# Cost-effectiveness analysis of nirsevimab and maternal RSVpreF vaccine strategies for prevention of Respiratory Syncytial Virus disease among infants in Canada: a simulation study

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## Summary

**Background** The cost-effectiveness of immunisation strategies with a long-acting monoclonal antibody (nirsevimab) and/or a protein-based maternal vaccine (RSVpreF) for protecting infants from Respiratory Syncytial Virus (RSV)-associated illness has not been previously determined for Canada. We estimated the health benefits and cost-effectiveness of nirsevimab for immunising the entire birth cohort, regardless of gestational age or other risk factors. Additionally, we evaluated the health benefits and cost-effectiveness of a combined strategy of year-round vaccination of pregnant women with RSVpreF and immunisation of infants at high risk, including those born preterm or with chronic conditions, with nirsevimab during the RSV season.

**Methods** We developed a discrete-event simulation model, parameterized with the data on medically-attended RSV infections among infants under one year of age from 2010 to 2019, including outpatient care, hospitalisations, and deaths. Intervention scenarios targeting twelve monthly birth cohorts and pregnant women, reflecting the 2021 census data for Ontario, Canada were evaluated over a follow-up time horizon of one year from birth. Taking into account the costs (in 2023 Canadian dollars) associated with RSV-related outcomes, we calculated the net monetary benefit using the quality-adjusted life-year (QALY) gained. Further, we determined the range of price-per-dose (PPD) for nirsevimab and RSVpreF within which the program was cost-effective. Cost-effectiveness analyses were conducted from both healthcare and societal perspectives.

**Findings** Using a willingness-to-pay of CAD$50,000 per QALY gained, we found that immunising the entire birth cohort with nirsevimab would be cost-effective from a societal perspective for a PPD of up to $290, with an annual budget impact of $83,978 for 1113 infants per 100,000 population. An alternative, combined strategy of vaccinating pregnant women and immunising only infants at high risk of severe disease would lead to a lower budget impact of $49,473 per 100,000 population with a PPD of $290 and $195 for nirsevimab and RSVpreF vaccine, respectively. This combined strategy would reduce infant mortality by 76%–85%, comparable to a 78% reduction achieved through a nirsevimab-only program of the entire birth cohort. The PPD for cost-effective programs with nirsevimab was sensitive to the target population among infants.

**Interpretation** Passive immunisation of infants under 6 months of age with nirsevimab and vaccination of pregnant women with RSVpreF could be a cost-effective strategy for protecting infants during their first RSV season.

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**Keywords:** RSV; Nirsevimab; RSVpreF vaccine; Simulation; Cost-effectiveness

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## Research in context

### Evidence before this study

Prevention of RSV disease in infants under 1 year of age has relied on palivizumab, a short-acting monoclonal antibody, administered monthly to infants at high risk of severe outcomes during the period in which RSV is circulating in annual epidemics. New preventive measures including nirsevimab (a long-acting monoclonal antibody for passively immunising infants) and RSVpreF (a protein-based vaccine for immunising pregnant women) have been developed to reduce the risk of severe RSV illness in the first six months of life.

We searched MEDLINE and SCOPUS, supplemented with internet searches (Google), to identify any studies evaluating the health benefits and cost-effectiveness of nirsevimab and RSVpreF vaccine against RSV disease among infants in Canada from January 2018 to May 2023. We used the terms "cost-effectiveness", "nirsevimab", "RSVpreF", "infant", and "long acting monoclonal antibody" to identify studies restricted to Canada. Our search, conducted in May 2023, identified only one study evaluating the effectiveness and cost-effectiveness of immunising infants with long-acting monoclonal antibody and vaccinating pregnant women, which is specific to Nunavik, a small Inuit population in the Canadian Arctic region, with a significant burden of RSV disease. We found no prior study evaluating the health benefits and cost-effectiveness of nirsevimab and RSVpreF vaccines in Canada with recently available efficacy estimates from randomised controlled clinical trials.

### Added value of this study

Using a discrete-event simulation model, we found that immunising the entire birth cohort with nirsevimab would be cost-effective from a societal perspective for a price-per-dose of up to $290. As a combined strategy, year-round vaccination of pregnant women with RSVpreF at $195 per dose, followed by immunising infants at high risk of severe RSV disease with nirsevimab at $290 per dose had a lower budget impact compared to immunising the entire birth cohort during the RSV season, while averting similar RSV-related infant mortality.

### Implications of all the available evidence

Prevention strategies against RSV disease in infants using nirsevimab and RSVpreF vaccine could be cost-effective. A combined strategy of these interventions could reduce the budget impact to the healthcare system compared to the nirsevimab-only program.

## Introduction

Respiratory Syncytial Virus (RSV) is the most common cause of lower respiratory tract illness (LRTI) in children under five years old worldwide.[1–3] with the highest burden in the first six months of life. In high income countries, 1–2% of the birth cohort is hospitalised for care of RSV-associated illness. The case fatality rate of hospitalised children can reach up to 2.8%.[1] The direct (e.g., outpatient and inpatient care) and indirect (e.g., loss of productivity, parental costs, and psychological health) costs of RSV disease among infants are substantial.[4–7]

In the absence of a preventive vaccine, efforts to curb the burden of RSV among infants in the last two decades have relied on passive immunisation with the anti-RSV monoclonal antibody palivizumab. Palivizumab is currently administered in five monthly doses to infants at high risk of severe RSV disease, including preterm infants and those with chronic conditions, during the local RSV epidemic seasons.[8] With the advent of structure-based vaccinology,[9] preventive interventions are being developed across active vaccine and passive-immunising platforms with the aim of passively protecting infants during the highest risk period directly or through maternal immunisation. For instance, nirsevimab is a long-acting monoclonal antibody to the RSV fusion protein in its pre-fusion conformation (preF)[10,11] that has been recently authorised for single dose administration to infants in Europe, Canada, and the United States. Another strategy to prevent RSV-associated illness in the first six months of life is immunisation of pregnant women with a preF RSV protein-based vaccine (RSVpreF), providing passive immunisation to the newborn through transplacental antibody transfer.[12] With the availability of these products, the landscape of RSV prevention and disease burden is likely to change. However, feasibility and cost-effectiveness of infant and maternal immunisation programs will play an important role in recommendations for use, such as providing long-acting monoclonal antibodies to the entire birth cohort during the RSV season, targeting only infants at high risk of severe RSV, vaccinating pregnant women, or a combination of these strategies.

In this study, we aimed to conduct a comprehensive cost-effectiveness analysis of RSV infant and maternal immunisation strategies based on population demographics in the Canadian south (i.e., southern provinces of Canada excluding the three northern territories and Nunavik in Quebec). We developed a discrete-event simulation model of RSV outcomes and calculated health benefits (i.e., reduction of RSV disease outcomes

such as outpatient care, hospitalisation, and death), net monetary benefit (NMB), incremental cost-effectiveness ratio (ICER), and the budget impact associated with immunisation programs. Accounting for the efficacy of nirsevimab and RSVpreF against RSV-related outcomes in infants, as well as direct and indirect costs of health outcomes and program implementation, we performed cost-effectiveness analyses from both the publicly funded health system (referred to as healthcare) and societal perspectives.

## Methods

### Model structure and study population

We developed a discrete-event simulation model (Fig. 1) with 1113 infants per 100,000 population as the birth cohort, reflecting the 2021 census data for Ontario, Canada.[13] Ontario is the most populous province in Canada with a population of ~15.5 million.[14] Twelve monthly birth cohorts were followed through the first year of their life, categorised as preterm with <29 weeks of gestational age (wGA), 29–32 wGA, 33–36 wGA,[15] and term infants with 37+ wGA.[16,17] Preterm infants comprised ~9% of the cohort, distributed as 7%, 17%, and 76% in the corresponding wGA.[15] We also considered chronic lung disease (CLD) and congenital heart disease (CHD) as two major risk factors associated with RSV disease outcomes. The rate of CLD was set to 28.1%, 4%, and 2.4% for wGA <29, 29–32, and 33–36, respectively, among preterm infants.[18] For CHD, we used an overall prevalence rate of 12.3 per 1000 live births in Canada.[19]

### RSV-related outcomes

The model was parameterized with estimates of the burden of RSV disease in different chronologic and gestational age groups. The annual incidence of medically-attended (MA) RSV cases per 100,000 population was sampled from the range 1001 to 2439, and distributed among infants under one year of age according to estimated rates and seasonality distribution (Supplementary Figure S1 and Table S2).[7] In our study, MA RSV refers to outpatient care (i.e., office visit or emergency department (ED) visit without hospital admission) or inpatient care (i.e., hospital admission in paediatric ward or intensive care unit, ICU). We considered the beginning of October as the start of RSV season, recognizing that the RSV season varies geographically and temporally (Supplementary Figure S3).[7,20]

