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Impact and cost-effectiveness analyses of vaccination for prevention of respiratory syncytial virus disease among older adults in Ontario: A Canadian Immunization Research Network (CIRN) study

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ABSTRACT

Background: Two prefusion F protein-based vaccines, Arexvy and Abrysvo, have been approved by Health Canada for protecting older adults against respiratory syncytial virus (RSV)-associated lower respiratory tract disease. We estimated the health benefits and cost-effectiveness of these vaccines under a publicly funded single-dose vaccination program in Ontario that targets residents of long-term care homes (LTCHs). Additionally, we evaluated an extended program that broadens vaccination to include community-dwelling older adults.

Methods: A discrete-event simulation model was parameterised with the burden of RSV disease including outpatient care, hospitalisation, and death among adults aged 60 years or older in Ontario, Canada. Accounting for direct and indirect costs (in 2023 Canadian dollars) associated with RSV-related outcomes, we calculated the net monetary benefit using quality-adjusted life-year (QALY) gained, and determined the range of price-per-dose (PPD) for vaccination programs to be cost-effective from both healthcare and societal perspectives over two RSV seasons. The incremental cost-effectiveness ratio (ICER) was calculated to estimate the additional costs required to gain one QALY.

Results: Using a willingness-to-pay of $50,000 per QALY gained, we found that vaccinating 90% of residents in LTCHs with Arexvy would be cost-effective from a societal perspective for a PPD up to $163, producing a mean ICER value of $49,984 (95% CI: $47,539 to $52,704) per QALY gained with a two-year budget impact of $463,468 per 100,000 older adults. The reduction of hospitalizations was estimated at 7.0% compared to the no-vaccination scenario. Extending the program to include community-dwelling older adults with a 74% coverage akin to influenza vaccination, Arexvy remains cost-effective for a PPD up to $139, with a mean ICER value of $49,698 (95% CI: 48,022 to 51,388) per QALY gained and a two-year budget impact of $8.63 million. Compared to the no-vaccination scenario, the extended program resulted in a 57.3% reduction in RSV-related hospitalisations.

Conclusions: Vaccinating residents of LTCHs against RSV disease would be cost-effective depending on PPD; extending the program to community-dwelling older adults would provide substantial health benefits, averting significant direct healthcare costs and productivity losses.

1. Introduction

Long recognised as a significant cause of illness in infants [1], respiratory syncytial virus (RSV) is now known to cause serious disease in older adults [2,3], especially among those with risk factors such as chronic obstructive pulmonary disorder, asthma, congestive heart

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failure, and immunocompromised status [4–8]. Severe RSV-related lower respiratory tract disease (LRTD) often leads to hospitalisation, resulting in significant short-term and long-term healthcare costs and productivity losses [9,10]. To reduce the burden of RSV disease among adults aged 60 years or older, two highly efficacious prefusion F protein-based vaccines (Arexvy and Abrysvo) have been developed [11,12]. A third vaccine also demonstrated high efficacy but is not marketed [13]. The US Food and Drug Administration and Health Canada have approved both Arexvy and Abrysvo for prevention of RSV LRTD in older adults [14]; guidance from the US Advisory Committee on Immunisation Practices is available in the US [15], but not yet for Canada.

While these vaccines are expected to reduce the health and economic burden of RSV LRTD in older adults, they may have substantial budget impact. Determining vaccination strategies that are cost-effective is essential to identify target populations and prioritisation for program implementation. The province of Ontario has introduced a publicly funded RSV vaccination program for the 2023–2024 respiratory season but only for residents of long-term care homes (LTCHs) and some retirement homes [16]. Although residents of congregate living settings like LTCHs are at high risk of severe disease outcomes, a significant portion of RSV-related hospitalisations still occur among community-dwelling older adults [4,17,18]. For example, an estimated 80.2% of hospitalised RSV cases aged 50 years or older in Canada were among community-dwelling older adults, with less than 10% being discharged to long-term care and assisted living settings [4]. No prior study has evaluated the health benefits and the cost-effectiveness of RSV immunisation programs for older adults living in either the community or LTCHs in Canada.

In this study, we conducted a cost-effectiveness analysis of single-dose RSV vaccination programs for older adults by adapting a discrete-event simulation model [19], with a synthetic population of adults aged 60 years or older reflecting the demographics of Ontario, a province with a population of approximately 15.5 million [20]. We estimated the additional health benefits achieved by expanding a vaccination program to community-dwelling older adults in addition to residents of LTCHs. We determined the range of vaccine price-per-dose (PPD) within which a vaccination program targeting only residents of LTCHs or broadening its scope to include community-dwelling older adults would be cost-effective. Considering direct and indirect costs of RSV disease outcomes, we performed the analysis from both the publicly funded health system (referred to as healthcare) and societal perspectives, and estimated the budget impact of each vaccination program.

2. Methods

2.1. Model structure and study population

We adapted a discrete-event simulation model with a population of 100,000 individuals, resembling demographics of older adults in Ontario, Canada stratified into age groups of 60–64, 65–69, 70–74, 75–79, 80–84, and 85 years or older [21]. We assumed that 140,000 of adults aged 65 years or older in Ontario live in LTCHs (i.e, 5,046 residents per 100,000 population of older adults), of whom 76% are 80 years of age or older [22,21]. The model was parameterised for disease outcomes based on secondary analyses of data for RSV-related hospitalisations among older adults in Ontario [9].

