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Research Paper

Effectiveness and cost-effectiveness of RSV infant and maternal immunization programs: A case study of Nunavik, Canada

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ABSTRACT

Background: Despite passive immunization with palivizumab to select high-risk children under two years of age, the health and economic burden of respiratory syncytial virus (RSV) remains substantial. We evaluated the effectiveness and cost-effectiveness of immunization programs with new generations of RSV prophylactics, including long-acting monoclonal antibodies (LAMA) and maternal vaccines, in terms of reducing hospitalizations in Nunavik, a Canadian Arctic region.

Methods: We developed an agent-based model of RSV transmission and parameterized it with the demographics and burden of RSV in Nunavik, Québec. We compared various immunization strategies, taking into account the costs associated with program delivery and calculating the incremental cost-effectiveness ratio (ICER) using quality-adjusted life-years (QALYs) gained as a measure of effectiveness. Scenario analyses included immunization with palivizumab and LAMA for infants under one year of age, and maternal vaccination in mild, moderate, and severe RSV seasons. Data were analysed from November 1, 2019 to May 1, 2021.

Findings: We found that a Nunavik pilot program with palivizumab which included healthy full-term infants aged 0–2 months in addition to those considered high-risk for complicated RSV disease is not cost-effective, compared to offering palivizumab only to preterm/chronically ill infants under 1 year of age. Using LAMA as prophylaxis produces ICER values of CAD $39,414/QALY (95% Credible Interval [CrI]: $39,314–$40,017) in a mild season (moderately cost-effective) and CAD $5,255/QALY (95% CrI: $5,222–$5,307) in a moderate season (highly cost-effective). LAMA was a dominant (cost-saving with negative incremental costs and positive incremental effects) strategy in a severe RSV season. Maternal vaccination combined with immunization of preterm/chronically ill infants 3–11 months was also a dominant (cost-saving) strategy in all seasons.

Interpretation: The switch from palivizumab in RSV immunization programs to new prophylactics would lead to significant savings, with LAMA being an effective strategy without compromising benefits in terms of reducing hospitalizations.

1. Introduction

Respiratory syncytial virus (RSV) inflicts a significant burden on global health systems [1–6], leading to an estimated 3.4 million hospital admissions in children younger than 5 years of age annually [5]. The major economic burden of RSV is attributable to hospitalization in the first year of life for management of lower respiratory tract infection (LRTI) due to bronchiolitis, pneumonia, apnea, or difficulty feeding [7–10]. The peak of RSV associated hospitalization occurs during winter months in temperate climates and rainy seasons in tropical regions [11–13]. RSV reinfection can also occur during the same or different epidemic seasons [14–16]. Infants at higher risk of complicated RSV disease

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Research in context

Evidence before this study

Prevention of respiratory syncytial virus (RSV) disease in high-risk infants under 1 year of age with palivizumab is an effective strategy to reduce hospitalizations. In light of efforts for the development of new RSV prophylactics, including long-acting monoclonal antibodies and maternal vaccines, there is a need to evaluate cost-effectiveness of infant immunization programs to inform policy in high-incidence Canadian arctic regions. Our literature search did not find any published studies assessing cost-effectiveness of the new RSV interventions in Canadian remote communities.

Added value of this study

In a modelled case study of a northern population in the province of Québec, Canada, we found that replacing palivizumab with a candidate long-acting monoclonal antibody (LAMA) or maternal vaccination results in a substantial reduction of immunization costs for program delivery, with LAMA presenting a cost-effective or even cost-saving strategy.

Implications of all the available evidence

LAMA and maternal vaccination can be a suitable RSV prophylactic for both healthy full-term and preterm/chronically ill infants in high-incidence areas, especially those with limited access to healthcare in remote communities.

requiring hospital support are those who are premature, or with underlying heart or lung diseases [17–20].

In Canada, the rates of RSV infection and hospitalizations are particularly high in the Arctic region. While RSV-associated hospitalization rates in Canada are 1 to 2 per thousand infants under 1 year of age [21,22], rates as high as 166 per 1000 live births have been observed in Nunavut [23]. In addition to the health and economic burden, infants from northern Inuit communities may require urgent air transfer outside their community to a southern tertiary care facility away from their families.

Nunavik is the homeland of the Quebec Inuit situated in the northern third of this Canadian province. Current RSV immunization programs in Nunavik recommend the administration of the anti-RSV monoclonal antibody, palivizumab (Synagis®) to prematurely-born infants under 6 months of age and children with certain comorbidities under 2 years of age during the RSV season [24–26]. Palivizumab is a passive immunizing agent that is dosed monthly for up to 5 doses each season [26–28]. Due to high RSV burden among newborn infants in this region, beginning the fall of 2017, Nunavik's immunization program expanded seasonal palivizumab's eligibility criteria to healthy full-term infants aged 0–2 months as a specific pilot project [24,25,29]. Palivizumab was offered to all high-risk and eligible healthy full-term infants during the RSV season. However, recent reviews by Nunavik Public Health and the Institut national de santé publique du Québec (INSPQ) raised concerns of the feasibility, ethical issues, and real-world effectiveness of palivizumab pilot program specific to healthy full-term infants in Nunavik [24,30], and the program was not continued. Given the high costs of palivizumab programs associated with monthly injections [23,31–33] and a high unmet medical need for RSV prevention, there is a need to evaluate the effectiveness and cost-effectiveness of alternative RSV prophylactic strategies for the infant population in Nunavik [27,34,35].

Currently, there are two strategies being considered to prevent the high burden of RSV in early infancy: maternal RSV vaccine, and/or long-acting anti-RSV F antibody for the infant [36]. Vaccines for infants are in early development. The only vaccine in phase 3 clinical development is a protein nanoparticle-based vaccine (ResVax™) which reported a 44.4% reduction in RSV-associated hospitalization rates within the first 90 days of life if administered before 33 weeks of pregnancy [37]. Six anti-RSV monoclonal antibodies for the infant are in development [36], with nirsevimab in phase 3. A long-acting monoclonal antibody (LAMA), nirsevimab, has been shown to provide a 70.1% reduction in LRTIs and a 78.4% decrease in hospitalizations among healthy preterm infants for up to 5 months [38]. The longer protective duration of newer anti-RSV monoclonals is especially important for high-risk children living in remote communities with limited access to healthcare. Identifying the optimal immunization strategies, however, will require an assessment of the effectiveness and cost-effectiveness of program delivery.