We allowed for a maximum of two MA RSV events per infant during the first year of life,[21] with a minimum time-interval of three months between the two events if the second episode occurred. The duration of symptomatic RSV disease for those receiving outpatient care was sampled between 5 and 8 days.[22] Hospitalisation rates for infants with MA RSV LRTI were based on their age at incidence as well as their wGA (Supplementary Figure S2 and Table S3). The likelihood of hospitalisation increased by 1.9 and 2.2 times for infants with CLD and CHD, respectively, compared to infants without these conditions.[23,24]

Among hospitalised cases, ICU admission varied in the range 41.3%–62.1%, 13.1%–53.6%, and 5.4%–30.0% among infants of ≤32, 33–35, and ≥36 wGA, respectively.[22] For infants ≤32 wGA, the duration of hospitalisation was sampled from Gamma distributions, with mean values of 6.1 and 9.5 days stay in a paediatric ward and ICU (Table 1), respectively.[22,25] For infants born at 33 or higher wGA, we sampled the duration of stay in paediatric ward and ICU from Gamma distributions with mean values of 3.9 and 5.2 days, respectively (Table 1).[22,25,35] The probability of experiencing a wheezing episode post hospitalisation was 0.31 during the first year of life.[36,37] The duration of a wheezing episode ranged from 5.2 to 9.8 days.[36,38] RSV-related mortality for hospitalised infants without CLD or CHD varied in the ranges 0.36%–3.3%, 0.02%–1.82%, and 0.02%–1% for infants of ≤32, 33–35, and 36 or higher wGA, respectively.[39–45] For hospitalised infants with CLD and CHD, mortality rates were 3.5%–5.1% and 3.4%–5.3%, respectively.[39]

### Costs of RSV-related outcomes

Direct costs borne by the healthcare system included office visit, ED visit, hospitalisation, as well as 30 days' follow up for hospitalised infants (Table 1). Indirect

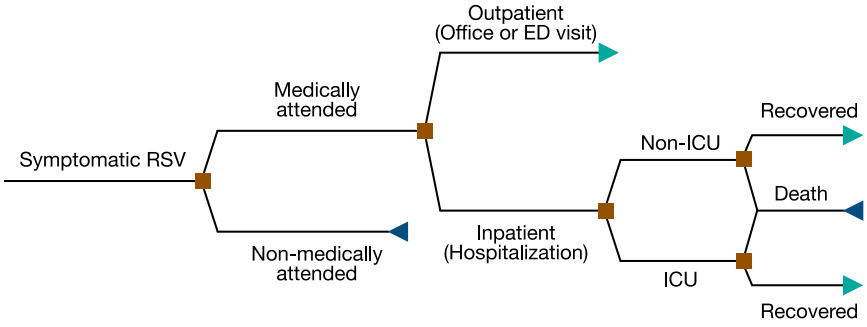


*Fig. 1:* Structure of discrete-event simulation model applied to scenarios in the presence and absence of interventions with different outcomes.

| wGA[a] | LoS[b] in paediatric ward: mean, distribution | LoS[b] in ICU: mean, distribution | References |
|---|---|---|---|
| ≤32 | 6.1, Gamma (12.71, 0.48) | 9.5, Gamma (20.22, 0.47) | 22,25,26 |
| ≥33 | 3.9, Gamma (6.08, 0.64) | 5.2, Gamma (12.38, 0.42) | |
| **RSV-related outcome** | **Mean disutility values** | **Distribution** | |
| Without RSV | 0.05 | Beta (19.2, 364.6) | 27–31 |
| Outpatient | 0.16 | Beta (53.6, 281.4) | |
| Paediatric ward | 0.41 | Beta (109.7, 157.9) | |
| ICU | 0.60 | Beta (159.4, 106.2) | |
| Wheezing | 0.04 | Beta (14.1, 338.4) | |
| | **Direct healthcare costs (Canadian $)** | **Unit** | |
| Office visit | $229 | Per visit | 25 |
| ED visit | $342 | Per visit | 32 |
| Paediatric ward | $1491 | Per day | 25 |
| ICU | $3638 | Per day | 25,33 |
| Wheezing | $229[c] | Per visit | 25 |
| **Age at hospitalisation** | **30 days' follow up costs** | | |
| <29 days | $1791 | Per hospitalised infant | 7 |
| 29–89 days | $1261 | | |
| 90 days to < 6 months | $423 | | |
| 6 months to < 1 year | $374 | | |
| **Other costs** | **Indirect costs** | | |
| Out-of-pocket expenses | $118 | Per day | 5 |
| Workdays loss | $147 | Per day | 5,34 |
| Loss of life | $2,292,572 | Per death | Calculated |

All costs are inflated to 2023 Canadian dollars. [a]Weeks of gestational age. [b]Length of stay. [c]Assumed to be the same as office visit.

***Table 1:*** **Model parameters used for cost-effectiveness analysis.**

costs included out-of-pocket expenses, loss of productivity by parents, and monetary loss of life due to RSV-related infant mortality. Out-of-pocket expenses for families with hospitalised infants were estimated at $118 per day for the duration of hospital stay to account for transportation, over-the-counter medications, meals, child care and other costs.[5] Indirect costs related to workdays lost for working parents (with an average absenteeism of 49%)[5] were calculated using the per capita personal income of CAD$53,675 per year (i.e., ~$147 per day) in Ontario.[34] We assumed total workdays lost were equal to the length of stay for hospitalised infants and one day for infants who required outpatient care.[5] We considered the recommended 1.5% discounting rate by the Canadian Agency for Drugs and Technologies in Health,[46] with an average lifespan of 82 years. Each RSV-related death was estimated to have a total discounted monetary loss of $2,292,572, calculated using the annual personal income, and discounted quality-adjusted life-year (QALY) loss of 45.3. All costs were converted and inflated to 2023 Canadian dollars.

### Infant and maternal RSV prevention strategies

Although year-round RSV activity was implemented in the model according to reported incidence and outcomes,[7,20] we considered infant immunisation with nirsevimab to start in October, corresponding to the putative start of RSV season (Supplementary Figure S3). Infants born off-season were immunised at the start of the RSV season following their birth. Based on the current recommendation for use of palivizumab, which is directed at preterm and selected infants at high risk of severe RSV disease,[22] we evaluated the following program options (Table 2) for passive immunisation with nirsevimab: (i) preterm infants ≤32 wGA and infants with CLD or CHD condition (L1); (ii) preterm infants ≤36 wGA and infants with CLD or CHD condition (L2); (iii) preterm infants (≤36 wGA), infants with CLD or CHD, and term infants born during RSV season (L3); and (iv) the birth cohort (L4). The coverage for these immunisation programs was set to 100% for the base-case analysis, but reduced to 80% for the secondary analysis (Supplementary Figures S5–S45 and Tables S6–S39).

Maternal immunisation (MI) was implemented as a year-round program, with vaccination of pregnant women who are in their last trimester before gestation week 33 (Supplementary Figure S3). In the base-case analysis, vaccination coverage was set to 100%. For the secondary analysis, we assumed a 60% coverage based

| Immunisation program | Target population | Immunisation coverage | |
|---|---|---|---|
| | | Basecase analysis | Secondary analysis |
| L1 | Infants ≤32 wGA, and infants with CLD or CHD | 100% | 80% |
| L2 | Infants ≤36 wGA, and infants with CLD or CHD | 100% | 80% |
| L3 | Infants ≤36 wGA, and infants ≥37 wGA born during the RSV season, and infants with CLD or CHD, | 100% | 80% |
| L4 | Birth cohort | 100% | 80% |
| MI | Pregnant women | 100% | 60% |
| LMI (combined strategy) | Infants ≤32 wGA, and infants with CLD or CHD | 100% | 80% |
| | Pregnant women | 100% | 60% |

wGA: weeks of gestational age; CLD: chronic lung disease; CHD: congenital heart disease.

*Table 2:* **Summary of immunisation programs, target populations, and immunisation coverages.**

on estimates of 2021 vaccination coverage against influenza and pertussis in pregnant women in Canada.[47]

To evaluate the combination of nirsevimab and RSVpreF, we implemented a program (LMI) that includes year-round vaccination of pregnant women followed by administration of nirsevimab to infants at high risk of severe RSV disease (i.e., preterm infants ≤32 wGA and infants with CLD or CHD condition) during RSV season. Table 2 summarises all the immunisation programs, target populations, and coverages for basecase and secondary analyses.

### Efficacy of nirsevimab and RSVpreF vaccine

We considered the efficacy of nirsevimab and RSVpreF against MA RSV LRTI and severe RSV LRTI. Conservatively, no efficacy against RSV infection or symptomatic RSV disease without medical attention was assumed. The efficacy of a single dose of nirsevimab against MA RSV-LRTI is estimated at 79.5% (95% CI: 65.9%–87.7%) through 150 days post-dose.[48] Mean efficacies against hospitalisation and very severe RSV LRTI (used against ICU admission in our model) are estimated at 77.3% (95% CI: 50.3%–89.7%) and 86% (95% CI: 62.5%–94.8%), respectively.[48]

We employed a sigmoidal decay to temporally disaggregate the constant efficacy values for up to 10 months,[49] while maintaining the same mean efficacy for the first 5 months as estimated in clinical trials (Supplementary Figure S4). As sensitivity analysis, we used constant vaccine efficacy profiles with mean estimates as reported in clinical trials, and a linear decline beginning at 5 months post immunisation (Supplementary Figure S4).