2.2. RSV vaccination scenarios

Two vaccination scenarios were considered. In the first scenario (S1), only residents of LTCHs were vaccinated with a 90% coverage, resulting in 4,541 vaccinated individuals per 100,000 older adults. In the second scenario (S2), in addition to vaccinating 90% of residents in LTCHs, community-dwelling adults aged 60 years or older were vaccinated with a coverage of 74% akin to 2022–23 seasonal influenza vaccination coverage of this population [23]. Scenario S2 resulted in 74,803 vaccinated individuals per 100,000 population of older adults. Vaccination was assumed to begin in September prior to the putative start of RSV season in October (Supplementary Fig. S1), and the target coverage for residents of LTCHs in S1 was achieved within 4 weeks. For S2, the target coverage of community-dwelling older adults reached within 8 weeks.

2.3. RSV-related outcomes

Medically-attended (MA) RSV cases (Fig. 1) were defined as either outpatient (i.e., physician office visits or emergency department (ED) visits) or inpatient (i.e., hospitalisation in the general ward or intensive care unit (ICU) admission). The annual incidence of MA RSV cases per 100,000 population was sampled from the range 833–1,840 for adults aged 60–69 years old, 846–1,846 for adults aged 70–79 years old, and 940–1,996 for those 80 years of age or older [24]. The incidence was further stratified by month based on the seasonality distribution of MA RSV cases derived from nine seasons from 2010–11 to 2018–19 [24]. Among MA RSV cases, 6–9% were considered to be outpatient with ED visits [25,26]. The annual incidence of hospitalisation was sampled from the range 118–172 [4], with the distribution of 18%, 26%, and 56% among adults aged 60–69, 70–79, and 80 years or older, respectively [9]. Prior to hospital admission, 24.7% of cases had a physician visit [4]. RSV-related admissions from LTCHs varied from 8% to 15% of the total hospitalisation [4,9]. MA RSV cases that were not hospitalised and had no ED visits were considered outpatient with physician visits for both residents of LTCHs and community-dwelling older adults.

Among hospitalised patients, 13.5% were admitted to ICU of whom 52.3% required the use of mechanical ventilation (MV) (Supplementary data analyses). These rates were applied to hospitalised patients from both LTCHs and community dwelling (Table 1). For the duration of hospital stay in the general ward, in ICU, and use of mechanical ventilation, a secondary analysis was conducted by fitting statistical distributions to reported length of stays associated with RSV-related hospitalisation of adults 60 years of age and older in Ontario (Supplementary data analyses). The duration of outcomes were sampled for each MA RSV case from their respective ranges and distributions (Table 2). RSV-related mortality rates among hospitalised patients were 7.6%, 8.1% and 14% for adults aged 60–69, 70–79, and 80 years or older, respectively [9].

2.4. Costs of RSV-related outcomes

Direct costs of RSV-related outcomes included physician visits, ED visits, hospitalisation, and hospital overhead (Table 2). For indirect costs, the loss of productivity was calculated for the duration of illness and outcomes as well as the monetary loss of life due to RSV-related mortality. Residents of LTCHs were assumed to be out of the labour force, and therefore had no market productivity. We also assumed that non-market productivity (e.g., performing household activities, caregiving, and volunteer services [10,29]) was negligible for residents of LTCHs.. In cost-effectiveness analysis from a societal perspective, we used the human capital approach and included the loss of both market and non-market productivity for community-dwelling older adults, by considering their participation rate in the labour force and the potential years of working-life lost (Supplementary Table S3) [30–32]. To calculate the total productivity loss in the event of death due to RSV, a growth rate of 1% in the median annual income was assumed. All costs were converted and inflated to 2023 Canadian dollars (See Supplementary Material).

2.5. Costs associated with vaccination

We varied the purchasing cost of a single dose of Arexvy and Abrysvo between $50 and $300 to determine the range of price-per-dose (PPD) within which a vaccination scenario was cost-effective. The cost of

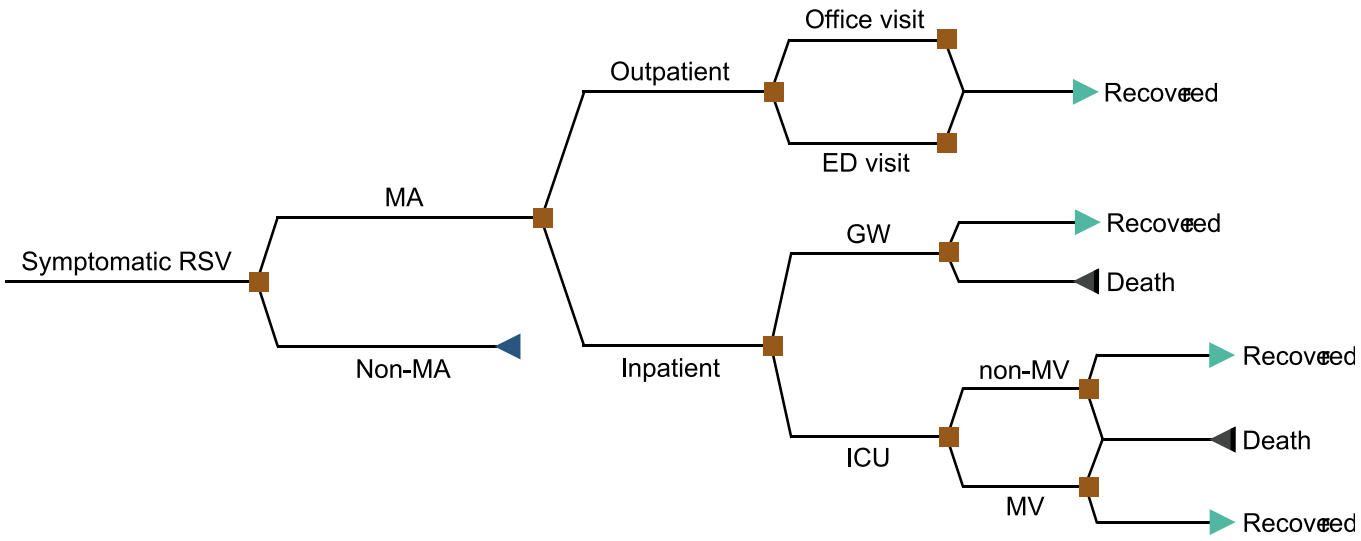

Fig. 1. Structure of the discrete-event simulation model for RSV-related outcomes. MA: medically attended; ED: emergency department; GW: general ward; ICU: intensive care unit; MV: mechanical ventilation.