To evaluate cost-effectiveness of immunization programs with the next generation of RSV prophylactics, we developed an agent-based transmission model, parameterized with the estimated RSV disease burden in Nunavik. We evaluated the effectiveness and cost-effectiveness of various prophylactic vaccination scenarios, taking into account the direct medical costs associated with program delivery and RSV hospitalizations among infants under one year of age in a single RSV season. The cost-effectiveness scenarios include several immunization programs using the reported effectiveness of palivizumab, nirsevimab (LAMA), and ResVax (maternal vaccines). We estimated the incremental cost-effectiveness ratio (ICER) by calculating the quality-adjusted life-year (QALY) using the change in utility values induced by the immunization strategy for mild, moderate, and severe RSV seasons.

2. Methods

2.1. Population setting

Nunavik, Québec is a part of the Canadian Arctic region and has a total population of about 13,000 people [39]. There are 14 villages in two sub-regions, Hudson and Ungava. Each sub-region of Nunavik has 1 regional hospital in addition to several nursing stations and maternity service centres. Patient visits first occur at local nursing stations and if specialized medical care is required, they will be airlifted to a regional hospital. Children who require more specialized care not available in Nunavik are evacuated to Montreal Children's Hospital by air ambulance [24,25].

2.2. Model structure

We developed a discrete-event agent-based simulation model which includes characteristics of RSV infection and the demographics and community structure of Nunavik (Appendix, Figs. A1–A3), consisting of age distribution [39,40], infant health status [24,25], and household composition and size [39]. The model population included a total of 13,284 individuals with an age stratification based on 2016 Statistics Canada census in Nunavik [39,40] and health status of preterm birth with and without comorbidities for infants under 1 year of age. We categorized the infant population into three age-groups: 0–2 months, 3–5 months, and 6–11 months of age. The model also included age groups of children aged 12–23 months, 24–35 months, 36–47 months, and 5–18 years of age. Adults represented individuals over 18 years of age.

Individuals were assigned randomly to a total number of 3625 households, with a maximum of 10 people per household, while ensuring that no household is occupied with only children under the age of 18. Disease transmission within households was informed by estimates of the secondary household attack rate during a single RSV season [41,42],. We quantified the severity of a season with the percentage of households in which the virus was introduced (Table 1).

Table 1
Description of model parameters and corresponding values.

Description	Value			Source
Secondary household attack rate				
Infants <1 year of age	Sampled from Beta(27.984, 16.016), mean: 63.6%			[41]
Duration of infection (days)				
Incubation period	4.98 (4.54 - 5.37)			[48]
Symptomatic period	6.16 (5.68 - 6.63)			[49]
Households infected with Respiratory syncytial virus (RSV), having at least 1 infant under 1 year of age				
Mild season	30–50%			Derived from [41,42]
Moderate season	50–70%			
Severe season	70–90%			
Length of hospital stay per RSV patient (days)				
	0–2 months	**3–5 months**	**6–11 months**	
paediatric ward	3.0 (1–8)	3.0 (1–7)	4.0 (1–10)	[24]
Intensive Care Unit (ICU)	12.5 (2–25)[1]	12.5 (2–25)[1,2]	9.5 (4–15)[1]	
Average cost of an RSV case (CAD$)				
outpatient visit	$1569			[31–33]
paediatric ward	$16,946			
ICU	$66,038 ($64,114 – $69,845)			
Disutility weights due to RSV infection per disease outcome[3]				
Without previous infection or outpatient visit	Sampled from Beta(19.2, 364.6), mean: 0.05			[32,50–52]
With previous infection	Sampled from Beta(45.8, 335.9), mean: 0.12			
outpatient visit	sampled from beta(53.6, 281.4), mean: 0.16			
paediatric ward	sampled from beta(109.7, 157.9), mean: 0.41			
ICU	Sampled from Beta(159.4, 106.2), mean: 0.60			
Proportion of ICU out of				
	Preterm/chronically ill		**Healthy**	
Regional admissions (without palivizumab)	15.5%		13.0%	[47]
Tertiary transfers (with palivizumab)	50%		50%	[46]
Duration of prophylactic efficacy for 1 dose (days)				
Palivizumab	30		30[4]	[53]
Maternal vaccine	90		90	[37]
Long-acting Monoclonal Antibodies (LAMA)	150		150[4]	[38]
Prophylactic efficacy				
	Preterm/chronically ill (months)			**Healthy (months)**	
Palivizumab	**0–2**	**3–5**	**6–11**	**0–2**	
Outpatient visit	48% (14–80)	48% (14–80)	48% (14–80)	48% (14–80)	[54,55]
Paediatric ward	20–90%	20–90%	20–67%	23.5%[5]	[20,53,56]
ICU	63.9%	63.9%	63.9%	43.9%[5]	[24,25,46,47]
Maternal vaccine					
Outpatient visit	14%			14%	[55]
Paediatric ward	24.7–61.9%	–	–	24.7–61.9%	[37]
ICU	31.9–75.0%	–	–	31.9–75.0%	
LAMA					
Outpatient visit	47% (20–80)	47% (20–80)	47% (20–80)	47% (20–80)	[38,55]
Paediatric ward	20–90%	20–90%	20–67%	23.5%	
ICU	63.9%	63.9%	63.9%	43.9%	Assumed the same as Palivizumab
Immunization costs per dose (CAD$)					
Palivizumab	$1065	$1567	$2048	$1065	[57]
Maternal vaccine	$1560	–	–	$1560	Assumed
LAMA	$1065	$1567	$2048	$1065	Assumed