The efficacy of RSVpreF is estimated at 57.1% (95% CI: 14.7%–79.8%) against MA RSV LRTI, 67.9% (95% CI: 34.6%–84.2%) against hospitalisation, and 81.8% (95% CI: 40.6%–96.3%) against severe MA RSV LRTI (used against ICU admission in our model) for the first 90 days of life.[12,50–52] Similar to nirsevimab, we used a sigmoidal decay to determine temporal vaccine efficacy over 10 months, with the same mean efficacy as estimated in clinical trials for the first 3 months after birth (Supplementary Figure S4). We also performed a sensitivity analysis using constant vaccine efficacy profiles with mean estimates from clinical trials, and a linear decline starting 3 months after birth (Supplementary Figure S4).

### Costs of RSV prevention strategies

We varied the single-dose cost of both nirsevimab and RSVpreF between $50 and $1000 to determine the price range within which an immunisation program would be cost-effective. Costs associated with dose administration was set to $15 for both infant and maternal immunisation.[53,54]

### Cost-effectiveness analysis

To determine whether a program was cost-effective for a given willingness-to-pay (WTP) threshold, we calculated the net monetary benefit (NMB) by $NMB = \Delta E \times WTP - \Delta C$, where $\Delta E$ represents QALYs gained using intervention compared to no intervention, and $\Delta C$ is the incremental costs.[55] A program was considered cost-effective if it resulted in a positive NMB. In the primary analysis, we calculated the monetary value of health using a WTP threshold of $50,000 per QALY gain.[56] In secondary analyses (Supplementary Figures S5–S45 and Tables S6–S39), we considered a lower threshold of $30,000[57] and a higher threshold of $70,000[58] corresponding to the per capita gross domestic product in Canada. We also estimated the ICER for each intervention as $\Delta C/\Delta E$, which provides a metric to measure the additional costs required to gain one QALY. Disutility values of RSV-related outcomes were sampled individually for each RSV case from their respective distributions (Table 1), and adjusted for the duration of illness and outcomes.[27–31] Utility values were calculated as (1 – sampled disutility) and used to derive total QALYs in each scenario by adding utility values during the illness and outside the illness duration in one year of life. We sampled a baseline disutility, and calculated the utility without RSV (Table 1), accounting

for non-RSV health related illnesses.[59] When immunisation was effective against MA RSV LRTI, preventing outpatient, we considered adjusted utility values for the duration of symptomatic RSV disease in non-MA infants. The distribution of QALY loss calculated using sampled disutility values were consistent with recent estimates (Supplementary Figure S46).[60]

We considered both healthcare and societal perspectives for cost-effectiveness analyses. The healthcare perspective included all direct medical costs of RSV-related disease and the immunisation program during the first year of life. In the base-case analysis, the societal perspective incorporated direct and indirect costs in the calculation of NMB and ICER, including productivity loss of parents, without considering the monetary loss of life due to RSV-related infant mortality. In the secondary analysis, we also included the monetary loss of life due to infant mortality in the societal perspective. Based on the results of cost-effectiveness analyses, we determined the budget impact of each immunisation program as the difference between immunisation costs and the total direct healthcare savings achieved in the program.

### Model implementation

For each scenario, the model was simulated stochastically using Monte-Carlo sampling for a total of 1000 realisations. All parameters were sampled from their respective distributions and individually for each infant, thus probabilistically accounting for the sensitivity of the model outcomes with respect to input parameters. For parameters for which a statistical distribution was unknown, we sampled uniformly from the estimated ranges. Point estimates of the model outcomes reflected the mean value of the 1000 Monte Carlo simulations. The uncertainty around the point estimates were derived using a nonparametric, bias-corrected and accelerated bootstrap technique with 1000 replicates, and 95% confidence intervals for the mean of estimates were constructed in scenarios evaluated. The computational model is available at https://github.com/affans/rsv_costeffectiveness.

### Ethics and guidelines

This study used publicly available estimates and data sources and thus no ethics approval was required. We followed guidelines set forth by the Consolidated Health Economic Evaluation Reporting Standards (CHEERS),[61] and Canadian Agency for Drugs and Technologies in Health.[46]

### Role of the funding source

The funders had no role in the study design, input collection or analysis, interpretation of results, or decision to submit the manuscript for publication.

## Results

We estimated the reduction of health outcomes and performed cost-effectiveness analyses of interventions for twelve monthly birth cohorts per 100,000 population, followed through the first year of their life.

### Health outcomes with sigmoidal vaccine efficacy profiles

For immunisation strategies in Table 2, we estimated that L1 would reduce RSV-related outpatient care by 2.0% (95% CI: 1.99–2.01%) and inpatient care by 6.2% (95% CI: 5.7%–6.6%) in the base-case analysis (Fig. 2A). Program extension to all preterm infants in L2 provided a marginal improvement in the reduction of outpatient care at 5.9% (95% CI: 5.8%–5.9%) and inpatient care at 11.1% (95% CI: 10.6%–11.6%). L3 was associated with a reduction of 38.9% (95% CI: 38.8%–39.0%) outpatient care and 61.2% (95% CI: 60.4%–62.1%) inpatient care. Administration of nirsevimab to the entire birth cohort in L4 reduced outpatient care by 63.4% (95% CI: 63.2%–63.5%), and inpatient care by 79.3% (95% CI: 78.7%–80.1%). The reduction in RSV-related infant mortality was 24.3% (95% CI: 16.9%–33.2%) in L1, 36.3% (95% CI: 26.8%–46.5%) in L2, 67.9% (95% CI: 58.8%–77.3%) in L3, and 77.8% (95% CI: 69.6%–85.3%) in L4 (Supplementary Table S6).

MI was estimated to reduce RSV-related outpatient care by 34.0% (95% CI: 33.9%–34.2%), inpatient care by 72.8% (95% CI: 72.1%–73.5%), and death by 72.4% (95% CI: 62.5%–81.9%) (Fig. 2A). For the immunisation program combining administration of nirsevimab and RSVpreF (LMI), we estimated a reduction of 35.2% (95% CI: 35.0%–35.3%) for outpatient care, 74.1% (95% CI: 73.5%–74.9%) for inpatient care, and 76.8% (95% CI: 67.1%–85.8%) for death, compared with no intervention (Supplementary Table S6).

### Health outcomes with constant vaccine efficacy profiles

In the base-case analysis, we estimated that L1 would reduce RSV-related outpatient and inpatient care by 2.0% (95% CI: 1.99–2.02%) and 6.1% (95% CI: 5.7%–6.6%), respectively (Fig. 2B). Program extension to all preterm infants in L2 provided a reduction of 5.8% (95% CI: 5.7%–5.8%) in outpatient care and 11.0% (95% CI: 10.5%–11.6%) for inpatient care. L3 was associated with a reduction of 38.1% (95% CI: 38.0%–38.2%) in outpatient care and 60.8% (95% CI: 60.0%–61.7%) for inpatient care. Immunising the entire birth cohort with nirsevimab in L4 reduced outpatient care by 62.3% (95% CI: 62.1%–62.4%) and inpatient care by 78.9% (95% CI: 78.2%–79.6%). The reductions in RSV-related infant mortality were estimated to be the same as the corresponding nirsevimab immunisation programs using sigmoidal vaccine efficacy profiles.