Table 1
Estimates of RSV-related outcomes in different age groups.

RSV-related outcome	Estimate	Age group, y
Proportion of MA RSV cases with ED visit	6% – 9%	≥ 60
Physician visit prior to hospital admission	24.7%	≥ 60
Proportion of hospitalisations from LTCHs	8% – 15%	≥ 60
Age distribution of hospitalised patients	18%	60 – 69
	26%	70 – 79
	56%	≥ 80
Proportion admitted to ICU	13.5%	≥ 60
Proportion of ICU patients using MV	52.3%	≥ 60
In-hospital mortality rate	7.6%	60 – 69
	8.1%	70 – 79
	14%	≥ 80

vaccine administration was set to $15 per dose adjusted from 2017 estimates [28].

2.6. Efficacy of RSV vaccines

To account for waning of vaccine-induced protection, two profiles of temporal decay for vaccine efficacy were considered. For the first profile, a non-linear, sigmoidal function was fitted over a 24-month period to derive point estimates with the same mean efficacy as estimated in clinical trials (Supplementary Fig. S2). For the second profile, efficacy estimates were used as reported in clinical trials over the follow-up periods, with a linear decline beginning at 18 months post vaccination (Supplementary Fig. S2). We used 82.6% vaccine efficacy for preventing outpatient care during the first RSV season post-vaccination, as estimated for a single dose of Arexvy against MA RSV-related LRTI. This efficacy reduced to 56.1% for the second RSV season [11,33]. For prevention of outpatient care using Abrysvo, a 65.1% efficacy was used through the end of the first RSV season, and 48.9% during the second RSV season [12,34]. RSV patients for whom the vaccine was effective against outpatient care were categorised as non-MA cases. The efficacy of Arexvy against severe RSV-related LRTD, applied against hospitalisation, is estimated at 94.1% over the first RSV season, and 64.2% for the second RSV season [11,33]. Abrysvo efficacy against severe RSV-related LRTD, preventing hospitalisation, is estimated at 88.9-% and 78.6% during the first and second RSV seasons [12,34].

Table 2
Model parameters for the duration of RSV-related outcomes and associated costs extracted from the literature or a secondary analysis of hospitalisation data for older adults in Ontario (**Supplementary data analyses**). All costs are converted to 2023 Canadian dollars. MA: medically attended; GW: general ward; ICU: intensive care unit; ED: emergency department.

RSV-related outcome	Mean, Distribution	Unit	Source
Duration of symptomatic disease for non-MA RSV cases	5, Uniform(2, 8)	days	[27]
Duration of symptomatic disease for MA RSV outpatient cases	10.5, Uniform(7, 14)	days	[26]
Time interval between symptoms onset and hospital admission	4.1, Gamma (4.3266, 0.9434)	days	Fitting to Ontario data
Length of stay in GW without ICU admission	10.5, Gamma (3.0658, 3.4254)	days	Fitting to Ontario data
Length of stay in GW prior to ICU admission	2.6, Gamma (2.0673, 1.2438)	days	Fitting to Ontario data
Length of stay in GW post ICU	12.5, Gamma (1.1092, 11.2493)	days	Fitting to Ontario data
Length of ICU stay with no mechanical ventilation use	5.3, Gamma (4.1049, 1.2876)	days	Fitting to Ontario data
Non-mechanical ventilation days in ICU	5.5, Gamma (1.5910, 3.4570)	days	Fitting to Ontario data
Mechanical ventilation days in ICU	10.8, Gamma (1.4306, 7.5620)	days	Fitting to Ontario data
Cost estimates			
Physician visit	$92	Per visit	[9]
ED visit	$562	Per visit	[9]
Hospital stay in GW	$1,052	Per day	Derived from secondary analysis of Ontario data
ICU stay without mechanical ventilation	$2,612	Per day	Derived from secondary analysis of Ontario data
ICU stay with mechanical ventilation	$3,426	Per day	Derived from secondary analysis of Ontario data
Hospital overhead	$117	Per admission	[9]
Vaccine administration	$15	Per dose	[28]

2.7. Cost-effectiveness analysis

Using quality-adjusted life-year (QALY), the net monetary benefit of vaccination scenarios was calculated by $NMB = \Delta E \times WTP - \Delta C$, where ΔE represents QALYs gained with vaccination compared to no intervention, ΔC is the incremental costs, and WTP is the willingness-to-pay to gain one QALY. A vaccination scenario was considered cost-effective if it resulted in a positive NMB. The monetary value of health was calculated using a WTP threshold of $50,000 per QALY gained [35]. To estimate the additional costs of gaining one QALY, the incremental cost-effectiveness ratio (ICER) was also calculated for each vaccination scenario as $\Delta C/\Delta E$. Using ICER estimates, acceptability curves were generated to illustrate the effect of changing WTP on the probability of a vaccination program being cost-effective.