[1] Numbers represent length of stay for RSV-associated admissions in a tertiary hospital [25]. We assumed that the length of stay in tertiary hospitals is the same as the length of stay for ICU admissions.
[2] There was no RSV-positive tertiary transfer associated with the age group 3–5 months during the years of 2014–2016 [25]. We therefore assumed the same length of stay as the age group 0–2 months.
[3] Utility was calculated as 1-Disutility.
[4] Assumed to be the same as the efficacy period for preterm/chronically ill.
[5] Derived from reference [24]. We used published hospitalization data in [24] and estimated effectiveness of palivizumab by 1- ($N_{intervention}$ / $N_{pre\text{-}intervention}$), where $N_{intervention}$ = healthy full-term hospitalizations in years 2017–2019 and $N_{pre\text{-}intervention}$ = healthy full-term hospitalizations in years 2014–2016. For pediatric wards, N refers to regional hospital cases. However, for ICU admissions, N refers to 50% of the ratio of tertiary cases to regional RSV hospitalized cases.

In our model (Appendix, Fig. A4), infants under 1 year of age were categorized as healthy full-term or preterm/chronically ill. The latter category (as high-risk) includes prematurely born infants under a chronological age of 6 months and infants with underlying comorbidities, such as chronic lung disease and hemodynamically significant heart disease. High-risk infants constitute approximately 10% of the birth cohort [25]. The model included an average of 360 healthy full-term and 26 preterm/chronically ill infants in a simulated population resembling the demographics of Nunavik [24,25].

2.3. RSV infection

Infants may acquire RSV infection through contact with infected household members such as school-aged children or adults [41,43,44]. Community-based studies in high-income countries show that older siblings and parents have an annual re-infection rate of 6%–20% [45]. We considered scenarios of mild, moderate, and severe RSV seasons, corresponding to the introduction of RSV infection in 30–50% (mild), 50–70% (moderate), and 70–90% (severe) of households with at least one infant under 1 year of age. The total number

of households with at least 1 infant can vary between simulations of different seasons. The model contained an average of 300 households, a proportion of which were exposed to the virus depending on the severity of the season.

After the introduction of RSV infection into a household, we obtained the number of infants in each age group that were infected in simulation scenarios for a time horizon of 1 year (including the RSV season). The probability of disease transmission among infants was sampled from a Beta distribution (Beta(27.984, 16.016)) with estimated mean secondary household attack rate of 63.6% among those under 1 year of age [41]. Disease transmission within household members was implemented probabilistically, and occurred as a result of rejection sampling (Bernoulli) trials, where the chance of success (i.e., occurrence of infection) was given by the sampled probability of transmission.

2.4. RSV disease outcomes

We assumed that, without interventions, all RSV-infected infants under 1 year of age manifest clinical disease and receive medical attention at a local nursing station (as an outpatient visit) or are admitted to a hospital (Appendix, Fig. A5). The model was calibrated to RSV-associated hospitalizations data (Appendix, Fig. A6) from regional and tertiary hospitals [24,25] to derive the proportion of infected infants seen as an outpatient in local nursing stations, and those requiring non-ICU (general ward) and ICU admissions in regional and tertiary hospitals, respectively. The calibration process incorporated the severity of the season by using RSV hospitalizations data for a six-year period of 2014–2019 [24,25]. For infants needing critical care in an ICU, we calibrated the model to the 50% of the transferred infants to a tertiary hospital for the years of 2014–2016 (Appendix, Fig. A7) [24,46], during which palivizumab immunization programs was implemented only for high-risk infants (preterm/chronically ill). To adjust ICU data to a scenario of no-intervention, we accounted for previous ICU estimates where no palivizumab was administered to children [47]. Without palivizumab protection, the proportion of ICU admissions out of regional hospitalizations for high-risk and healthy full-term infants was previously estimated to be 15.5% and 13%, respectively [47]. We used these estimates to calculate the efficacy of palivizumab in reducing ICU rates among preterm/chronically ill and healthy full-term infants.

The clinical data reported from RSV-related infection among Nunavik's infants considered the laboratory-confirmed RSV cases by rapid antigen detection test (RADT) or real-time polymerase chain reaction (PCR) assay [24]. This may have underestimated the total number of RSV infections since laboratory testing in infants only occurred through physicians during the 2014–2016 years. Since 2017, about 95% of all admitted infants with respiratory illness have been tested for RSV [24]. To account for underestimation of RSV infection, we used adjusted rates estimated for both underdetection due to 60% RADT sensitivity test and number of undiagnosed infections among those not tested (Supplementary Table A. 1a and 1b in [24]).

2.5. RSV immunization programs

We evaluated the impact of six RSV prevention strategies, summarized in Table 2, on reducing medically-attended (outpatient) visits and hospitalizations for infants under 1 year of age. The pilot immunization program in Nunavik provided 5 doses of palivizumab for eligible infants during the RSV season (January to June), each dose administered every month. Eligible children included preterm infants under 6 months of age, chronically ill infants under 2 years of age, and healthy full-term infants aged 0–2 months at the start of the RSV season or born during the season [24,25]. We compared the pilot strategy in Nunavik to the alternative program in which only preterm/chronically ill infants were eligible to receive palivizumab. We extended our analyses to evaluate effectiveness and cost-effectiveness of RSV prevention strategies with prospective prophylactic candidates, including LAMA (e.g., MEDI8897, Nirsevimab™, by MedImmune [38]) and maternal RSV vaccine (e.g., RSV F-nanoparticle vaccine, ResVax™, by NovaVax [37]).

Passive immunization against RSV has not been demonstrated to prevent infection and, therefore, the proposed programs may not have an impact on RSV incidence. However, palivizumab is shown to be effective in reducing the incidence of hospitalization and in preventing outpatient visits associated with RSV infection in infants [20,54]. In our model, interventions affect the disease outcomes, and prophylaxis effectiveness was applied to reduce outpatient visits, hospitalizations, and ICU admissions for age groups under 1 year old. The household prevalence in each scenario of mild, moderate, and severe season was assumed to be constant irrespective of the interventions, and RSV attack rates only changed in households according to the severity of the season.