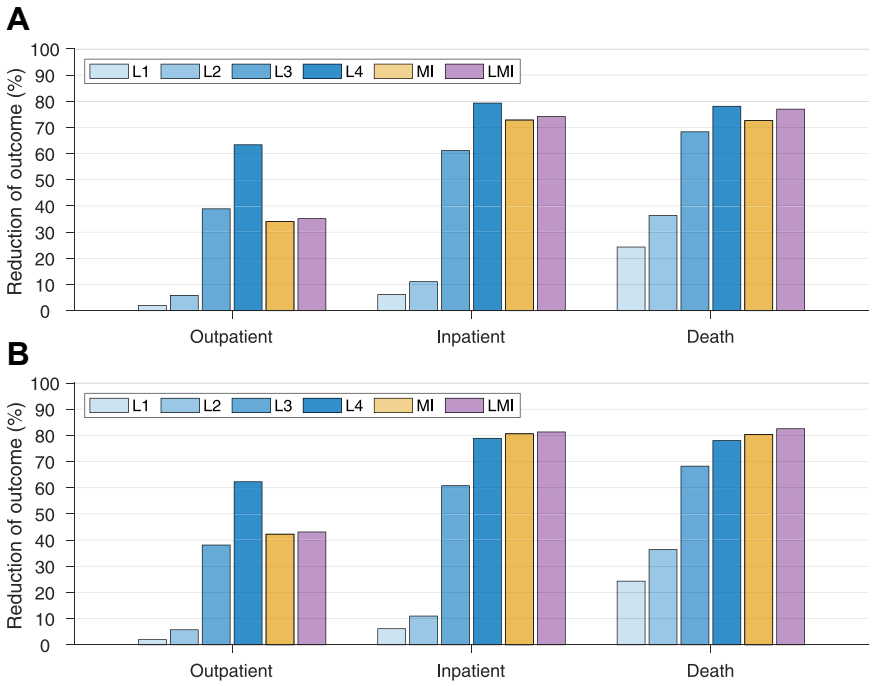


*Fig. 2:* Overall reduction of RSV-related outpatient care (office and ED visits), inpatient care (paediatric ward and ICU admissions), and death among infants under one year of age for standalone immunisation programs with nirsevimab (L1, L2, L3, L4) and RSVpreF (MI), and combined nirsevimab and RSV-preF immunisation program (LMI), compared to the scenario without any prevention strategy. Panel (A) and (B) correspond to the sigmoidal and constant vaccine efficacy profiles, respectively.

MI was estimated to reduce RSV-related outpatient care by 42.3% (95% CI: 42.1%–42.4%), inpatient care by 80.6% (95% CI: 80.0%–81.2%), and death by 82.1% (95% CI: 71.4%–88.9%) (Fig. 2B). For the combined immunisation program, we estimated that LMI would reduce outpatient care by 43.1% (95% CI: 43.0%–43.3%), inpatient care by 81.3% (95% CI: 80.6%–81.9%), and death by 82.3% (95% CI: 74.0%–90.2%), compared with no intervention (Supplementary Table S6).

### Cost-effectiveness of standalone nirsevimab and RSVpreF prevention programs

We determined the price-per-dose (PPD) of nirsevimab below which the standalone infant immunisation programs were cost-effective at the WTP of $50,000 per QALY gained. From a healthcare perspective (Table 3), the maximum PPD for a positive NMB was $615 in L1, and reduced to $375 in L2, $300 in L3, and $215 in L4 using sigmoidal vaccine efficacy profiles (Fig. 3C). Corresponding to these PPDs, the probabilities of L1, L2, L3, and L4 being cost-effective were 50%, 56%, 79%, and 99%, respectively. For MI, the maximum PPD was $160, at which the program was cost-effective with the probability of 68%. From a societal perspective (Table 3) with sigmoidal vaccine efficacy profiles, the maximum PPD for a positive NMB was estimated to be $705 in L1, $455 in L2, $385 in L3, and $290 in L4 (Fig. 3D). The probabilities of these programs being cost-effective at their maximum PPD were 52%, 51%, 83%, and 55% in L1, L2, L3, and L4, respectively. MI was cost-effective for a PPD up to $200, with the probability of 87%.

Using constant vaccine efficacy profiles, we estimated similar PPD for nirsevimab immunisation programs evaluated. From a healthcare perspective (Table 4), the maximum PPD for a positive NMB was $610 in L1, and reduced to $370 in L2, $295 in L3, and $215 in L4 (Fig. 3E). Corresponding to these PPDs, the probabilities of L1, L2, L3, and L4 being cost-effective were 54%, 69%, 90%, and 86%, respectively. For MI, the maximum PPD was $185 (Fig. 3E), with cost-effectiveness probability of 81%. From a societal perspective (Table 4) with constant vaccine efficacy profiles, the maximum PPD for a positive NMB was estimated to be $700 in L1, $450 in L2, $380 in L3, and $285 in L4 (Fig. 3D). The probabilities of these programs being cost-effective at their maximum PPD were 55%, 58%, 82%, and 78% in L1, L2, L3, and L4, respectively. MI was cost-effective for a PPD up to $235, with the probability of 83%.

### Cost-effectiveness of a combined nirsevimab and RSVpreF prevention program

LMI was cost-effective for various combinations of PPD values for nirsevimab and RSVpreF (Fig. 4). Here, we

| Prevention strategy | Maximum PPD, $ | Incremental costs, $ (95% CI) | QALYs gained (95% CI) | ICER, $/QALY (95% CI) | Budget Impact per 100,000 population, $ |
|---|---|---|---|---|---|
| *Healthcare perspective* | | | | | |
| L1 | 615 | 1199 (−380 to 2700) | 0.024 (0.018–0.032) | 49,577 (−14,712 to 125,242) | 1225 |
| L2 | 375 | 1648 (−105 to 3392) | 0.036 (0.028–0.045) | 45,924 (−2959 to 103,322) | 1668 |
| L3 | 300 | 3235 (−163 to 6588) | 0.094 (0.082–0.107) | 34,331 (−1682 to 72,362) | 3303 |
| L4 | 215 | 467 (−3878 to 4708) | 0.111 (0.099–0.124) | 4200 (−34,697 to 43,384) | 503 |
| MI | 160 | 4501 (764–8262) | 0.109 (0.096–0.123) | 41,321 (6800 to 78,174) | 4546 |
| *Societal perspective* | | | | | |
| L1 | 705 | 1153 (−453 to 2725) | 0.024 (0.018–0.032) | 47,467 (−18,071 to 128,490) | 4606 |
| L2 | 455 | 1779 (−119 to 3608) | 0.036 (0.028–0.045) | 49,618 (−3025 to 110,691) | 9976 |
| L3 | 385 | 2705 (−1342 to 6703) | 0.094 (0.082–0.107) | 28,634 (−13,811 to 73,395) | 52,738 |
| L4 | 290 | 5195 (68–10,285) | 0.111 (0.099–0.124) | 46,749 (597–95,262) | 83,978 |
| MI | 200 | 2816 (−1495 to 7037) | 0.109 (0.096–0.123) | 25,815 (−13,217 to 66,816) | 49,066 |

All strategies were compared to the baseline with no intervention.

*Table 3:* **Model estimates of cost-effectiveness analyses associated with infant and maternal immunisation programs as standalone prevention strategies from healthcare and societal perspectives at the WTP of $50,000 per QALY gained using sigmoidal vaccine efficacy profiles.**

considered maximum PPDs derived for L1 and L4 programs in combination with MI at which LMI program was cost-effective (Tables 5 and 6). From a healthcare perspective, at PPD of $615 for nirsevimab with sigmoidal vaccine efficacy profiles, LMI was cost-effective (NMB>0) for a PPD up to $140 for RSVpreF, with probability of 100% at the WTP threshold of $50,000 per QALY gained (Table 5). Reducing PPD for nirsevimab to $215, LMI was cost-effective for a PPD up to $155 for RSVpreF with the probability of 96%. From a societal perspective, LMI with a PPD of $705 for nirsevimab and $180 for RSVpreF was cost-effective with the probability of 98% (Table 5). LMI was also cost-effective for a combination PPD of $290 and $195 for nirsevimab and RSVpreF, respectively, with the probability of 95%.

With constant vaccine efficacy profiles, LMI was cost-effective from a healthcare perspective at PPD of $610 for nirsevimab and $165 for RSVpreF, with the probability of 0.96% at the WTP threshold of $50,000 per QALY gained (Table 6). Reducing PPD for nirsevimab to $215, LMI was cost-effective at a PPD of $180 for RSVpreF with the probability of 82%. From a societal perspective, LMI with constant vaccine efficacy profiles was cost-effective at a PPD of $700 for nirsevimab and $215 for RSVpreF, with the probability of 78% (Table 6). LMI was also cost-effective for a combination PPD of $285 and $230 for nirsevimab and RSVpreF, respectively, with the probability of 63%.

## Budget impact

The total number of nirsevimab doses per 100,000 population was 38, 104, 582, and 1113 in L1, L2, L3, and L4, respectively (Fig. 3A). For sigmoidal vaccine efficacy profiles, the annual budget impact of these interventions to the healthcare system would be $1225 in L1, $1668 in L2, $3303 in L3, and $503 in L4 (per 100,000 population) at the maximum PPD estimated for each program to be cost-effective (Table 3). For MI, the total number of RSVpreF vaccine doses was 1113 per 100,000 population (Fig. 3A), resulting in an annual budget impact of $4546 (per 100,000 population) to the healthcare system. From a societal perspective, the annual budget impact per 100,000 population was estimated at $4606, $9976, $52,738, and $83,978 for PPD of $705 in L1, $455 in L2, $385 in L3, and $290 in L4, respectively (Table 3). The annual budget impact for MI with a PPD of $200 would be $49,066 per 100,000 population.