Total QALYs in each scenario were calculated based on the health utility values related to RSV disease and outcomes among different age groups in the study population (Supplementary Table S2) [19]. To calculate total QALYs, we sampled utility values for each RSV case from age-specific Beta distributions [19], and applied the weights associated with RSV-related outcomes, while adjusting for the duration of illness and outcome. Cost-effectiveness analysis was conducted from both healthcare and societal perspectives over a time horizon of two RSV seasons post-vaccination. The budget impact to the healthcare system was estimated as the difference between immunisation costs and the total direct healthcare savings achieved in the vaccination program. All costs and outcomes were discounted at an annual rate of 1.5% as recommended by the Canadian Agency for Drugs and Technologies in Health [36].

2.8. Model implementation and simulations

The model was simulated using Monte-Carlo sampling for a total of 1000 independent realisations. In each realisation, model parameters (Table 1, Supplementary Table S2) were sampled for each individual independently from their respective distributions or estimated ranges. This approach probabilistically accounts for the sensitivity of the outcomes with respect to input values. To generate 95% confidence intervals around point estimates, we employed a nonparametric, bias-corrected and accelerated bootstrap technique with 1000 replicates. The computational model is available at: https://github.com/affans/rsv-canada-adults.

2.9. Secondary analyses

We performed secondary analyses to consider a higher WTP of CDN $70,000 per QALY gained (Supplementary Tables S8, S9), and conducted additional sub-scenarios for S2, where vaccination of community-dwelling older adults included either only those aged ≥ 65 years or only those aged ≥ 75 years (Supplementary Tables S10–S17). We also carried out deterministic sensitivity analyses by sampling the model parameters from their associated distributions or ranges (Supplementary Table S7), and calculating partial rank correlation coefficient for simulated scenarios with PPD as the response variable to determine the relative importance of parameters on estimated PPD (Supplementary Fig. S6).

2.10. Ethics and guidelines

RSV-related hospitalisation data for the secondary analyses were provided by the Canadian Immunization Research Network (CIRN) Serious Outcomes Surveillance (SOS) Network as anonymized data. Written informed consent was obtained at the time of enrolment for each patient in accordance with each participating hospital site research ethics boards (REB) policies and included future testing for other respiratory pathogens (ClinicalTrials.gov identifier NCT01517191). Guidelines for Consolidated Health Economic Evaluation Reporting Standards (CHEERS) were followed [37].

3. Results

3.1. Reduction of RSV-related outcomes

Using Arexvy with sigmoidal vaccine efficacy profiles, vaccination of LTCH residents with 90% coverage (S1) resulted in mean reductions of 2.3%, 8.4%, and 8.4% in outpatient care, inpatient care, and death, respectively, during the first RSV season after vaccination (Fig. 2A). Similar reduction of outcomes were achieved using Abrysvo with sigmoidal vaccine efficacy profiles. Extending the program to include vaccination of community-dwelling older adults with 74% coverage (S2), Arexvy reduced outpatient care by 52.1%, inpatient care by 69.3%, and death by 69.6%. Using Abrysvo resulted in mean reductions of 38.1 %, 66.5 %, and 66.6 % in outpatient care, inpatient care, and death, respectively. When linear vaccine efficacy profiles were used, we found no significant change in the reduction of outcomes compared to the sigmoidal vaccine efficacy profiles in both S1 and S2 scenarios (Fig. 2B).

Considering two RSV seasons following vaccination, sigmoidal vaccine efficacy profiles estimated that Arexvy would reduce outpatient care by 1.6%, inpatient care by 6.0%, and death by 6.2% in the S1 scenario (Fig. 2C). The reduction of outcomes using Abrysvo was similar. Extending the vaccination program to S2 with Arexvy resulted in mean reductions of 38.4%, 50.1% and 50.1% in outpatient care, inpatient care, and death, respectively. Similarly, using Abrysvo in S2 reduced outpatient care by 27.8%, inpatient care by 49.7%, and death by 49.7% (Fig. 2C). When linear vaccine efficacy profiles were considered, estimated reduction of outcomes with Arexvy and Abrysvo in S1 were similar to those estimated with the sigmoidal vaccine efficacy profiles (Fig. 2D). Program extension in S2 reduced outpatient care, inpatient care, and death by 42.9%, 57.3%, and 57.5% using Arexvy, and by 33.5%, 61.2%, and 61.0% using Abrysvo, respectively.

3.2. Cost-savings of vaccination programs

Vaccinating only residents of LTCHs with 90% coverage, cost-savings of outpatient care ranged from $3,320 to $4,585 during the first RSV season, and from $4,727 to $7,332 during two RSV seasons per 100,000 population of adults aged 60 years or older (Supplementary Tables S4, S5). Cost-savings of RSV-related inpatient care ranged from $197,117 to $212,352 during the first RSV season and from $288,403 to $361,235 over two RSV seasons per 100,000 population of adults aged 60 years or older. Net savings of outpatient and inpatient care increased substantially when vaccination was extended to community-dwelling older adults. Savings for outpatient care ranged from $67,148 to $89,558 during the first RSV season, and from $97,379 to $146,680 over two RSV seasons per 100,000 adults aged 60 years or older. Savings associated with inpatient care ranged from $1.59 to $1.69 million during the first RSV season, and from $2.39 to $2.93 million over two RSV seasons. We also found that S2 can avert substantial productivity losses exceeding $2.31 million during the first season, and $3.44 million over two RSV seasons (Supplementary Tables S4, S5).