For palivizumab programs (S2 and S6), we assumed monthly administration of the prophylactic to eligible children (with eligibility

Table 2
Scenarios of Respiratory Syncytial Virus (RSV) immunization programs.

Baseline Scenario (S)	Target population	Alternative strategy	Target population
S1 No Intervention	None	**S2** Palivizumab	Preterm infants (0–5 months) Chronically ill infants (< 1 year old)[1]
		S3 Long-acting Monoclonal Antibodies (LAMA)	Preterm infants (0–5 months) Chronically ill infants (< 1 year old)[1]
		S4 Maternal vaccine	Pregnant women[2] (Last trimester before week 33)
		S5 Maternal vaccine + LAMA for preterm and chronically ill infants	Pregnant women[2] (Last trimester before week 33) Preterm infants (3–5 months) Chronically ill infants (3–11 months old)
S2 Palivizumab	Preterm infants (0–5 months) Chronically ill infants (< 1 year old)[1]	**S6** (S2 + Palivizumab for healthy infants) Pilot strategy in Nunavik	Healthy full-term infants (0–2 months)[3] Preterm infants (0–5 months) Chronically ill infants (< 1 year old)[1]
S3 Long-acting Monoclonal Antibodies (LAMA)	Preterm infants (0–5 months) Chronically ill infants (< 1 year old)	**S7** (S3 + LAMA for healthy infants)	Healthy full-term infants (0–2 months)[3] Preterm infants (0–5 months) Chronically ill infants (< 1 year old)

[1] Nunavik recommends the administration of palivizumab for chronically ill infants under 2 years of age. However, our model only considers infants under 1 year of age.
[2] For pregnant women giving birth 1 or 2 months prior to the start of RSV season (in November and December), or during the season (from January to June).
[3] Healthy full-term infants born between October 1 and May 31 of the next calendar year are eligible until they reach 6 months of age or until the end of RSV season.

criteria described in Table 2 based on age and health status) for a total of 5 doses during a season. For immunization with LAMA only (S3 and S7), a single dose of the prophylactic was given to eligible infants during the RSV season with a protection duration of 150 days [38]. Maternal vaccines (S4 and S5) were offered to pregnant women in the last trimester (before gestational week 33), who were giving birth 1 or 2 months prior to the start of the RSV season, or during the season, with an effective protection period of 90 days from birth. In scenario S4, maternal vaccination was the only immunization program. However, in scenario S5, we considered additional protection with monthly LAMA shots after the 90-day mark post-birth, so that eligible infants were protected for the rest of RSV season after maternal protection had waned.

2.6. Cost-effectiveness

To evaluate the cost-effectiveness of each immunization program in Table 2, we computed the incremental cost-effectiveness ratio (ICER) using quality-adjusted life-years (QALYs) gained as a measure of effectiveness. We first compared four scenarios of Palivizumab (S2), LAMA (S3), maternal vaccination (S4), and maternal vaccination plus LAMA for preterm and chronically ill infants (S5) to the scenario of no intervention (S1) individually. For each scenario, we calculated the ratio of difference in net costs (ΔC) to the difference in net effectiveness (ΔE). We then compared two additional scenarios (i) S6 with the comparator S2, and (ii) S7 with the comparator S3. The S6 program is an extended immunization strategy that includes S2 with incremental costs due to additional immunization of healthy full-term infants (0–2 months) with palivizumab. Similarly, S7 is an extended program that includes S3 with the addition of healthy full-term infants (0–2 months) for immunization with LAMA.

QALYs were calculated based on disutilities corresponding to the severity and duration of disease, with disutility weights obtained from published studies [32,50–52]. For severe cases needing hospitalization, we considered a disutility weight of 0.41 for the duration of stay in paediatric ward and 0.6 for the duration of ICU [50–52]. Disutility weights were 0.16 during outpatient treatment, and 0.12 with a previous RSV infection (post treatment) [32,50]. Averted outpatient visits of mild (or asymptomatic) RSV infection were assigned a disutility weight of 0.05 [32]. These disutility weights were assumed to be the same for healthy and preterm/chronically ill infants.

We considered direct costs borne by the healthcare system for a symptomatic RSV case, including physician consultation, treatment, paediatric ward and/or ICU admission, transportation including a, and parental accommodation [31–33]. For immunization programmes in Table 2, we considered age-specific costs associated with vaccination of infants, with 5% wastage and $50 administration fee [57]. In the absence of vaccine pricing information for LAMA and maternal vaccine, we considered the same age-specific cost of palivizumab per kilogram for a single dose of LAMA and an average cost of $1560 for maternal vaccination with ResVax (Table 1). All costs were converted to 2021 Canadian dollars [58]. For a single RSV season, we did not apply the discounting rate in our cost-effectiveness analysis. Our study adheres to guidelines outlined by Consolidated Health Economic Evaluation Reporting Standards (CHEERS) for health interventions.

We calculated the empirical ICER value based on 500 Monte Carlo simulations over a time horizon of one year using the formulae

$$\text{ICER} = \frac{\Delta C}{\Delta E} = \frac{\text{Costs}_{\text{alternative scenario}} - \text{Costs}_{\text{baseline scenario}}}{\text{QALYs}_{\text{alternative scenario}} - \text{QALYs}_{\text{baseline scenario}}}$$

Intuitively, the ICER value represents the total costs incurred to gain a single QALY. In order to account for the uncertainty around this point estimate, we constructed 95% credible intervals by applying a non-parametric bootstrap (with 500 replicates) to the Monte Carlo simulations.