For the combined immunisation program with sigmoidal vaccine efficacy profiles, LMI was associated with an annual budget impact of $467 per 100,000 population with PPD of $615 and $140 for nirsevimab and RSVpreF, respectively (Table 5). When the PPD for nirsevimab and RSVpreF changed to $215 and $155, respectively, the budget impact of LMI was estimated at $2135. From a societal perspective, the budget impact of MLI per 100,000 population was estimated at $48,368 with a PPD of $705 and $180 for nirsevimab and RSVpreF, respectively (Table 5). Changing the corresponding PPDs to $290 and $195 resulted in a similar budget impact of $49,473 per 100,000 population.

Using constant vaccine efficacy profiles, we estimated the annual budget impact of infant immunisation programs with nirsevimab to the healthcare system to be $1144 in L1, $1330 in L2, $2354 in L3, and $3050 in L4 per 100,000 population at the maximum PPD estimated for each program to be cost-effective (Table 4). MI resulted in a total annual budget impact of $4010 to the healthcare system at the maximum PPD. From a societal perspective, the annual budget impact per 100,000 population was estimated at $4525, $9637, $51,790, and $80,960 for PPD of $700 in L1, $450 in L2,

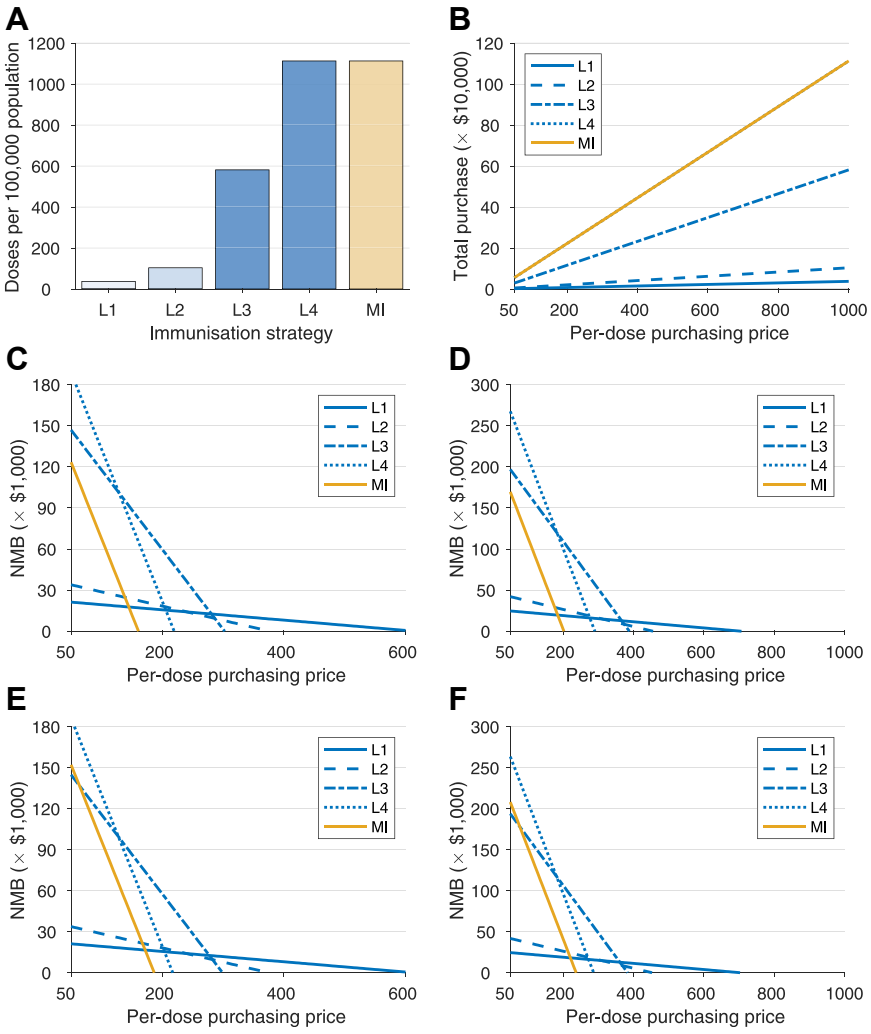


***Fig. 3:*** Required doses of nirsevimab and RSVpreF per 100,000 population for immunisation strategies (A), with total purchasing costs (B), and the estimated net monetary benefit (NMB) as a function of price-per-dose at the WTP threshold of $50,000 per QALY gained. Panels (C) and (D) correspond to the analysis from healthcare and societal perspectives, respectively, with sigmoidal vaccine efficacy profiles. Panels (E) and (F) correspond to the analysis from the healthcare and societal perspectives, respectively, with constant vaccine efficacy profiles. Note: in panel B, curves for MI and L4 are superposed.

$380 in L3, and $285 in L4, respectively (Table 4). The annual budget impact for MI with a PPD of $235 would be $59,660 per 100,000 population.

For the combined immunisation program with constant vaccine efficacy profiles, LMI was associated with an annual budget impact of $2099 per 100,000 population with PPD of $610 and $165 for nirsevimab and RSVpreF, respectively (Table 6). When the PPD for nirsevimab and RSVpreF changed to $215 and $180, respectively, the budget impact of LMI per 100,000 population was estimated at $3954. From a societal perspective, the budget impact of MLI per 100,000 population was estimated at $61,130 with a PPD of $700 for nirsevimab and $215 for RSVpreF (Table 6). Changing the corresponding PPDs to $285 and $230 resulted in a similar annual budget impact of $62,234 per 100,000 population.

## Secondary analyses

The results of secondary analyses for reduced coverage of nirsevimab and RSFpreF using both sigmoidal and constant vaccine efficacy profiles, without and with monetary loss of life due to RSV-related infant mortality, are provided in the Supplementary Material. The reduction of RSV-related infant mortality was 18%–25% higher in the nirsevimab-only program with 80% coverage of the birth cohort compared with the combined program with 60% coverage of RSVpreF

| Prevention strategy | Maximum PPD, $ | Incremental costs, $ (95% CI) | QALYs gained (95% CI) | ICER, $/QALY (95% CI) | Budget impact per 100,000 population, $ |
|---|---|---|---|---|---|
| *Healthcare perspective* | | | | | |
| L1 | 610 | 1117 (−397 to 2642) | 0.024 (0.018–0.031) | 46,135 (−15,407 to 123,253) | 1144 |
| L2 | 370 | 1303 (−443 to 3025) | 0.036 (0.028–0.045) | 36,306 (−11,975 to 91,544) | 1330 |
| L3 | 295 | 2311 (−1131 to 5714) | 0.094 (0.082–0.106) | 24,716 (−11,905 to 63,068) | 2354 |
| L4 | 215 | 3017 (−1327 to 7221) | 0.110 (0.098–0.123) | 27,348 (−11,810 to 67,888) | 3050 |
| MI | 185 | 3991 (−45 to 8032) | 0.117 (0.104–0.131) | 34,041 (−362 to 71,355) | 4010 |
| *Societal perspective* | | | | | |
| L1 | 700 | 1114 (−507 to 2722) | 0.024 (0.018–0.031) | 45,987 (−19,668 to 127,807) | 4525 |
| L2 | 450 | 1584 (−332 to 3462) | 0.036 (0.028–0.045) | 44,162 (−8803 to 105,052) | 9637 |
| L3 | 380 | 2751 (−1242 to 6664) | 0.094 (0.082–0.106) | 29,422 (−13,081 to 73,612) | 51,790 |
| L4 | 285 | 3439 (−1753 to 8664) | 0.110 (0.098–0.123) | 31,187 (−15,679 to 80,821) | 80,960 |
| MI | 235 | 3554 (−1100 to 8303) | 0.117 (0.104–0.131) | 30,317 (−9310 to 73,014) | 59,660 |

All strategies were compared to the baseline with no intervention.