3.3. QALYs gained

In the S1 scenario, Arexvy with sigmoidal vaccine efficacy profiles resulted in 5.80 (95% CI: 5.46 to 6.13) QALYs gained over the first RSV season, and 8.13 (95% CI: 7.73 to 8.52) QALYs gained over two RSV seasons (Table 3). A program using Abrysvo with sigmoidal efficacy profiles saved 5.63 (95% CI: 5.31 to 5.96) QALYs during the first RSV season and 7.97 (95% CI: 7.58 to 8.35) QALYs over two RSV seasons. Similar gains in QALY were estimated for Arexvy and Abrysvo with linear vaccine efficacy profiles in this scenario. Extended vaccination program, S2 saved 52.52 (95% CI: 51.49 to 53.63) and 49.46 (95% CI: 48.41 to 50.52) QALYs during the first RSV season using Arexvy and

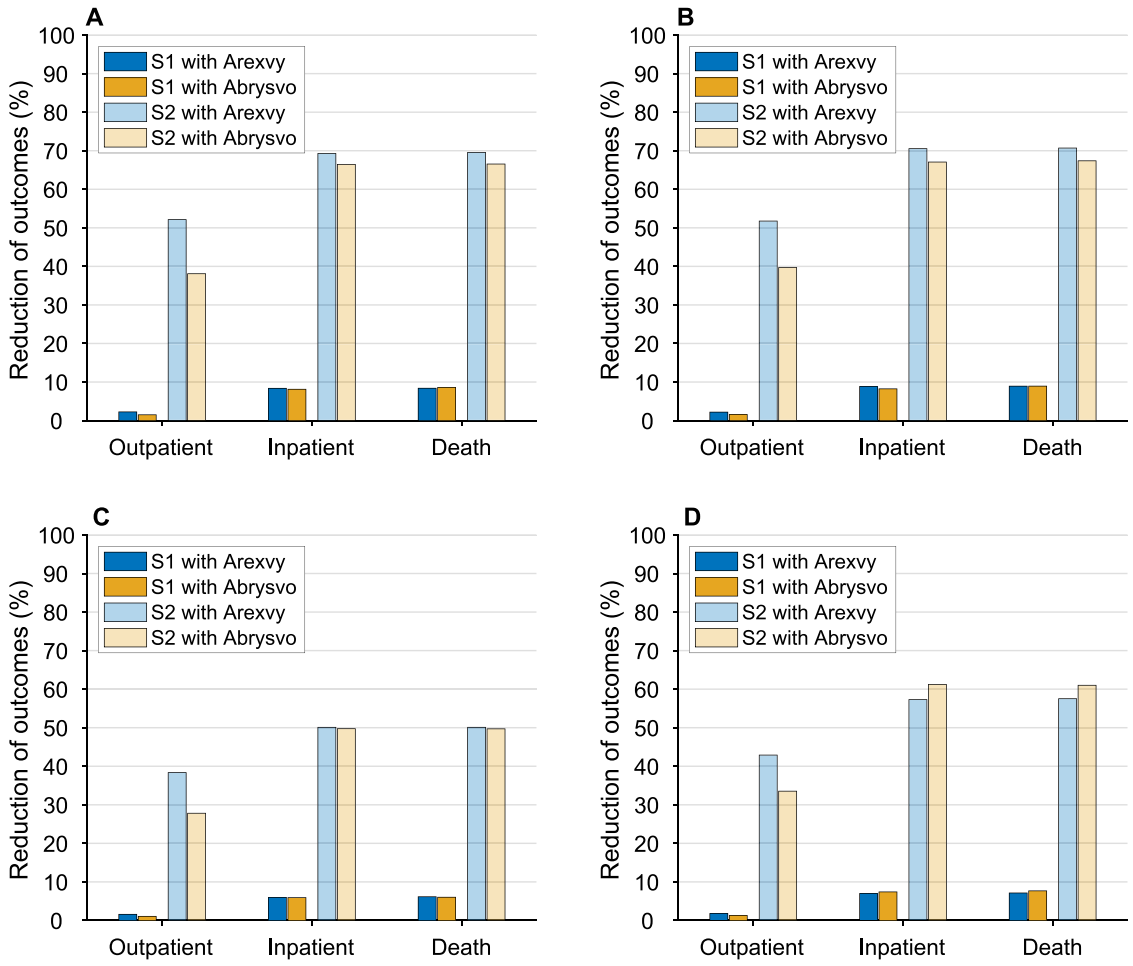

Fig. 2. Reduction of RSV-related outcomes among adults 60 years of age or older, compared to the scenario without vaccination over the first RSV season (**A, B**) and two RSV seasons (**C, D**) post-vaccination, with sigmoidal (**A, C**) and linear (**B, D**) vaccine efficacy profiles. Scenarios correspond to vaccination of only residents of LTCHs (S1), and vaccination of both residents of LTCHs and community-dwelling older adults (S2).

Table 3
Model estimates of QALYs saved in vaccination programs with Arexvy and Abrysvo in a population of 100,000 adults aged 60 years or older. S1: vaccination of only LTCH residents with 90% coverage; S2: vaccination of LTCH residents with 90% coverage and community-dwelling older adults with 74% coverage.

