Canadian Journal of Health Technologies
August 2023 Volume 3 Issue 8

CADTH Health Technology Review

Cost-Effectiveness of an RSVpreF Vaccine for Prevention of Respiratory Syncytial Virus Outcomes in Infants

Samantha Verbrugghe
Quenby Mahood
Sean Tiggelaar

Table of Contents

List of Tables

List of Figures

Abbreviations

EMA	European Medicines Agency
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
JBI	Joanna Briggs Institute
LRTI	lower respiratory tract infection
mAb	monoclonal antibody
OECD	Organisation for Economic Co-operation and Development
PPC	Preferred Product Characteristics
RSV	respiratory syncytial virus
RSVpreF	RSV prefusion F protein-based vaccine

Key Messages

- From CADTH's search of the economic literature, 4 economic studies were identified that assessed the cost-effectiveness of respiratory syncytial virus (RSV) immunization during pregnancy in high-income countries, including 1 study set in Nunavik, Quebec. Only 1 of these studies specifically considered the product of interest (RSVpreF), and only in a scenario analysis.
- In the 4 identified studies that evaluated the cost-effectiveness of RSV immunization during pregnancy, the outcomes predicted by the models focused on those related to infants. There is a lack of evidence on outcomes — thus cost-effectiveness — for the persons who are pregnant.
- The results from the 4 studies varied considerably. RSV immunization during pregnancy ranged from being more effective and associated with lower total costs (dominant) to more than $200,000 per quality-adjusted life-year gained when compared with no intervention. The results depended on the modelled region, efficacy, pricing, and severity of the RSV season.
- In 2 studies, year-round RSV immunization during pregnancy was not considered cost-effective compared with seasonal RSV prophylaxis with long-acting monoclonal antibodies (mAbs), such as nirsevimab, when the price per dose was the same as that of the long-acting mAb. RSV immunization during pregnancy was estimated to become cost-effective when its acquisition cost per dose was 2 to 5 times lower than that of the long-acting mAb.

Background and Rationale

Respiratory syncytial virus (RSV), a common respiratory illness, infects almost all children worldwide by 2 years of age.[1,2] Most infections occur in annual epidemics, which occur seasonally from fall to early spring in temperate climates and during the rainy season in tropical climates.[1,2] RSV is a significant cause of morbidity and mortality in infants and is the leading cause of lower respiratory tract infections (LRTIs), such as bronchiolitis and pneumonia, and the leading cause of hospitalizations in children younger than 2 years of age.[3] Risk factors for developing severe RSV in infants include premature birth, congenital heart disease, chronic lung disease, cystic fibrosis, Down syndrome, immunocompromising conditions, and severe neuromuscular disease.[4,5]

Passive RSV prophylaxis has been available; palivizumab (Synagis), a humanized monoclonal antibody (mAb), was approved for use by Health Canada for the prevention of serious LRTIs caused by RSV in pediatric patients at high risk of RSV disease.[6] The recommended dosing of palivizumab typically consists of 4 injections given monthly at the onset of and continuing throughout the RSV season, with an extra dose considered in remote Northern areas of Canada that have longer RSV outbreaks.[7] A long-acting mAb, nirsevimab (Beyfortus), was recently approved by Health Canada[8] for the prevention of LRTIs caused by RSV in neonates and infants during their first RSV season or children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Nirsevimab has similarly been approved by the European Medicines Agency (EMA)[9] and is under review by the US FDA.[10] Nirsevimab can be given as a single dose at birth or just before (or at) the commencement of the RSV season.[8,9]

Currently, no vaccines have been authorized for the prevention of RSV disease. In November 2022, Pfizer announced the results of the MATISSE trial, a phase III trial assessing a candidate known as RSVpreF, a bivalent RSV prefusion F protein-based vaccine (Abrysvo) for use during pregnancy for RSV prevention in infants up to 6 months of age.[11] As of May 2023, the EMA, the FDA, and Health Canada have all accepted market authorization submissions for RSVpreF immunization during pregnancy as well as for the immunization of older adults.[12-14]

Research Question

What is the cost-effectiveness of RSVpreF immunization during pregnancy for infants and for people who are pregnant?