***Table 4:*** **Model estimates of cost-effectiveness analyses associated with infant and maternal immunisation programs as standalone prevention strategies from healthcare and societal perspectives at the WTP of $50,000 per QALY gained using constant vaccine efficacy profiles.**

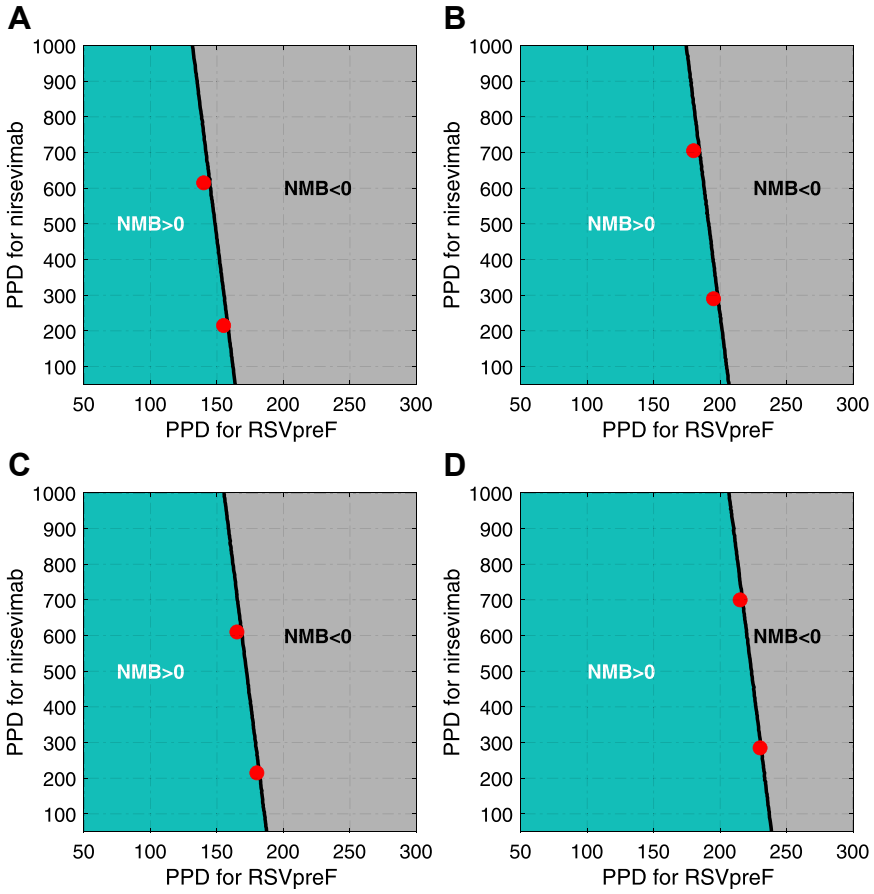


***Fig. 4:*** Net monetary benefit (NMB) of the combined infant and maternal immunisation program at the WTP of $50,000 per QALY gained as a function of PPD for nirsevimab and RSVpreF. Panels (A) and (B) correspond to the analysis from healthcare and societal perspectives, respectively, with sigmoidal vaccine efficacy profiles. Panels (C) and (D) correspond to the analysis from the healthcare and societal perspectives, respectively, with constant vaccine efficacy profiles. Red circles correspond to the PPD values in Tables 5 and 6. The black line represents the maximum PPD for RSVpreF vaccine and nirsevimab at which the combined strategy is cost-effective.

| Nirsevimab PPD, $ | RSVpreF PPD, $ | Incremental costs, $ (95% CI) | QALYs gained (95% CI) | ICER, $/QALY (95% CI) | Budget impact per 100,000 population, $ |
|---|---|---|---|---|---|
| *Healthcare perspective* | | | | | |
| 615 | 140 | 432 (−3496 to 4245) | 0.112 (0.099–0.126) | 3853 (−30,616 to 38,887) | 467 |
| 215 | 155 | 2041 (−1846 to 5892) | 0.112 (0.099–0.126) | 18,193 (−16,004 to 54,135) | 2135 |
| *Societal perspective* | | | | | |
| 705 | 180 | 650 (−3854 to 5042) | 0.112 (0.099–0.126) | 5797 (−33894 to 46,014) | 48,368 |
| 290 | 195 | 1738 (−2653 to 6132) | 0.112 (0.099–0.126) | 15,511 (−23,306 to 56,333) | 49,473 |

All strategies were compared to the baseline with no intervention.

*Table 5:* **Model estimates of cost-effectiveness analyses associated with the combined infant and maternal immunisation program from healthcare and societal perspectives at the WTP of $50,000 per QALY gained using sigmoidal vaccine efficacy profiles.**

vaccination of pregnant women and 80% coverage of infants at high risk with nirsevimab (Supplementary Table S9). However, the annual budget impact of the combined strategy per 100,000 population was at least 45% lower than the nirsevimab-only program for the corresponding PPD estimates from a societal perspective (Supplementary Tables S10–S13). We also estimated the reduction of direct healthcare costs (outpatient and inpatient care) and indirect costs (loss of productivity and out-of-pocket expenses) achieved from interventions (Supplementary Tables S4 and S5). Our results show that PPD for cost-effective programs with nirsevimab is sensitive to the target groups among the infant population, but remained relatively robust with respect to the efficacy profiles of nirsevimab and the coverage of immunisation.

## Discussion

In this study, we evaluated the cost-effectiveness immunisation programs against RSV disease using nirsevimab administered to infants and RSVpreF vaccine administered to pregnant women as new preventive measures. Seasonal administration of nirsevimab to the entire birth cohort could be cost-effective at a sufficiently low PPD. However, this strategy would entail a substantial budget impact. For example, immunising an entire birth cohort of 140,126 infants (i.e., average number of births between 2010 and 2022)[16,62] in Ontario, Canada, would require an annual budget impact of over $10.6 million with the maximum PPD of $290 estimated for nirsevimab from a societal perspective and a WTP of $50,000 per QALY gained. We found that a combined program of year-round vaccination of pregnant women with RSVpreF, followed by immunising those infants at high risk of severe RSV disease with nirsevimab was comparable to an extended nirsevimab-only program for the entire birth cohort in reducing RSV-related mortality among infants, but required a lower annual budget impact. In the combined strategy, the annual budget impact in Ontario would be ~$6.3 million with a PPD of $290 for nirsevimab and $195 for RSVpreF vaccine. Our results remained qualitatively consistent at different WTP thresholds, with the target population being an important factor in determining the range of PPD for cost-effective immunisation strategies.

Previous studies have evaluated the cost-effectiveness of prevention strategies against RSV disease in infants, including long-acting monoclonal antibody, maternal vaccination, and potential active vaccination of infants.[27,29,63–68] These studies have been conducted in different population settings including the United States,[67] England and Wales,[66,68] Norway,[69] other European countries,[64] and low- and middle-income countries,[63,65] indicating the potential for cost-effective immunisation programs. However, no previous work has evaluated cost-effectiveness of these interventions in Canada, except one study that is specific to Nunavik, a

| Nirsevimab PPD, $ | RSVpreF PPD, $ | Incremental costs, $ (95% CI) | QALYs gained (95% CI) | ICER, $/QALY (95% CI) | Budget impact per 100,000 population, $ |
|---|---|---|---|---|---|
| *Healthcare perspective* | | | | | |
| 610 | 165 | 2046 (−1994 to 6095) | 0.119 (0.106–0.133) | 17,243 (−16,725 to 53,016) | 2099 |
| 215 | 180 | 3911 (−272 to 7989) | 0.119 (0.106–0.133) | 32,932 (−2311 to 69,494) | 3954 |
| *Societal perspective* | | | | | |
| 700 | 215 | 3990 (−697 to 8678) | 0.119 (0.106–0.133) | 33,598 (−5820 to 75,142) | 61,130 |
| 285 | 230 | 5083 (266–9849) | 0.119 (0.106–0.133) | 42,805 (2217 to 85,356) | 62,234 |

All strategies were compared to the baseline with no intervention.

*Table 6:* **Model estimates of cost-effectiveness analyses associated with the combined infant and maternal immunisation program from healthcare and societal perspectives at the WTP of $50,000 per QALY gained using constant vaccine efficacy profiles.**

small population in the Canadian Arctic region, with significant burden of RSV disease.[27] Furthermore, published studies evaluating cost-effectiveness of long-acting monoclonal antibody and maternal vaccination have relied on early efficacy estimates of these products with varying assumptions across population and epidemiological contexts. Our study provides a comprehensive cost-effectiveness analysis of these RSV preventive measures, with the most recent efficacy estimates, in a population setting reflective of the Canadian south. Moreover, we have provided a comparison between various programs using nirsevimab and RSVpreF vaccine, as well as a combined strategy for vaccination of pregnant women followed by immunisation of infants at high risk.

Published studies have employed different approaches including cohort, decision-tree, and transmission dynamic models.[29,63–68] Our analysis is based on a discrete-event simulation model, following a birth cohort up to one year of age, without consideration of RSV transmission dynamics. Employing transmission dynamic models could allow for the evaluation of population-wide benefits of immunisation programs. However, since the effect of nirsevimab and RSVpreF in reducing RSV infection or transmission is not yet known, estimating the indirect benefits of immunisation, including herd effects, may be difficult.

