases)




Number of reported cases and rates of infectious syphilis** in Canada, by sex, from 2014 to 2023



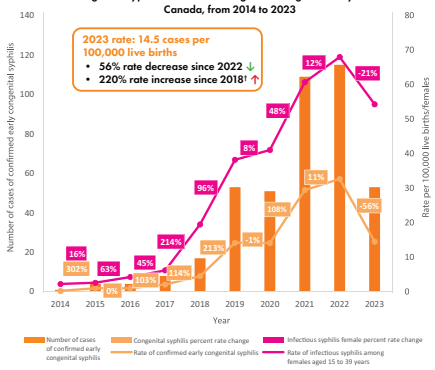

Note: While it appears incidence rates are declining, to keep the number of cases declining towards the global targets,† it is crucial we continue to address actions outlined in the STBBI action plan.

## CONGENITAL SYPHILIS

**53** CASES IN 2023

In 2023, there were 174 reported cases of confirmed early congenital syphilis, probable early congenital syphilis, syphilitic stillbirths, and unknown-stage congenital syphilis.‡

Number of reported cases and rates of confirmed early congenital syphilis and rates among females aged 15-39 years in Canada, from 2014 to 2023

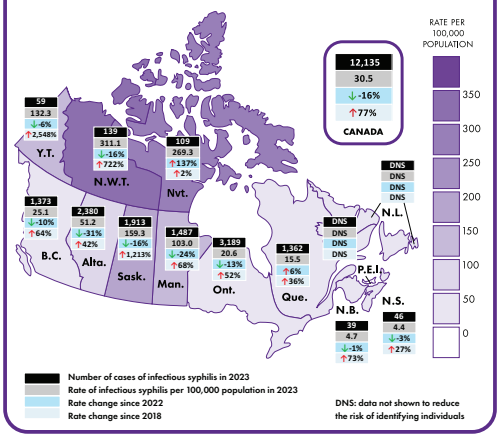



Note: While it appears incidence rates are declining, to keep the number of cases declining towards the global targets,† it is crucial we continue to address actions outlined in the STBBI action plan.

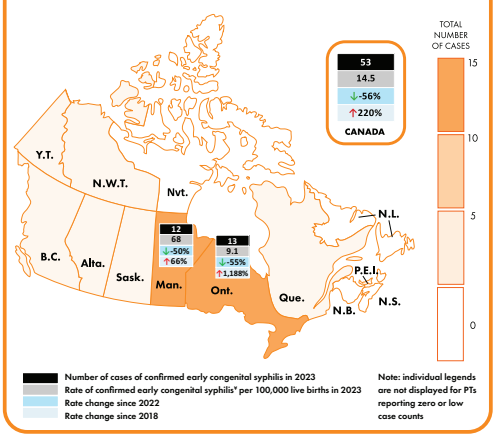
**TO LEARN MORE ABOUT SYPHILIS, CLICK HERE: CANADA.CA/SYPHILIS**

NATIONAL EPIDEMIOLOGIC TRENDS[8]

## INFECTIOUS SYPHILIS




## CONGENITAL SYPHILIS




EPIDEMIOLOGIC TRENDS IN PROVINCES AND TERRITORIES[8]

Social and structural determinants of health and health inequities play a role in the differences in rates of syphilis across different populations.[11]

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

Reporting between 2020 and 2022 occurred in the context of the COVID-19 pandemic, which continues to have an impact on sexually transmitted and blood-borne infection (STBBI) services.[9]

See the Notes section in the text description.

# CCDR

## CANADA COMMUNICABLE DISEASE REPORT

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