Methods

A review of the economic literature was undertaken to identify previously published economic evidence regarding the cost-effectiveness of RSV immunization during pregnancy for infants and for people who are pregnant.

Literature Search Methods

An information specialist conducted a literature search on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search approach was customized to retrieve a limited set of results, balancing comprehensiveness with relevancy. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the research questions and selection criteria. The main search concepts were RSVpreF or respiratory syncytial virus vaccines. CADTH-developed search filters were applied to limit retrieval to economic studies, citations related to health utilities or quality of life, and for background, health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons. No limits were applied. The search was completed on March 24, 2023. Regular alerts updated the search until May 8, 2023.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Criteria	Description
Population	Infants, people who are pregnant
Intervention	RSV immunization during pregnancy
Comparator	No RSV prophylactic intervention, RSV prophylaxis in newborns or infants (e.g., long-acting mAbs [nirsevimab], short-acting mAbs [palivizumab])
Outcomes	Quality-adjusted life-years, disability-adjusted life-years, incremental cost per event or event avoided
Study designs	Full economic analyses (i.e., cost-effectiveness analyses, cost-utility analyses)

mAb = monoclonal antibody; RSV = respiratory syncytial virus.

Exclusion Criteria

Studies were excluded based on the following:

- did not meet the selection criteria outlined in Table 1
- were duplicate publications
- were published in languages other than English or French
- were not conducted in countries identified as high income by the World Bank[15]
- were systematic reviews whose primary cost-effectiveness studies were otherwise captured or excluded
- were published before 2013.

Data Extraction and Critical Appraisal

During data extraction, the following were collected: author, publication year, country, currency, source of funding, study design, modelling approach, study perspective, discounting, time horizon, outcomes, source of clinical efficacy, study population characteristics, and results. The quality of included studies were critically appraised by 1 reviewer using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Economic Evaluations.[16] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Cost-effectiveness outcomes were reported as unadjusted and adjusted. If adjusted, outcomes were adjusted to 2023 Canadian dollars using Organisation for Economic Co-operation and Development (OECD) purchasing power parity rates[17] and inflation rates from the Bank of Canada.[18]

Summary of Evidence

Quantity of Research Available

A total of 242 citations were identified in the literature search. Following screening of titles and abstracts, 218 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. Additionally, 1 potentially relevant publication was retrieved from the grey literature search

for full-text review. Of these articles, 21 publications were excluded for various reasons, and 4 publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flow chart of the study selection.

Of the 4 economic evaluations identified, 2 used static cohort models,[19,20] 1 used a discrete-event agent-based simulation,[2] and 1 used a decision-tree model.[21] All 4 were model-based studies. One study was set in Norway,[20] 1 was in 6 European countries,[19] 1 was in the Nunavik region of Canada,[2] and 1 was in the US.[21] Table 2 in Appendix 1 provides an overview of the characteristics of the 4 included studies.

Summary of Critical Appraisal

The 4 studies ranged from meeting 5 to 8 of the 11 JBI quality appraisal checklist criteria[16] (Appendix 1, Table 3) when considering their applicability to assessing the cost-effectiveness of immunization during pregnancy using the product RSVpreF. None of the studies were based on well-established clinical efficacy for RSVpreF, none included all issues of concern to users (e.g., none considered the cost-effectiveness of immunizing during pregnancy, including costs and benefits, to the people who are pregnant), and it was unclear whether the studies were generalizable to the Canadian population or to the Canadian population as a whole in the case of the study set in Nunavik, Quebec.