## Limitations

A strength of our study is the stratification of the infant population by wGA and critical risk factors of CLD and CHD, which allowed us to utilise available estimates associated with RSV outcomes in infants. However, our model has several limitations. First, for efficacy of nirsevimab against RSV disease outcomes, we relied on reported estimates for infants of ≥29 wGA.[48] If the efficacy among preterm infants <29 wGA is lower than those ≥29 wGA, the maximum PPD for cost-effectiveness may be lower than our estimates. Second, the efficacy of a single dose of nirsevimab may vary based on weight.[10,11] We also assumed that PPD for nirsevimab is not affected by the weight-based dosage. Third, the model includes only CLD and CHD as risk factors; however, other risk factors may be considered such as cystic fibrosis, Down syndrome, and immunocompromise,[22] which were not considered in our analysis due to the lack of specific estimates. Furthermore, the National Advisory Committee on Immunisation recommends only hemodynamically significant CHD infants for use of palivizumab, as opposed to all infants with congenital heart disease.[22] Although the proportion of CHD infants who have hemodynamically significant disease could be as high as 79% (95% CI: 62%–91%),[70] in the absence of such estimates in Canada, we considered all CHD infants in the base-case analysis and 80% of them in the secondary analysis of combined nirsevimab and RSVpreF immunisation program. Fourth, we note that maternal vaccination is recommended during the third trimester of pregnancy and therefore a proportion of preterm birth mothers may not receive RSVpreF prior to their infants' birth or in time for effective transplacental antibody transfer, which could be considered under our secondary analysis with 60% vaccine coverage of pregnant women. Finally, we recognize that the feasibility of different immunisation programs to deliver interventions to pregnant women and infants seasonally are not considered here, and will impact decision making.

## Conclusion

Our simulation study shows that prevention strategies against RSV disease in infants using nirsevimab and RSVpreF could be cost-effective. Passive immunisation of all infants experiencing their first RSV season would require a PPD under $290 to become cost-effective without considering the monetary loss of life due to RSV-related infant mortality. However, this program would incur a higher budget impact to the healthcare system than a cost-effective strategy that combines year-round maternal vaccination with seasonal administration of nirsevimab to infants who are currently eligible for palivizumab.

### Contributors

SMM and AS had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. SMM and JML were responsible for the decision to submit the manuscript.

Study design: SMM, JML.
Model framework design: SMM.
Data collection and input parameters: SMM, EA.
Computational model: AS.
Statistical analysis: SMM.
Analysis and interpretation of the results: All authors.
Drafting of the manuscript: All authors.
Obtained funding: SMM, APG.

### Data sharing statement

All data and the computational model are available at https://github.com/affans/rsv_costeffectiveness.

### Declaration of interests

JM Langley's institution, Dalhousie University, has received funds for clinical trials conducted by the Canadian Center for Vaccinology from GSK, Janssen, Sanofi, Immunovaccine, Inventprise, Merck, Pfizer, VIDO, VBI and Entos. SM Moghadas previously had advisory roles for Janssen Canada and Sanofi for cost-effectiveness of their products. Other authors declare that they have no competing interests.

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### Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lana.2023.100629.

**References**

1 Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. *Lancet*. 2017;390:946–958.
2 Borchers AT, Chang C, Gershwin ME, Gershwin LJ. Respiratory syncytial virus—a comprehensive review. *Clin Rev Allergy Immunol*. 2013;45:331–379.
3 Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis. *Lancet*. 2022;399:2047–2064.
4 Thampi N, Knight BD, Thavorn K, et al. Health care costs of hospitalization of young children for respiratory syncytial virus infections: a population-based matched cohort study. *CMAJ Open*. 2021;9:E948–E956. https://doi.org/10.9778/cmajo.20200219.
5 Mitchell I, Defoy I, Grubb E. Burden of respiratory syncytial virus hospitalizations in Canada. *Can Respir J*. 2017;2017:1–9.
6 McLaurin KK, Farr AM, Wade SW, Diakun DR, Stewart DL. Respiratory syncytial virus hospitalization outcomes and costs of full-term and preterm infants. *J Perinatol*. 2016;36:990–996.
7 Rafferty E, Paulden M, Buchan SA, et al. Evaluating the individual healthcare costs and burden of disease associated with RSV across age groups. *Pharmacoeconomics*. 2022;40:633–645.
8 National Advisory Committee on Immunization (NACI), Moore D, Sinilaite A, Killikelly A. Summary of the National Advisory Committee on Immunization (NACI) statement update on the recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants. *Can Commun Dis Rep*. 2022;48:363–366.
9 Graham BS. The journey to RSV vaccines — heralding an era of structure-based design. *N Engl J Med*. 2023;388:579–581.
10 Griffin MP, Yuan Y, Takas T, et al. Single-dose nirsevimab for prevention of RSV in preterm infants. *N Engl J Med*. 2020;383:415–425.
11 Hammitt LL, Dagan R, Yuan Y, et al. Nirsevimab for prevention of RSV in healthy late-preterm and term infants. *N Engl J Med*. 2022;386:837–846.
12 Pfizer. Pfizer announces positive top-line data of phase 3 global maternal immunization trial for its bivalent respiratory syncytial virus (RSV) vaccine candidate. https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-global; 2022. Accessed March 16, 2023.
13 Statistics Canada. Census profile. 2021 census of population. https://www12.statcan.gc.ca/census-recensement/2021/dp-pd/prof/index.cfm?Lang=E. Accessed April 15, 2023.
14 Government of Ontario. Ontario demographic quarterly: highlights of first quarter. http://www.ontario.ca/page/ontario-demographic-quarterly-highlights-first-quarter. Accessed April 15, 2023.
15 Johnston KM, Gooch K, Korol E, et al. The economic burden of prematurity in Canada. *BMC Pediatr*. 2014;14:93. https://doi.org/10.1186/1471-2431-14-93.
16 Born Ontario. Number of Live Births and Stillbirths in Ontario, by month: March 2021–February 2022. https://www.bornontario.ca/en/news/stillbirths-in-ontario-recent-data.aspx. Accessed April 15, 2023.
17 Statistics Canada. Live births, by month. https://www150.statcan.gc.ca/t1/tbl1/en/tv.action?pid=1310041501. https://doi.org/10.25318/1310041501-eng; 2023.
18 Isayama T, Lee SK, Mori R, et al. Comparison of mortality and morbidity of very low birth weight infants between Canada and Japan. *Pediatrics*. 2012;130:e957–e965. https://doi.org/10.1542/peds.2012-0336.
19 Liu S, Joseph KS, Luo W, et al. Effect of folic acid food fortification in Canada on congenital heart disease subtypes. *Circulation*. 2016;134:647–655.
20 Zheng Z, Pitzer VE, Shapiro ED, Bont LJ, Weinberger DM. Estimation of the timing and intensity of reemergence of respiratory syncytial virus following the COVID-19 pandemic in the US. *JAMA Netw Open*. 2021;4:e2141779. https://doi.org/10.1001/jamanetworkopen.2021.41779.
21 Nduaguba SO, Tran PT, Choi Y, Winterstein AG. Respiratory syncytial virus reinfections among infants and young children in the United States, 2011–2019. *PLoS One*. 2023;18:e0281555. https://doi.org/10.1371/journal.pone.0281555.
22 National Advisory Committee on Immunization. Recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants. https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/palivizumab-respiratory-syncitial-virus-infection-infants.html#a5.5. Accessed March 16, 2023.
23 Ratti C, Greca AD, Bertoncelli D, Rubini M, Tchana B. Prophylaxis protects infants with congenital heart disease from severe forms of RSV infection: an Italian observational retrospective study: palivizumab prophylaxis in children with congenital heart disease. *Ital J Pediatr*. 2023;49:4. https://doi.org/10.1186/s13052-022-01399-z.
24 Paes B, Fauroux B, Figueras-Aloy J, et al. Defining the risk and associated morbidity and mortality of severe respiratory syncytial virus infection among infants with chronic lung disease. *Infect Dis Ther*. 2016;5:453–471.
25 Lanctôt KL, Masoud ST, Paes BA, et al. The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32–35 weeks: a Canadian-based analysis. *Curr Med Res Opin*. 2008;24:3223–3237.
26 Lanari M, Anderson EJ, Sheridan-Pereira M, et al. Burden of respiratory syncytial virus hospitalisation among infants born at 32–35 weeks' gestational age in the Northern Hemisphere: pooled analysis of seven studies. *Epidemiol Infect*. 2020;148:e170. https://doi.org/10.1017/S0950268820001661.
27 Nourbakhsh S, Shoukat A, Zhang K, et al. Effectiveness and cost-effectiveness of RSV infant and maternal immunization programs: a case study of Nunavik, Canada. *eClinicalMedicine*. 2021;41:101141. https://doi.org/10.1016/j.eclinm.2021.101141.
28 Tam DY, Banerji A, Paes BA, et al. The cost effectiveness of palivizumab in term Inuit infants in the Eastern Canadian Arctic. *J Med Econ*. 2009;12:361–370.
29 Pouwels KB, Bozdemir SE, Yegenoglu S, et al. Potential cost-effectiveness of RSV vaccination of infants and pregnant women in Turkey: an illustration based on bursa data. *PLoS One*. 2016;11:e0163567. https://doi.org/10.1371/journal.pone.0163567.
30 Roy LM. *Deriving health utility weights for infants with Respiratory Syncytial Virus (RSV)*; 2014. https://open.library.ubc.ca/soa/cIRcle/collections/ubctheses/24/items/1.0074259. Accessed March 16, 2023.
31 Weiner LB, Masaquel AS, Polak MJ, Mahadevia PJ. Cost-effectiveness analysis of palivizumab among pre-term infant populations covered by Medicaid in the United States. *J Med Econ*. 2012;15:997–1018.
32 Canadian Institute for Health Information. Hospital spending. https://www.cihi.ca/sites/default/files/document/hospital-spending-highlights-2020-en.pdf; 2020. Accessed March 16, 2023.
33 Canadian Institute for Health Information. *Care in Canadian ICUs*; 2016:1–36. https://secure.cihi.ca/free_products/ICU_Report_EN.pdf. Accessed March 16, 2023.
34 Statistics Canada. *Gross domestic product (GDP) at basic prices, by industry, provinces and territories*; 2023. https://doi.org/10.25318/3610040201-eng.
35 Anderson E, Krilov LR, DeVincenzo JP, et al. SENTINEL1: an observational study of respiratory syncytial virus hospitalizations among U.S. Infants born at 29 to 35 Weeks' gestational age not receiving immunoprophylaxis. *Am J Perinatol*. 2016;34:51–61.
36 Bozaykut A, Paketci A, Gonul Sezer R, Paketci C. Evaluation of risk factors for recurrent wheezing episodes. *J Clin Med Res*. 2013;5:395–400. https://doi.org/10.4021/jocmr1543w.
37 Schauer U, Hoffjan S, Bittscheidt J, et al. RSV bronchiolitis and risk of wheeze and allergic sensitisation in the first year of life. *Eur Respir J*. 2002;20:1277–1283.
38 Zhou Y, Tong L, Li M, et al. Recurrent wheezing and asthma after respiratory syncytial virus bronchiolitis. *Front Pediatr*. 2021;9:649003. https://doi.org/10.3389/fped.2021.649003.
39 Welliver RC, Checchia PA, Bauman JH, Fernandes AW, Mahadevia PJ, Hall CB. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. *Curr Med Res Opin*. 2010;26:2175–2181.
40 Checchia PA, Nalysnyk L, Fernandes AW, et al. Mortality and morbidity among infants at high risk for severe respiratory syncytial virus infection receiving prophylaxis with palivizumab: a systematic literature review and meta-analysis. *Pediatr Crit Care Med*. 2011;12:580–588.
41 Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus–associated hospitalizations among children less than 24 months of age. *Pediatrics*. 2013;132:e341–e348. https://doi.org/10.1542/peds.2013-0303.
42 Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. *J Pediatr*. 2003;143:150–156.