Vaccination program	**S1 (95% CI)**		**S2 (95% CI)**	
Sigmoidal vaccine efficacy profiles	Arexvy	Abrysvo	Arexvy	Abrysvo
First RSV season	5.80 (5.46 to 6.13)	5.63 (5.31 to 5.96)	52.52 (51.49 to 53.63)	49.46 (48.41 to 50.52)
Two RSV seasons	8.13 (7.73 to 8.52)	7.97 (7.58 to 8.35)	75.69 (74.28 to 77.11)	74.55 (73.29 to 75.76)
Linear vaccine efficacy profiles				
First RSV season	5.76 (5.42 to 6.09)	5.68 (5.32 to 6.00)	53.55 (52.44 to 54.61)	49.57 (48.49 to 50.60)
Two RSV seasons	9.30 (8.91 to 9.69)	10.11 (9.68 to 10.57)	87.07 (85.63 to 88.56)	91.85 (90.44 to 93.20)

Abrysvo, respectively, with sigmoidal vaccine efficacy profiles. Similar gains in QALY were estimated using linear vaccine efficacy profiles. Over two RSV seasons, Arexvy and Abrysvo with sigmoidal vaccine efficacy profiles saved 75.69 (95% CI: 74.28 to 77.11) and 74.55 (95% CI: 73.29 to 75.76) QALYs, respectively (Table 3). The corresponding QALYs gained with linear vaccine efficacy profiles over two RSV seasons were estimated to be higher at 87.07 (95% CI: 85.63 to 88.56) and 91.85 (95% CI: 90.44 to 93.20).

3.4. Cost-effectiveness of vaccination scenarios

We determined the maximum PPD below which vaccination programs with Arexvy and Abrysvo would be cost-effective (i.e., when NMB $>$ 0) from a societal perspective at a WTP of $50,000 per QALY gained (Table 4). Under S1, the maximum PPD for a positive NMB was $139 for Arexvy and $137 for Abrysvo with sigmoidal vaccine efficacy profiles. The corresponding cost-effectiveness probability at these PPD values were 59% and 56% (Fig. 3A). When linear vaccine efficacy profiles were considered, Arexvy and Abrysvo were cost-effective for a PPD up to $163 and $177, respectively, with 51% probability of being cost-effective (Fig. 3B). Under S2 with sigmoidal vaccine efficacy profiles, the maximum PPD for Arexvy and Abrysvo were estimated at $119 and $114, respectively, with 71% and 64% probability of being cost-effective. The maximum PPD increased to $139 for Arexvy and $143 for Abrysvo with linear vaccine efficacy profiles (Table 4). At these PPD values, Arexvy and Abrysvo were cost-effective with the probability of 64% and 85%, respectively.

From a healthcare perspective, the results of cost-effectiveness analysis of the S1 program were the same as those from a societal

Table 4
Model estimates of cost-effectiveness analyses from a societal perspective with Arexvy and Abrysvo over two RSV seasons in a population of 100,000 adults aged 60 years or older at the WTP of $50,000 per QALY gained. S1: vaccination of only LTCH residents with 90% coverage; S2: vaccination of LTCH residents with 90% coverage and community-dwelling older adults with 74% coverage.

Vaccination program	Maximum PPD, $	Incremental costs, $ (95% CI)	ICER (95% CI)	Probability of being cost-effective	Budget impact per 100,000, $
S1 with sigmoidal vaccine efficacy profiles					
Arexvy	139	403,800 (397,092 to 410,190)	49,653 (46,874 to 52,798)	59%	403,935
Abrysvo	137	397,176 (390,006 to 404,052)	49,806 (46,943 to 52,876)	56%	397,261
S2 with sigmoidal vaccine efficacy profiles					
Arexvy	119	3,744,784 (3,663,943 to 3,820,288)	49,478 (47,461 to 51,394)	71%	7,499,833
Abrysvo	114	3,744,784 (3,663,943 to 3,820,288)	49,711 (48,130 to 51,505)	64%	7,153,181
S1 with linear vaccine efficacy profiles					
Arexvy	163	464,770 (456,942 to 471,943)	49,984 (47,539 to 52,704)	51%	464,809
Abrysvo	177	505,032 (496,869 to 513,417)	49,977 (47,290 to 52,696)	51%	505,157
S2 with linear vaccine efficacy profiles					
Arexvy	139	4,327,387 (4,251,514 to 4,405,923)	49,698 (48,022 to 51,388)	64%	8,644,633
Abrysvo	143	4,516,731 (4,439,231 to 4,599,771)	49,175 (47,659 to 50,781)	85%	8,775,157