Summary of Findings

Base-case analyses for all studies were conducted from the health care payer perspective, with 1 study also reporting a societal perspective alongside its health care base case[21] and another reporting 2 different societal perspectives as scenario analyses.[19] One study incorporated increased risk of long-term sequelae (i.e., asthma and recurrent wheezing) in the base case,[21] and 2 studies considered such sequelae in scenario analyses.[19,20] The models supporting the economic evaluations all followed a cohort of infants born during 1 year until they reached 1 year[2] or 5 years of age,[19,20] except for 1 study that considered a time horizon of 5 years for health care utilization, 10 years for impact on asthma or/or wheezing, and lifetime for loss of productivity due to premature death (loss of productivity applies to societal perspective only).[21] Discount rates ranged from 3% to 4% for costs and 1.5% to 4% for effects, with 1 study not discounting due to its 1-year time horizon.[2] One study reported direct industry funding for editorial support,[21] while the remaining 3 reported arms-length funding through national or international RSV research consortia and networks that had governmental, academic, and industry partners.[2,19,20] Cost-effectiveness was reported as incremental cost-effectiveness ratios (ICERs), mostly represented as the incremental cost per additional quality-adjusted life-year (QALY), and through cost-effectiveness acceptability frontiers in which sequential analyses were conducted. For the remainder of this review, reported ICERs and cost-effectiveness acceptability frontier thresholds are reported as 2023 Canadian dollars, with conversion conducted using OECD Purchasing Price Parity rates for the year of the original currency[17] and then inflated to 2023 dollars using the Bank of Canada inflation calculator.[18] A summary table of the main findings of each identified economic study, including the original unadjusted results, is available in Appendix 1, Table 4.

Two studies,[19,20] reporting results for 7 modelled countries, directly compared year-round immunization during pregnancy to no intervention and to long-acting mAb interventions. These mAb interventions included various seasonal strategies in which a long-acting mAb was given to infants born in some range of months during local RSV season, as well as to programs in which infants born in October through April received the mAb at birth, while those born in May through September received a "catch-up" dose of the mAb in their first October. Both of these studies assumed that the efficacy of immunization during pregnancy would be equivalent to Preferred Product Characteristics (PPCs) for RSV vaccinations in pregnancy published by WHO, which call for a product with a 70% efficacy lasting at least 4 months.[22] One of the studies also conducted a scenario analysis incorporating recently reported efficacy results from the RSVpreF MATISSE trial, in which 6-month data reported a reduction of medically attended RSV of 51.3% and of severe medically attended RSV of 69.4%.[11] The efficacy of long-acting mAbs was derived from the MELODY nirsevimab trial.[23]

One study[2] compared various individual strategies (i.e., seasonal immunization during pregnancy, seasonal immunization during pregnancy plus a long-acting mAb for preterm and chronically ill infants, a short-acting mAb for preterm and chronically ill infants, and a long-acting mAb for preterm and chronically ill infants) to no intervention. Immunization during pregnancy was not directly compared with mAb-based interventions, and mAb-based interventions for healthy infants were only compared with the same intervention given to only preterm and chronically ill infants. The efficacy of immunization during pregnancy in this study was derived from the ResVax trial, PREPARE, which failed to meet its primary end point for reduction in RSV-associated, medically significant LRTIs at 3 months.[24] In this model, the efficacy of immunization during pregnancy was predicted to be 14% for preventing outpatient visits, 24.7% to 61.9% for preventing pediatric ward stays, and 31.9% to 75.0% for preventing intensive care unit (ICU) stays.

The final study[21] compared a hypothetical vaccine that prevented RSV starting at birth, either in the form of immunization during pregnancy or a vaccine given to neonates, with no intervention. The efficacy of this vaccine was assumed to be 50% for all RSV-related outcomes and was predicted to have a half-life of 12 months in the base case, with 1-way sensitivity analyses varying efficacy and duration.

Influential parameters reported as affecting results within studies included underlying differences between modelled countries in terms of RSV burden and health care system organization,[19] effectiveness and duration of effect used for the interventions,[19-21] severity of RSV season,[2,20] and the acquisition costs of immunization during pregnancy and mAbs.[19-21]