The Canadian Agency for Drugs and Technologies in Health (CADTH) recommends interventions with ICER values under $50,000 per QALY to be considered for implementation [59]. However, there are several programs accepted with ICER values above this threshold with the highest ICER value of $131,100 per QALY [60]. In a commonly referenced study for most Canada-based cost-effectiveness analyses [59], ICER values of under $20,000 per QALY are strongly recommended for RSV interventions. ICER values between $20,000 to $100,000 per QALY are moderately recommended for integration. As per previously published studies in a Canadian context, we considered an alternative strategy to be highly cost-effective if the ICER value per QALY remained below the willingness to pay threshold of $20,000 per QALY, and moderately cost-effective for ICER values between $20,000 and $100,000 per QALY. For negative ICER values, the alternative strategy was dominant (cost-saving with $\Delta C < 0$ and $\Delta E > 0$).

2.7. Model implementation

We implemented the RSV transmission model in Julia language, and parameterized it with estimates in Table 1. For each season, we introduced RSV infection to a number of households randomly (depending on the severity of the season, Table 1) and recorded the number of infections that occurred among infants under 1 years of age in each simulation based on the secondary attack rate sampled from a Beta distribution (Table 1). We repeated these simulations (500 independent Monte-Carlo replications) for each scenario of mild, moderate, or severe season to derive the distribution of infections among infants. For each simulation, the proportions of RSV infected infants that required hospitalization (i.e., paediatric ward) and ICU admission were estimated using the incidence data for hospitalization in different age groups [24,25]. The remaining infected infants were considered as outpatient visits. Depending on the intervention scenario, we then applied the effectiveness of the prophylactic measure to the target group to determine averted outpatient visits, hospital and ICU admissions, which subsequently affected both costs incurred and QALYs gained (Table 1).

To account for the uncertainty in key model parameters, we sampled parameter values from ranges and relevant statistical distributions. For example, each independent Monte-Carlo simulation was initialized with random household compositions (i.e., distribution of adults and children), and the secondary household attack rate was sampled from a Beta distribution. Furthermore, the effectiveness of interventions in reducing hospitalization, ICU, and outpatient visits, as well as utility weights were sampled from their respective ranges and distributions. The results of each scenario were averaged over all replications, and 95% credible intervals for the estimates were generated using the bias-corrected and accelerated bootstrap method. All parameters were informed by published studies (Table 1). The computational model is available at: https://github.com/ABM-Lab/RSV_ABM-Lab.

2.8. Ethics statement

This study used non-identifiable data from published studies, and did not require ethics approval.

2.9. Role of funding source

The funding source had no role in the design of the study, analysis of the model, interpretation of the results, writing of the paper, or decision to publish the study.

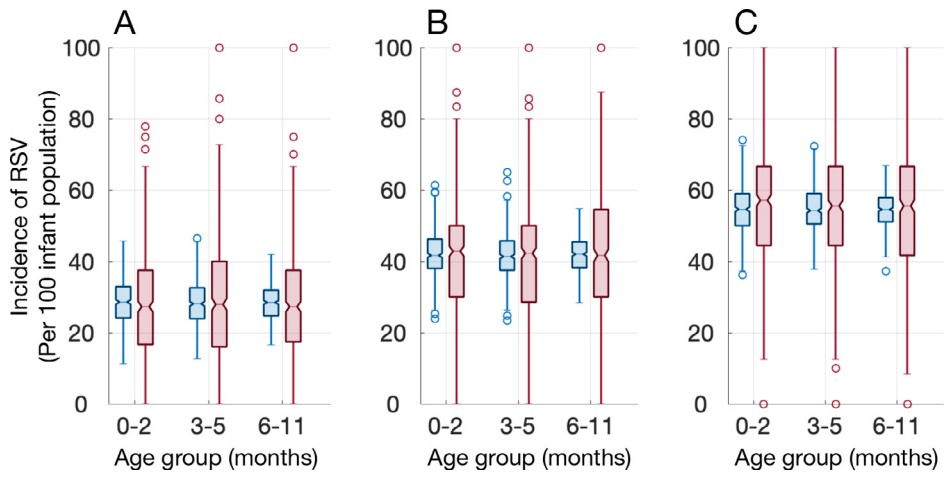

Fig. 1. Box plots of the projected incidence of Respiratory syncytial virus (RSV) infection per 100 healthy (blue) and preterm/chronically ill (red) infants under one year of age during (A) mild season, (B) moderate season, and (C) severe season in Nunavik. Horizontal line in the notched boxes indicate medians; boxes represent interquartile range (IQR); Whiskers indicate extended range from minimum (25th percentile − 1.5 IQR) to maximum (75th percentile + 1.5 IQR); and circles show outliers.

3. Results

3.1. RSV incidence

The median number of RSV infections was projected to be 28.6 (Interquartile range (IQR): 24.2–33.0), 28.1 (IQR: 23.8–32.4), and 28.5 (IQR: 24.8–32.1) per 100 healthy infants aged 0–2, 3–5, and 6–11 months, respectively, during a mild season (Fig. 1). For the same age groups, we projected a median of 27.3 (IQR: 16.9–37.7), 27.9 (IQR: 145.9–39.9), and 27.3 (IQR: 17.2–37.3) infections per 100 preterm/chronically ill infants. There was no difference in median infection rates between healthy and preterm/chronically ill infants in all age groups during a mild season (Wilcoxon test, p-values>0.17). For a moderate season, the median RSV infection rate was estimated to be 41.7 (IQR: 37.6 – 45.8) in 0–2 months, 41.4 (IQR: 37.2–45.5) in 3–5 months, and 42.0 (IQR: 38.4–45.6) in 6–11 months of age per 100 healthy infants. For the same age groups among 100 preterm/chronically ill infants, median infections were projected to be 42.8 (IQR: 32.9–52.9), 42.3 (IQR: 31.5–53.0), and 41.7 (IQR: 29.4–54.0). The Wilcoxon test showed no significant difference in infections between healthy and preterm/chronically ill infants in a moderate season (Wilcoxon test, p-values>0.26). During severe seasons, the median of RSV infections increased to 54.6 (IQR: 50.1–59.1) in 0–2 months, 54.2 (IQR: 49.9–58.5) in 3–5 months, and 54.5 (IQR: 51.1–57.9) in 6–11 months of age per 100 healthy infants. For the same age groups among 100 preterm/chronically ill infants, median infections were 57.1 (IQR: 46.0–68.3), 55.5 (IQR: 44.4–66.7), and 55.5 (IQR: 43.1–68.1). There was no significant difference between the incidence of RSV among healthy and preterm/chronically ill infants (Wilcoxon test, *p*-values>0.24).