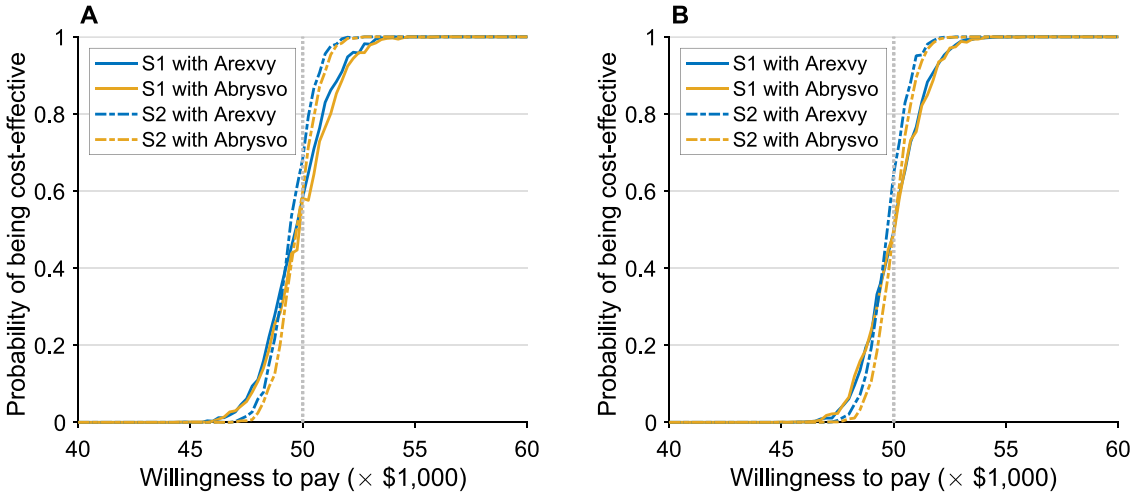

Fig. 3. Acceptability curves using the maximum PPD estimated for vaccination programs (Table 4) with sigmoidal (**A**) and linear (**B**) vaccine efficacy profiles. Scenarios correspond to maximum PPD of: (**A**) $139 for Arexvy in S1, $137 for Abrysvo in S1, $119 for Arexvy in S2, and $114 for Abrysvo in S2; (**B**) $163 for Arexvy in S1, $177 for Abrysvo in S1, $139 for Arexvy in S2, and $144 for Abrysvo in S2. The dotted-line corresponds to the WTP threshold of $50,000 per QALY gained. S1: Vaccination of only residents of LTCHs; S2: vaccination of both residents of LTCHs and community-dwelling older adults.

perspective (Supplementary Table S6). For the S2 program, Arexvy and Abrysvo with sigmoidal vaccine efficacy profiles were cost-effective for a PPD up to $69 and $68, respectively. At their maximum PPD, Arexvy and Abrysvo were cost-effective with probabilities of 74% and 67%. When linear vaccine efficacy profiles were considered, the maximum PPD increased to $81 for Arexvy and $87 for Abrysvo, with the respective probabilities of 88% and 59% being cost-effective (Supplementary Table S6).

3.5. Budget impact

With sigmoidal vaccine efficacy profiles, we estimated the budget impact to the healthcare system at the maximum PPD estimates from a societal perspective, after discounting for the savings achieved through the reductions of outpatient and inpatient care over two RSV seasons, to range from $0.39 to $0.40 million in S1 and from $7.15 to $7.50 million in S2 in a population of 100,000 adults aged 60 years or older (Table 4). When linear vaccine efficacy profiles were used, the budget impact ranged from $0.46 to $0.51 million in S1, and from $8.64 to $8.78 million in S2.

3.6. Secondary Analyses

For the additional scenarios of vaccinating community-dwelling adults older than 65 years of age, we estimated higher PPD values for cost-effectiveness of Arexvy and Abrysvo. For example, in the sub-scenario of S2 in which community-dwelling adults aged 75 years or older were vaccinated, we estimated a maximum PPD (from a societal perspective) to range from $184 to $227 at the WTP of $50,000 per QALY gained, depending on the vaccine and its efficacy profile (Supplementary Table S14). This scenario had at least 42% lower incremental costs than the primary S2 scenario in which adults aged 60 years or older were vaccinated, resulting in over 54% reduction in budget impact. The lower incremental costs in this sub-scenario were primarily

due to the exclusion of adults aged 60 to 74 years of age from the vaccination program. However, given that over 80% of RSV-related hospitalisations in older adults occur among those aged 70 years or older, the program was cost-effective at higher PPD values compared to those estimated for the primary S2 scenario (Table 4). As our deterministic sensitivity analysis demonstrates, parameters associated with RSV-related hospitalizations exert the most significant influence on estimates of PPD (Supplementary Fig. S6). Similar results were observed when examining scenarios with a higher WTP of $70,000 per QALY gained (Supplementary Tables S6, S8–S17).

4. Discussion

This study provides the first analysis of two prefusion F protein-based RSV vaccines in older Canadian adults, quantifying the health benefits and cost-effectiveness of Arexvy and Abrysvo for vaccinating residents of LTCHs and community-dwelling older adults in Ontario. We found that targeting only high-risk individuals in congregate settings (e.g., LTCHs) would provide marginal reductions in RSV-related outcomes among older adults. However, expanding vaccination to community-dwelling older adults would substantially enhance the health benefits in terms of reducing RSV-associated outpatient care, inpatient care, and mortality, while averting significant direct healthcare costs, consistent with our recent analysis of these RSV vaccines in the United States [19]. The cost burden of RSV disease among older adults is predominantly driven by hospitalisations. Based on a deterministic sensitivity analysis, we found that the length of stay in the general ward for patients without ICU admission, the proportion of patients in ICU using mechanical ventilation, and mechanical ventilation days for ICU patients had the largest positive association with estimates of PPD (Supplementary Fig. S6).

Our results indicate that using Arexvy for the extended program would be cost-effective for a PPD up to $139 from a societal perspective (Table 4), and a PPD up to $81 from a healthcare perspective (Supplementary Table S6). At the provincial level, an extended program vaccinating 2.8 million (74%) of adults aged 60 years or older in Ontario would require a two-year budget impact of up to $242 million, covering the costs of both purchasing vaccines at $139 per dose and administration. Without this investment in a publicly funded vaccination program, the productivity loss associated with RSV-related outcomes among older adults could be as high as $120 million over two RSV seasons, limiting the real-world impact and indirect health benefits of RSV vaccines.

We found that over the first RSV season, health benefits of Arexvy and Abrysvo in terms of reducing outcomes and saving QALYs were similar when considering waning of immunity that follows either a sigmoidal or a linear decay (Table 3, Fig. 2). However, the linear waning resulted in a larger reduction of outcomes and higher QALYs gained over two RSV seasons compared with sigmoidal waning, suggesting that the health benefits and cost-effectiveness of vaccination are sensitive to assumptions about the durability of vaccine efficacy. We also note that the difference between efficacy profiles has a more pronounced effect on QALYs gained and PPD estimates when a larger proportion of the population is vaccinated, especially when considering adults aged 70 years or older who account for the majority of RSV hospitalisations. Although the efficacy of Arexvy against severe LRTI was higher than Abrysvo over the first follow-up period (of ~ first 7 months) in both sigmoidal and linear profiles, this trend was reversed for the second RSV season, which resulted in a comparable reduction of severe outcomes for both vaccines over two RSV seasons (Fig. 2), with similar PPD estimates in simulated scenarios.