Evaluations Comparing Immunization During Pregnancy to No Intervention

All 4 studies compared immunization during pregnancy to no intervention, although ICERs for this comparison were manually recalculated within the current review for 2 of the studies using reported incremental costs and QALYs.[19,20] Estimated ICERs, when considering a health care system perspective, ranged widely from immunization during pregnancy being dominant (less costly, more effective) compared with no treatment in Nunavik during moderate and severe RSV seasons[2] and in Finland[19] to costing more than $200,000 per QALY gained in Nunavik during mild RSV seasons[2] as well as in the Netherlands[19] and Norway.[20] When considering a societal perspective that added direct nonmedical costs (travel, meals, lodging) per hospitalization, parental income loss per RSV event, and lifetime income loss for infants who

died, 1 study reported an ICER of $105,022 per QALY gained for immunization during pregnancy compared with no intervention.[21] Further details can be found in Appendix 1, Table 4. Reasons for this range of ICERs include differences in model parameter inputs, such as immunization during pregnancy efficacy and duration assumptions; underlying rates of RSV-related primary care visits, hospitalizations, and recurrent wheezing or asthma; QALY decrements attributed to primary care visits, hospitalizations, and recurrent wheezing or asthma; and the associated costs of treatment.

One study[21] also reported ICERs for immunization during pregnancy compared with no treatment of $348,573 per life-year gained, and $30,921 per hospitalization avoided when considering the health care system perspective. Another study reported that when seasonal immunization during pregnancy was combined with a seasonal long-acting mAb for preterm and chronically ill infants, immunization during pregnancy plus mAb was dominant (less costly, more effective) over no treatment in RSV seasons of all severities.[2]

Evaluations Comparing Immunization During Pregnancy to a Long-Acting mAb

Two studies[19,20] conducted sequential analyses in which, in addition to no treatment, year-round immunization during pregnancy was directly compared with 1 or more year-round and seasonal long-acting mAb strategies as well as to seasonal mAb strategies that included a catch-up dose at the start of RSV season for infants born outside of RSV season. The studies reported cost-effectiveness acceptability frontiers outlining the most cost-effective strategy across a range of willingness-to-pay per QALY thresholds.

Both of these studies assumed an immunization during pregnancy efficacy of 70% lasting for 4 months in their base case, and long-acting mAb efficacy and duration was represented by nirsevimab data. In all 7 countries modelled within these 2 studies, year-round immunization during pregnancy was dominated (i.e., was more costly and less effective) by various seasonal mAb strategies and thus was not the most cost-effective strategy at any willingness-to-pay threshold. Results reportedly did not substantially differ in the study, which included a scenario that incorporated recently released RSVpreF data, because the longer (6 month) duration of action was offset by lower efficacy rates for primary care visits at 6 months compared with WHO PPC efficacy at 4 months used in the base case.[18] Sequential results also did not substantially differ from those of the base case when partial societal (including caregiver productivity loss) or full societal (including caregiver productivity and leisure time loss) perspectives were taken within this study; immunization during pregnancy was still not the most cost-effective strategy at any willingness-to-pay threshold.[19] A summary of the cost-effectiveness frontier in each modelled country within these studies can be found in Appendix 1, Table 4.

Of particular interest is that these 2 studies conducted pricing threshold analyses, with 1 study reporting that immunization during pregnancy would be a cost-effective option compared with a long-acting mAb if the immunization during pregnancy was priced at least 50% lower per dose than the mAb,[19] while the other study estimated that immunization during pregnancy would need to be priced 2 to 5 times lower than the long-acting mAb to be cost-effective.[20] These results are similar to 2 economic studies that estimated that the maximum cost-effective purchase price per person or per fully protected person was lower for year-round immunization during pregnancy compared with seasonal long-acting mAb for newborns (i.e., immunization during pregnancy needed to be priced lower than the mAb to be cost-effective),[25,26] although

1 of these studies reported that when immunization during pregnancy was used seasonally, the maximum cost-effective price per person was similar to that of seasonal mAb.[26]

Discussion

The review identified 4 economic evaluations conducted in high-income countries that assessed the cost-effectiveness of RSV immunization during pregnancy compared with no intervention; of these, 2 economic evaluations compared immunization during pregnancy with long-acting mAb intervention strategies. All studies evaluated the benefits and costs of RSV immunization during pregnancy for infants, but none considered the potential benefit of RSV immunization during pregnancy to the people who are pregnant. Although health benefits and potential cost offsets in people who are pregnant may be relatively limited due to low rates of RSV-related morbidity and mortality in healthy adults younger than 50 years, it is likely the overall cost-effectiveness of RSV immunization during pregnancy was slightly underestimated due to this omission, and the cost-effectiveness of RSV prevention in people who are pregnant is unknown.