3.2. Impact of immunization programs on RSV-associated hospitalizations

For each immunization program described in Table 2, we estimated the number of RSV-associated hospital admissions per 100 population among healthy and preterm/chronically ill infants under 1 year of age (Fig. 2). In all age groups, hospitalization rates increased as the severity (attack rate) of the season worsened from mild to severe, with the highest rates being associated with no intervention (S1). In any season, the lowest hospitalization rates among healthy infants aged 0–2 months were achieved with LAMA or maternal vaccination (S3 and S4). However, there was no statistically significant difference in hospitalization rates among preterm/chronically ill infants aged 0–2 months (Wilcoxon test, p-value>0.4). For healthy infants aged 3–11 months (Fig. 2A–2C), we found no difference in hospitalization rates between immunization strategies as no intervention was offered to these age groups. For preterm/chronically ill infants, all immunization strategies resulted in similar overall hospitalization rates, with the exception of S4 which underperformed in infants aged 3–11 months (Fig. 2D–2F). The reduction of hospitalizations achieved in high-risk infants under 1 year of age with LAMA (S5) and maternal vaccine plus LAMA (S7) was similar to the pilot program with palivizumab in Nunavik (S6), but differed significantly in cost-effectiveness (Tables 3–5). The reduction of hospitalizations due LAMA (S3) was similar when compared to passive immunization of preterm/chronically ill infants with palivizumab (S2)

3.3. Cost-effectiveness of RSV immunization programs

We found that during a mild RSV season, the immunization program for high-risk infants with palivizumab (S2) results in average of 0.084 undiscounted QALYs with incremental costs of $84,750 (Table 3), compared to no intervention (S1). This produces an undiscounted ICER of $1011,139 per QALYs gained, suggesting that the program is not cost-effective. In a moderate RSV season, the same immunization program (S2) generates an increased QALYs of 0.166 with a substantially lower incremental cost of $2279 (Table 4). In this case, the use of palivizumab leads to an undiscounted ICER of $13,926 per QALYs gained, suggesting that the immunization program is highly cost-effective as per threshold of ICER < $20,000 per QALY (Appendix, Fig. A8). The probability of S2 being highly cost-effective was 99.2% (Appendix, Fig. A8). We found that in a severe season, immunizing high-risk infants with palivizumab would be cost-saving (Table 5). When the immunization program with palivizumab expanded to include healthy infants of age 0–2 months (S6), the undiscounted QALYs increased significantly as compared to immunizing only high-risk infants (S2). However, the incremental costs were substantially higher with ICER values exceeding the $100,000 threshold of moderately cost-effective, suggesting that the program is not cost-effective irrespective of the severity of the season (Tables 3–5).

Replacing palivizumab with LAMA for vaccination of high-risk infants (S3) was shown to be cost-saving in all scenarios of mild, moderate, and severe seasons (Tables 3-5). The use of LAMA was a dominant strategy and resulted in the lowest saving of over $883,539 per QALY. Inclusion of healthy infants aged 0–2 months in the immunization program with LAMA (S7) in addition to high-risk infants was deemed to be moderately cost-effective (with ICER value of $39,414 per QALY) in a mild season, highly cost-effective (with ICER value of

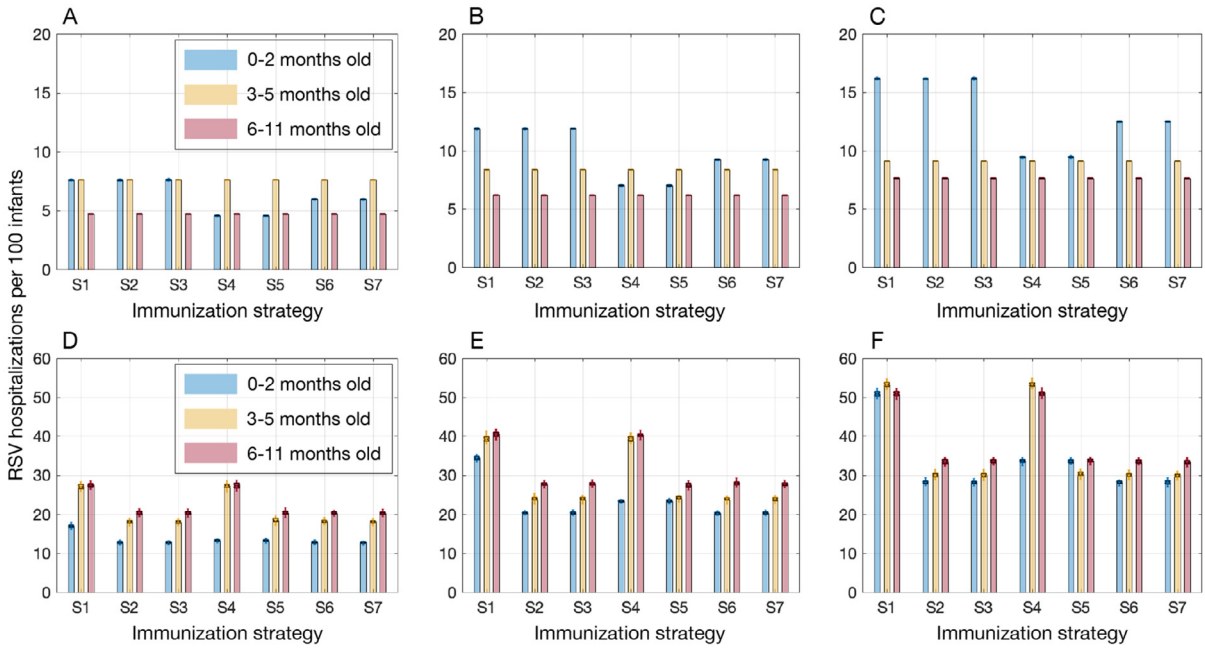

Fig. 2. Projected hospital admissions of Respiratory Syncytial Virus (RSV) infection in Nunavik. Projected age-specific RSV-associated hospitalizations per 100 infants under one year of age for different immunization strategies (Table 2). Coloured bar graphs correspond to the average of hospitalizations for (A-C) healthy and (D-F) preterm/chronically ill infants during mild (A and D), moderate (B and E), and severe (C and F) seasons for scenarios S1-S7 described in Table 2. Boxplots on bar graphs indicate the interquartile range (IQR) and whiskers represent extended range from minimum (25th percentile − 1.5 IQR) to maximum (75th percentile + 1.5 IQR).