43 Szabo SM, Gooch KL, Bibby MM, et al. The risk of mortality among young children hospitalized for severe respiratory syncytial virus infection. *Paediatr Respir Rev*. 2013;13:S1–S8.
44 Tam J, Papenburg J, Fanella S, et al. Pediatric Investigators Collaborative Network on infections in Canada study of respiratory syncytial virus–associated deaths in pediatric patients in Canada, 2003–2013. *Clin Infect Dis*. 2019;68:113–119.
45 Wingert A, Pillay J, Moore DL, et al. Burden of illness in infants and young children hospitalized for respiratory syncytial virus: a rapid review. *Can Commun Dis Rep*. 2021;47:381–396.
46 CADTH. *Guidelines for the economic evaluation of health technologies: Canada*. Ottawa. 4th ed.; 2017. https://www.cadth.ca/sites/default/files/pdf/guidelines_for_the_economic_evaluation_of_health_technologies_canada_4th_ed.pdf. Accessed March 16, 2023.
47 Government of Canada. *Results of the survey on vaccination during pregnancy 2021*; 2022. https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/survey-vaccination-during-pregnancy-2021.html. Accessed March 16, 2023.
48 Simões EAF, Madhi SA, Muller WJ, et al. Efficacy of nirsevimab against respiratory syncytial virus lower respiratory tract infections in preterm and term infants, and pharmacokinetic extrapolation to infants with congenital heart disease and chronic lung disease: a pooled analysis of randomised controlled trials. *Lancet Child Adolesc Health*. 2023;7:180–189.
49 Ortega-Sanchez IR. *Economics of preventing respiratory syncytial virus lower respiratory tract infections (RSV- LRTI) among US infants with nirsevimab*. 2023.
50 Kampmann B, Madhi SA, Munjal I, et al. Bivalent prefusion F vaccine in pregnancy to prevent RSV illness in infants. *N Engl J Med*. 2023;388:1451–1464.
51 Munjal I. *Safety and efficacy of RSV bivalent PreF maternal vaccine*; 2023. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-02/slides-02-23/rsv-pediatric-06-munjal-508.pdf. Accessed June 25, 2023.
52 Fleming-Dutra K. *Evidence to recommendations framework: Pfizer maternal RSVpreF vaccine*; 2023. https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2023-06-21-23/03-RSV-Mat-Ped-Fleming-Dutra-508.pdf. Accessed June 25, 2023.
53 Papenburg J, Saleem M, Teselink J, et al. Cost-analysis of withdrawing immunoprophylaxis for respiratory syncytial virus in infants born at 33–35 weeks gestational age in Quebec. *Pediatr Infect Dis J*. 2020;39:694–699.
54 McGirr AA, Schwartz KL, Allen U, Solomon M, Sander B. The cost-effectiveness of palivizumab in infants with cystic fibrosis in the Canadian setting: a decision analysis model. *Hum Vaccines Immunother*. 2017;13:599–606.
55 Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making*. 1998;18:S68–S80.
56 Pichon-Riviere A, Drummond M, Palacios A, Garcia-Marti S, Augustovski F. Determining the efficiency path to universal health coverage: cost-effectiveness thresholds for 174 countries based on growth in life expectancy and health expenditures. *Lancet Glob Health*. 2023;11:e833–e842. https://doi.org/10.1016/S2214-109X(23)00162-6.
57 Ochalek J, Lomas J, Claxton K. *Assessing health opportunity costs for the Canadian health care systems*; 2018. http://www.pmprb-cepmb.gc.ca/CMFiles/Consultations/new_guidelines/Canada_report_2018-03-14_Final.pdf. Accessed March 16, 2023.
58 The World Bank. GDP per capita (current US$)–Canada. https://data.worldbank.org. Accessed March 16, 2023.
59 Greenough A. Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. *Arch Dis Child*. 2004;89:673–678.
60 Hodgson D, Atkins KE, Baguelin M, et al. Estimates for quality of life loss due to Respiratory Syncytial Virus. *Influenza Other Respir Viruses*. 2020;14:19–27.
61 Husereau D, Drummond M, Augustovski F, et al. Consolidated health economic evaluation reporting Standards 2022 (CHEERS 2022) statement: updated reporting guidance for health economic evaluations. *Health Policy OPEN*. 2022;3:100063. https://doi.org/10.1186/s12916-021-02204-0.
62 Statista. Number of births in Ontario, Canada 2022. Statista. https://www.statista.com/statistics/578584/number-of-births-in-ontario-canada/. Accessed March 16, 2023.
63 Laufer RS, Driscoll AJ, Baral R, et al. Cost-effectiveness of infant respiratory syncytial virus preventive interventions in Mali: a modeling study to inform policy and investment decisions. *Vaccine*. 2021;39:5037–5045.
64 Getaneh AM, Li X, Mao Z, et al. Cost-effectiveness of monoclonal antibody and maternal immunization against respiratory syncytial virus (RSV) in infants: evaluation for six European countries. *Vaccine*. 2023;41:1623–1631.
65 Koltai M, Moyes J, Nyawanda B, et al. Estimating the cost-effectiveness of maternal vaccination and monoclonal antibodies for respiratory syncytial virus in Kenya and South Africa. *BMC Med*. 2023;21:120. https://doi.org/10.1186/s12916-023-02806-w.
66 Hodgson D, Pebody R, Panovska-Griffiths J, Baguelin M, Atkins KE. Evaluating the next generation of RSV intervention strategies: a mathematical modelling study and cost-effectiveness analysis. *BMC Med*. 2020;18:348. https://doi.org/10.1186/s12916-020-01802-8.
67 Kieffer A, Beuvelet M, Sardesai A, et al. Expected impact of universal immunization with nirsevimab against RSV-related outcomes and costs among all US infants in their first RSV season: a static model. *J Infect Dis*. 2022;226:S282–S292.
68 Hodgson D, Koltai M, Krauer F, Flasche S, Jit M, Atkins KE. Optimal respiratory syncytial virus intervention programmes using nirsevimab in England and Wales. *Vaccine*. 2022;40:7151–7157.
69 Li X, Bilcke J, Vázquez Fernández L, et al. Cost-effectiveness of respiratory syncytial virus disease prevention strategies: maternal vaccine versus seasonal or year-round monoclonal antibody program in Norwegian children. *J Infect Dis*. 2022;226:S95–S101.
70 Bergman G, Hærskjold A, Stensballe LG, Kieler H, Linder M. Children with hemodynamically significant congenital heart disease can be identified through population-based registers. *Clin Epidemiol*. 2015;7:119–127.