Limitations

The identified studies used a range of inputs to estimate the efficacy of immunization during pregnancy and duration within their models, including WHO PPC recommendations, data from the failed ResVax PREPARE trial, and author assumptions. Data from the MATISSE RSVpreF trial was new at the time of this review, and only available as part of a press release from its sponsor, Pfizer.[11] Only 1 of the included studies incorporated data from this trial, and only as a scenario analysis with incomplete reporting.[19] This scenario applied efficacy over a 6-month duration using rates reported for the 6-month follow-up period of the MATISSE trial (medically attended RSV of 51.3%; severe medically attended RSV of 69.4%).[11] The study did not conduct a scenario incorporating the higher efficacy rates reported at the 90-day primary end point of the trial over a 3-month duration (medically attended RSV of 57.1%; severe medically attended RSV of 81.8%).[11] Very young infants are at higher risk of severe RSV disease than those approaching 6 months of age,[19,22] thus an alternate scenario considering these higher efficacy rates over a shorter duration may have been informative. As such, the efficacy inputs used in the included studies may not be reflective of the efficacy of RSVpreF in preventing severe RSV outcomes in very young infants.

Most studies[19-21] (n = 3) did not consider the cost-effectiveness of seasonal immunization during pregnancy strategies in which only persons due to give birth during, just before, and/or just after (to ensure preterm infants would also be protected) RSV season would be vaccinated. Because year-round immunization during pregnancy was dominated by seasonal long-acting mAb strategies in the studies directly comparing them,[19,20] a comparison of seasonal immunization during pregnancy compared with seasonal mAb strategies may have been of interest. Conversely, the included study set in Nunavik only considered seasonal immunization during pregnancy, thus the cost-effectiveness of year-round immunization during pregnancy was not assessed in this setting.[2]

The included studies used a range of sources to estimate QALY decrements associated with RSV-related primary care visits, hospitalizations, ICU stays, and recurrent wheezing or asthma. Measuring QALY loss in

very young children is challenging, increasing the uncertainty in resulting estimates of cost-effectiveness for interventions, including RSVpreF, aimed at improving quality of life in young pediatric populations. Most studies did not incorporate deaths avoided due to RSV prevention strategies because of very low rates of RSV-related deaths in high-income countries[20] (such deaths occur primarily in critically ill infants who were likely to experience premature death even without RSV infection)[19] or for unstated reasons.[2] This may underestimate the cost-effectiveness of RSVpreF should a portion of these deaths be avoided in clinical practice. The model that did include RSV-related mortality prevention estimated that 66 deaths would be avoided in the US by vaccinating 4.2 million live births.[21] These deaths avoided accounted for 21% of the QALY gains in the model, a figure which likely overestimates any potential mortality benefit that might be realized with RSV immunization during pregnancy in practice, thus the model likely underestimates the ICER.

Generalizability

Most of the included studies may be broadly generalizable to the Canadian health care system because the eligibility criteria screened for economic evaluations conducted in high-income countries, as defined by the World Bank.[15] Further, 3 of the included studies were set in countries with public health care systems similar to Canada,[27] with the exception of a single study set in the US.[21]

The assumed price per dose of immunization during pregnancy varied widely within the included studies, ranging from $73 to $1,736 (2023 Canadian dollars). At the time of this review, RSVpreF was under review but not yet approved or available in Canada, the US, or the European Union.[12-14] As such, the price at which RSVpreF will be available is unknown, increasing uncertainty in its cost-effectiveness.

The sole economic model set in Canada considered the population of Nunavik, Quebec.[2] Although highly relevant to decision-makers in Nunavik and similar regions, the high rates of RSV infections and associated hospitalizations, as well as the high costs and family burden associated with potential medical transport from remote Arctic regions,[2] likely reduces generalizability of cost-effectiveness results to non-Arctic regions of Canada. Additionally, the estimated cost per immunization during pregnancy dose was very high in this study compared with the others and may not be reflective of future costs that would be paid by Canadian health care payers for RSVpreF.