$5255 per QALY) in a moderate season, and cost-saving (with saving of $7049 per QALY) in a severe season.

We found that maternal vaccination with ResVax (S4) during the last trimester in a mild season is not a cost-effective strategy. The undiscounted QALYs gained in this scenario was the lowest (0.0639) compared to any other immunization strategy, with incremental costs of $14,502, resulting in an ICER value of $227,286. However, the same strategy would be cost-saving (dominant) in a moderate or severe RSV season (Tables 3–5). When maternal vaccination is combined with immunization of preterm and chronically ill infants aged 3–11 months using LAMA (S5), the strategy would be cost-saving (dominant) in all scenarios of mild, moderate and severe seasons.

Overall, we found that administration of LAMA to healthy infants aged 0–2 months and preterm/chronically ill infants under 1 year of age (S7) outperforms the pilot strategy of offering palivizumab to the same target groups (S6). Similarly, maternal immunization in combination with immunization of preterm/chronically ill infants aged 3–11 months with LAMA (S5) outperforms (S6, pilot program in Nunavik) and would be a cost-saving strategy.

4. Discussion

As a new generation of RSV prophylactics, including long-acting monoclonal antibodies and maternal vaccines [35], are being developed, it is key to understand their health and economic impact in developing more effective and cost-effective RSV prevention programs. In this study, we developed an agent-based simulation model of RSV infection to evaluate the cost-effectiveness of different RSV immunization programs in the context of a northern Canadian population. Our results indicate that the pilot program in Nunavik, which expanded the eligibility of palivizumab to include healthy infants aged 0–2 months (S6), is not a cost-effective strategy compared to the previous program (S2) covering only high-risk infants (i.e., preterm infants under 6 months and chronically ill infants under 1 year of age). However, replacing palivizumab with LAMA in the expanded program (S7) can be moderately or highly cost-effective (depending on the severity of the RSV season), and even cost-saving in a severe RSV season with similar benefits in terms of hospitalizations averted. Our results also show that immunization programs with the maternal

Table 3
Estimates of incremental costs (CDN $), Quality-adjusted Life Years (QALYs), and Incremental Cost-effectiveness Ratio (ICER) values with their 95% credible intervals derived from cost-effectiveness analysis of scenarios (S) in Table 2 during a mild Respiratory Syncytial Virus (RSV) season.

Baseline	Alternative	Difference in costs ($)	QALYs gained	ICER ($/QALY)
S1	S2	84,750 (789,86 90,093)	0.0840 (0.0780 0.0898)	1011,139 (1007,586 1026,033)
S1	S3	−71,927 (−77,598 −66,406)	0.0814 (0.0757 0.0867)	−883,539 (−885,162 −881,099)
S1	S4	14,502 (9766 18,929)	0.0639 (0.0617 0.0660)	227,286 (224,758 234,854)
S1	S5	−25,785 (−32,246 −19,776)	0.1258 (0.1199 0.1314)	−204,621 (−205,981 −200,668)
S2	S6	392,677 (387,785 397,530)	0.8905 (0.8318 0.9451)	441,023 (440,315 444,423)
S3	S7	35,084 (32,603 37,447)	0.8906 (0.8324 0.9452)	39,414 (39,314 40,017)

Table 4
Estimates of incremental costs (CDN $), Quality-adjusted Life Years (QALYs), and Incremental Cost-effectiveness Ratio (ICER) values with their 95% credible intervals derived from cost-effectiveness analysis of scenarios (S) in Table 2 during a moderate Respiratory Syncytial Virus (RSV) season.

Baseline	Alternative	Difference in costs ($)	QALYs gained	ICER ($/QALY)
S1	S2	2279 (−5279 9309)	0.1660 (0.1581 0.1736)	13,926 (12,669 15,755)
S1	S3	−154,831 (−162,779 −147,163)	0.1661 (0.1580 0.1734)	−931,845 (−932,832 −930,793)
S1	S4	−65,136 (−71,241 −59,113)	0.1109 (0.1078 0.1141)	−587,402 (−588,340 −586,545)
S1	S5	−144,187 (−152,765 −136,214)	0.2196 (0.2114 0.2275)	−656,784 (−658,011 −655,615)
S2	S6	367,582 (363,082 372,147)	1.7660 (1.6903 1.8387)	208,015 (207,848 208,376)
S3	S7	9291 (7024 11,566)	1.7677 (1.6931 1.8416)	5255 (5222 5307)

vaccine and LAMA, using data from the candidate products ResVax and nirsevimab, respectively, are highly cost-effective or cost-saving as compared to the pilot strategy in Nunavik.

Our results contrast previous studies [23,57,61], which suggested palivizumab as a cost-effective strategy for immunizing healthy full-term infants residing in remote communities of the Canadian Arctic. These studies assumed a similar effectiveness of palivizumab in healthy full-term infants as in preterm Inuit infants (88%–98% risk reduction). However, recent data from the expanded RSV immunization program in Nunavik over a three-year period (2017–2019) shows that the immunization of healthy full-term infants with palivizumab was ineffective in reducing hospitalizations among healthy newborns [24]. In our analysis, we considered an extreme scenario with a 23.5% effectiveness of palivizumab for healthy infants aged 0–2 months in reducing hospitalization and 43.9% for decreasing ICU admissions based on recently published data [24] (footnote 4 and 5 in Table 1), which are significantly lower than the ranges assumed in studies [23,57,61]. Our analyses show that the use of palivizumab for the protection of healthy full-term infants is not a cost-effective strategy, even under an optimal scenario with a relatively high effectiveness of palivizumab compared to the recent estimates [24].