4.1. Strengths and limitations

A strength of this study is the analysis of two distinct subpopulations of older adults: those residing in LTCHs and those living in the community. Although the research utilises a pre-established model for assessing the cost-effectiveness of RSV vaccines among older adults in the United States [19], the incorporation of outcomes and associated costs at the individual level derived from Ontario-specific data enabled us to estimate the additional health benefits resulting from extending the RSV vaccination program to community-dwelling older adults. Considering both LTCHs and community-dwelling subpopulations, the insights derived from this analysis offer important information to guide the forthcoming recommendations by the National Advisory Committee on Immunization (NACI) in Canada regarding the optimal utilisation of RSV vaccines.

The study model has several limitations to consider. First, our approach adopts a discrete-event structure without involving the complex dynamics of disease transmission. Thus, other potential benefits of vaccination, such as reduction of susceptibility to infection or viral shedding, were not considered. Second, estimates of non-market productivity (i.e., performing household activities, caring for others and helping people, and volunteer services) were not available for the study population in Ontario. Therefore, estimates of non-market productivity for older adults in the United States were used. Third, our results rely on reported vaccine efficacy estimates during the follow up periods for two RSV seasons. However, the real-world effectiveness and durability of these vaccines are still unknown and would be affected by the characteristics of the target population with comorbidities, RSV-associated risk factors, immunosenescence, as well as the type of programs that would be needed to deliver a vaccine to this population prior to the RSV season, potentially concurrently with influenza or COVID-19 vaccine programs. Fourth, we did not consider vaccine adverse reactions, or longer-term sequelae of RSV infection (e.g., wheezing and asthma), which may affect cost-effectiveness analysis. Finally, our analysis did not account for additional indirect costs attributed to out-of-pocket expenses, or productivity losses due to informal care provided by families of community-dwelling patients.

4.2. Implications

Our estimates of health benefits and averted economic losses are under the assumption that the majority of older adults are vaccinated against RSV. However, the economic benefits depend on whether community-dwelling older adults are included in publicly funded programs, in addition to vaccine acceptability and effectiveness of program delivery. Given the recent introduction of RSV vaccines in 2023, there is no real-world experience of vaccine program implementation in LTCHs or at the community level in Canada. Although the specifics of program implementation fall outside the scope of this study, administering the RSV vaccine at the same visit as the annual influenza vaccine may be an efficient approach to limit provider visits and potentially improve uptake. While both Arexvy and Abrysvo have shown efficacy in the second year post-vaccination and when administered concomitantly with influenza vaccines, the longer term efficacy of these vaccines remains uncertain. For programs that aim to vaccinate older adults on a biennial basis, establishing a vaccine registry information for RSV vaccine recipients becomes essential to maintain accurate records for subsequent doses.

Our cost-effectiveness analysis indicates a price range of $139 to $177 per single dose of RSV vaccines (Table 4), which is similar to the price range of some other vaccines for older adults, such as the shingles vaccine, which varies between $140 and $200 per dose in Canada [38]. Despite the NACI recommending shingles vaccine for all adults 50 years of age or older [38], only a small subset of this population is included in publicly funded vaccination programs in some Canadian provinces. The out-of-pocket costs of the shingles vaccine have contributed to its low coverage among older adults [39], which is likely to be mirrored for RSV vaccination if publicly funded programs are limited to residents of LTCHs and congregate settings.

4.3. Conclusion

Our study shows that a publicly funded program to vaccinate community-dwelling older adults in addition to LTCH residents at high risk of severe outcomes could be cost-effective and substantially reduce the direct and indirect health and economic burden of RSV disease.

5. Contributors

SMM and JML conceived the study; SMM designed the model framework; CEB and SMM collected input parameters; AS developed the computational model and performed simulations; SMM analysed Ontario data, the simulation data, and wrote the first draft of the manuscript; GR, APG, JJL, and JML provided insights into the analysis and interpretation of the results; all authors contributed to the writing and revision of the final draft.

6. Data sharing agreement

All data and the computational model are available at: https://github.com/affans/rsv-canada-adults.

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CRediT authorship contribution statement

Affan Shoukat: Writing – review & editing, Software, Methodology. **Carolyn E. Bawden:** Resources, Data curation. **Gergely Röst:** Writing – review & editing, Resources. **Jason J. LeBlanc:** Writing – review & editing, Resources. **Alison P. Galvani:** Writing – review & editing, Supervision, Resources. **Joanne M. Langley:** Writing – review & editing, Resources, Funding acquisition, Conceptualization. **Seyed M. Moghadas:** Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A Shoukat, is employed at BlueDot. GSK is a client of BlueDot. The contractual relationship between GSK and BlueDot began after the work in this study was completed, and is unrelated to this study. 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. JJ LeBlanc reports advisory roles to Pfizer, Merck, Janssen, and Sanofi, outside the work presented here. SM Moghadas previously had advisory roles for Janssen Canada and Sanofi unrelated to this study. Other authors declare that they have no competing interests.

Data availability

All data and computational model are available at: https://github.com/affans/rsv-canada-adults.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2024.02.041.

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