Conclusions

Four economic studies were identified regarding the cost-effectiveness of RSV immunization during pregnancy in high-income countries. All 4 identified studies that evaluated the cost-effectiveness of RSV immunization during pregnancy modelled outcomes for infants. However, there is a lack of evidence on outcomes for the persons who are pregnant.

When compared to no intervention, the cost-effectiveness of immunization during pregnancy ranged from dominant (more effective and less costly) to more than $200,000 per QALY gained, depending on the modelled region, efficacy, pricing, and severity of the RSV season.

When compared with seasonal RSV prophylaxis with long-acting mAbs such as nirsevimab, year-round immunization during pregnancy was not considered cost-effective when the price per dose was the same as that of the long-acting mAb. Immunization during pregnancy was estimated to become cost-effective when its acquisition cost per dose was 2 to 5 times lower than that of the long-acting mAb.

Most studies did not incorporate efficacy data from immunization during pregnancy trials, and only 1 study included data specific to the product RSVpreF in a scenario analysis. Given the between-study variation in assumed immunization during pregnancy efficacy, immunization during pregnancy acquisition costs, QALY measures, mortality assumptions, and setting, substantial uncertainty remains regarding the cost-effectiveness of immunization during pregnancy with RSVpreF in Canada.

References

1. Paes BA, Mitchell I, Banerji A, Lanctôt KL, Langley JM. A decade of respiratory syncytial virus epidemiology and prophylaxis: translating evidence into everyday clinical practice. *Can Respir J.* 2011;18(2):e10-19. PubMed
2. 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. PubMed
3. Ektare V, Lang J, Choi Y, Finelli L. The clinical impact of multiple prevention strategies for respiratory syncytial virus infections in infants and high-risk toddlers in the United States. *Vaccine.* 2022;40(42):6064-6073. PubMed
4. Stein RT, Bont LJ, Zar H, et al. Respiratory syncytial virus hospitalization and mortality: systematic review and meta-analysis. *Pediatr Pulmonol.* 2017;52(4):556-569. PubMed
5. Löwensteyn YN, Phijffer E, Simons JVL, et al. Respiratory syncytial virus-related death in children with down syndrome: the RSV GOLD study. *Pediatr Infect Dis J.* 2020;39(8):665-670. PubMed
6. Synagis (palivizumab): sterile solution for intramuscular (50 mg/0.5 mL and 100 mg/1 mL) [product monograph]. Mississauga (ON): AstraZeneca Canada Inc; 2021 Jul 09: https://pdf.hres.ca/dpd_pm/00062121.PDF. Accessed 2023 Apr 17.
7. Public Health Agency of Canada. Recommended use of palivizumab to reduce complications of respiratory syncytial virus infection in infants; an Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI) 2022; https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/palivizumab-respiratory-syncitial-virus-infection-infants.html, 2023 Jun 09.
8. Beyfortus (nirsevimab injection): solution for injection, 100 mg/mL, intramuscular use (50 mg and 100 mg single use, pre-filled syringe) [product monograph]. Mississauga (ON): AstraZeneca Canada Inc; 2023 Apr 19: https://pdf.hres.ca/dpd_pm/00070439.PDF. Accessed 2023 May 08.
9. Annex I: summary of product characteristics: beyfortus (nirsevimab). Amsterdam (NL): European Medicines Agency; [2022]: https://www.ema.europa.eu/en/documents/product-information/beyfortus-epar-product-information_en.pdf. Accessed 2023 Apr 18.
10. AstraZeneca. Nirsevimab US regulatory submission accepted for the prevention of RSV lower respiratory tract disease in infants and children up to age 24 months. 2023 Jan 05; https://www.astrazeneca.com/media-centre/press-releases/2023/nirsevimab-us-regulatory-submission-accepted-for-the-prevention-of-rsv-lower-respiratory-tract-disease-in-infants-and-children.html. Accessed 2023 Apr 18.
11. Pfizer Inc. Pfizer announces positive top-line data of phase 3 global maternal immunization trial for its bivalent respiratory syncytial virus (RSV) vaccine candidate. 2022 Nov 1; https://www.pfizer.com/news/press-release/press-release-detail/pfizer-announces-positive-top-line-data-phase-3-global. Accessed 2023 Apr 17.
12. Pfizer Inc. U.S. FDA accepts biologics license application for Pfizer's respiratory syncytial virus maternal vaccine candidate for priority review. 2023 Feb 21; https://www.pfizer.com/news/press-release/press-release-detail/us-fda-accepts-biologics-license-application-pfizers, 2023 Apr 17.
13. Pfizer Canada. Pfizer Canada initiates submission to Health Canada for its bivalent respiratory syncytial virus (RSV) vaccine. 2023 Apr 14; https://www.pfizer.ca/en/media-centre/pfizer-canada-initiates-submission-to-health-canada-for-its-bivalent-respiratory-syncytial-virus-rsv-vaccine. Accessed 2023 Apr 18.
14. Pfizer Inc. Pfizer receives positive FDA Advisory Committee votes supporting potential approval for vaccine candidate to help combat RSV in older adults. 2023 Feb 28; https://www.pfizer.com/news/press-release/press-release-detail/pfizer-receives-positive-fda-advisory-committee-votes, 2023 Apr 18.
15. World Bank Group. The world by income and region, 2021. 2023; https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html. Accessed 2023 Apr 17, 2023.
16. Critical appraisal tools for use in JBI systematic reviews: checklist for economic evaluations. Adelaide (AU): The Joanna Briggs Institute; 2020: https://jbi.global/critical-appraisal-tools. Accessed 2023 Mar 10.