One of the goals in this study was to provide a wide perspective and evidence for policy decision-makers regarding cost-effectiveness of palivizumab and new generation of RSV prophylaxis for infants in remote communities. Similar to previous studies [50,62–64], our results show that immunization of high-risk infants with palivizumab, compared to no intervention, would be a cost-effective, and may even be a cost-saving, strategy depending on the severity of the season. We estimated an undiscounted ICER value below $20,000 for a moderate season, and a net saving of $290,034 (95% CrI: $292,097, $288,699) per QALY for a severe season in Nunavik. These findings corroborate a recent systematic review [64], reporting that 90% of published studies have ICER values < $50,000 (2017, US$) per QALY for RSV immunization programs with palivizumab for high-risk infants. Furthermore, our analysis agrees with Hodgson et al. [65], in which LAMA and maternal vaccines have shown to be cost-effective replacements for palivizumab depending on the purchasing price of these prospective prophylactics. We note that previous studies outside Canadian context may not be applicable to the population setting we considered in our analysis, which includes a geographically dispersed population with remote communities. Further, no other study for a similar population setting in Canada has evaluated cost-effectiveness of RSV interventions with new generation of prophylactics.

A strength of our analysis is the use of detailed Nunavik hospitalization data over six years (2014–2019) in the population of infants under 1 year of age, which showed considerable variability between seasons [24,25]. However, the results should be interpreted within the contexts of study limitations. There still remains uncertainty around characteristics of the new-generation of RSV prophylactics that would influence model parameterizations. In the absence of vaccine pricing information for nirsevimab (LAMA) and maternal vaccine ResVax, we considered the same age-specific cost of palivizumab per kilogram for a single dose. Furthermore, the efficacy of nirsevimab has only been evaluated in healthy preterm infants in clinical trials thus far [38] and its effectiveness in infants with underlying medical conditions remains unknown. We did not account for re-infection during our time horizon of one year, and assumed that infants recovered from RSV infection would be immune for the rest of RSV season. However, RSV reinfection is often associated with mild or

Table 5
Estimates of incremental costs (CDN $), Quality-adjusted Life Years (QALYs), and Incremental Cost-effectiveness Ratio (ICER) values with their 95% credible intervals derived from cost-effectiveness analysis of scenarios (S) in Table 2 during a severe Respiratory Syncytial Virus (RSV) season.

Baseline	Alternative	Difference in costs ($)	QALYs gained	ICER ($/QALY)
S1	S2	−72,045 (−82,065 −62,660)	0.2484 (0.2382 0.2582)	−290,034 (−292,097 −288,699)
S1	S3	−227,282 (−237,507 −217,361)	0.2511 (0.2402 0.2610)	−905,256 (−906,069 −904,322)
S1	S4	−124,503 (−134,323 −114,168)	0.1538 (0.1496 0.1582)	−809,332 (−810,628 −807,651)
S1	S5	−234,599 (−247,291 −221,712)	0.3008 (0.2915 0.3100)	−779,744 (−781,020 −778,744)
S2	S6	339,735 (334,860 344,633)	2.6181 (2.5276 2.7058)	129,726 (129,379 129,840)
S3	S7	−18,453 (−21,665 −15,274)	2.6195 (2.5281 2.7078)	−7049 (−7072 −7007)

asymptomatic, uncomplicated upper/lower respiratory tract infection [15]. Since our analysis was restricted to a single season, we calculated undiscounted QALY and ICER values. We also omitted case fatality due to RSV disease during the time horizon in our study, which is estimated to be ~1% of all Canadian Inuit infants hospitalized with RSV-confirmed infection [32]. Our model did not include RSV asymptomatic infection as its proportion among infants under 1 year of age is estimated to be small, with lower viral loads and significantly reduced probability of disease transmission [66]. While RSV asymptomatic infection is more common in older age groups, interventions considered in our study are primarily offered to infants under 1 year of age. Accordingly, our cost-effectiveness analysis considered only this age group. Finally, although the pilot program in Nunavik recommended the administration of palivizumab for chronically ill infants under 2 years of age, our analysis of effectiveness and cost-effectiveness considered only infants under 1 year of age.

It is worth noting that our study was mainly focused on estimating the cost-effectiveness of the RSV immunization programs without consideration of the feasibility and acceptability of the strategies. A recent study [30] disclosed significant concerns and challenges among health-care workers regarding the pilot RSV immunization program in Nunavik as a result of limited human resources, lack of evidence regarding the effectiveness of palivizumab for healthy full-term infants, and ethical and communication challenges in the Inuit population.

In conclusion, long-acting monoclonal antibodies (LAMA) and maternal vaccines would substantially reduce costs of program delivery compared to palivizumab. In particular, switching from palivizumab to LAMA with the characteristics of nirsevimab in RSV immunization programs would be cost-effective or even cost-saving without increasing RSV-associated hospitalizations, especially in remote communities with limited access to healthcare. Furthermore, utilizing single-dose LAMA reduces the logistical challenges associated with multiple injections of palivizumab, and would likely increase uptake of RSV immunization.

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Contributors

SMM, JML and SAH were responsible for conception and design. SN and AS developed the model and performed simulations for effectiveness and cost-effectiveness analyses. JML and SN parameterized the model and contributed to collection of data and resources. SN and SMM drafted the manuscript. All authors analyzed and interpreted the results. All authors contributed to writing and revising the manuscript for accuracy of its content and approved its publication.

Data sharing statement

Data were collected from publicly available sources. All codes used for agent-based simulation and ICER analysis/estimation are available at: https://github.com/ABM-Lab/RSV_ABM-Lab.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2021.101141.

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