17. Organisation for Economic Co-operation and Development. Purchasing power parities for GDP and related indicators. 2023; https://stats.oecd.org/Index.aspx?DataSetCode=PPPGDP. Accessed 2023 Apr 24.

18. Bank of Canada. Inflation calculator. 2023; https://www.bankofcanada.ca/rates/related/inflation-calculator/. Accessed 2023 Apr 24.

19. 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(9):1623-1631. PubMed

20. Li X, Bilcke J, Vazquez Fernandez 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(Suppl 1):S95-S101. PubMed

21. Regnier SA. Respiratory syncytial virus immunization program for the United States: impact of performance determinants of a theoretical vaccine. *Vaccine.* 2013;31(40):4347-4354. PubMed

22. WHO preferred product characteristics for Respiratory Syncytial virus (RSV) vaccines. Geneva: World Health Organization; 2017: https://www.who.int/publications/i/item/WHO-IVB-17.11. Accessed 2023 Apr 24.

23. 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(9):837-846. PubMed

24. Madhi SA, Polack FP, Piedra PA, et al. Respiratory syncytial virus vaccination during pregnancy and effects in infants. *New Engl J Med.* 2020;383(5):426-439. PubMed

25. Cromer D, van Hoek AJ, Newall AT, Pollard AJ, Jit M. Burden of paediatric respiratory syncytial virus disease and potential effect of different immunisation strategies: a modelling and cost-effectiveness analysis for England. *Lancet Public Health.* 2017;2(8):e367-e374. PubMed

26. 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(1):348. PubMed

27. 2015 International Profiles of Health Care Systems. Washington (DC): Commonwealth Fund; 2016: https://www.commonwealthfund.org/sites/default/files/documents/___media_files_publications_fund_report_2016_jan_1857_mossialos_intl_profiles_2015_v7.pdf. Accessed 2023 May 11.

28. Feltes TF, Cabalka AK, Meissner HC, et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr.* 2003;143(4):532-540. PubMed

29. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk Infants. *Pediatrics.* 1998;102(3):531-537. PubMed

30. Gilca R, Billard MN, Zafack J, et al. Effectiveness of palivizumab immunoprophylaxis to prevent respiratory syncytial virus hospitalizations in healthy full-term <6-month-old infants from the circumpolar region of Nunavik, Quebec, Canada. *Prev Med Rep.* 2020;20:101180. PubMed

Appendix 1: Results of Included Studies

Note this appendix has not been copy-edited.

Figure 1: Selection of Included Studies

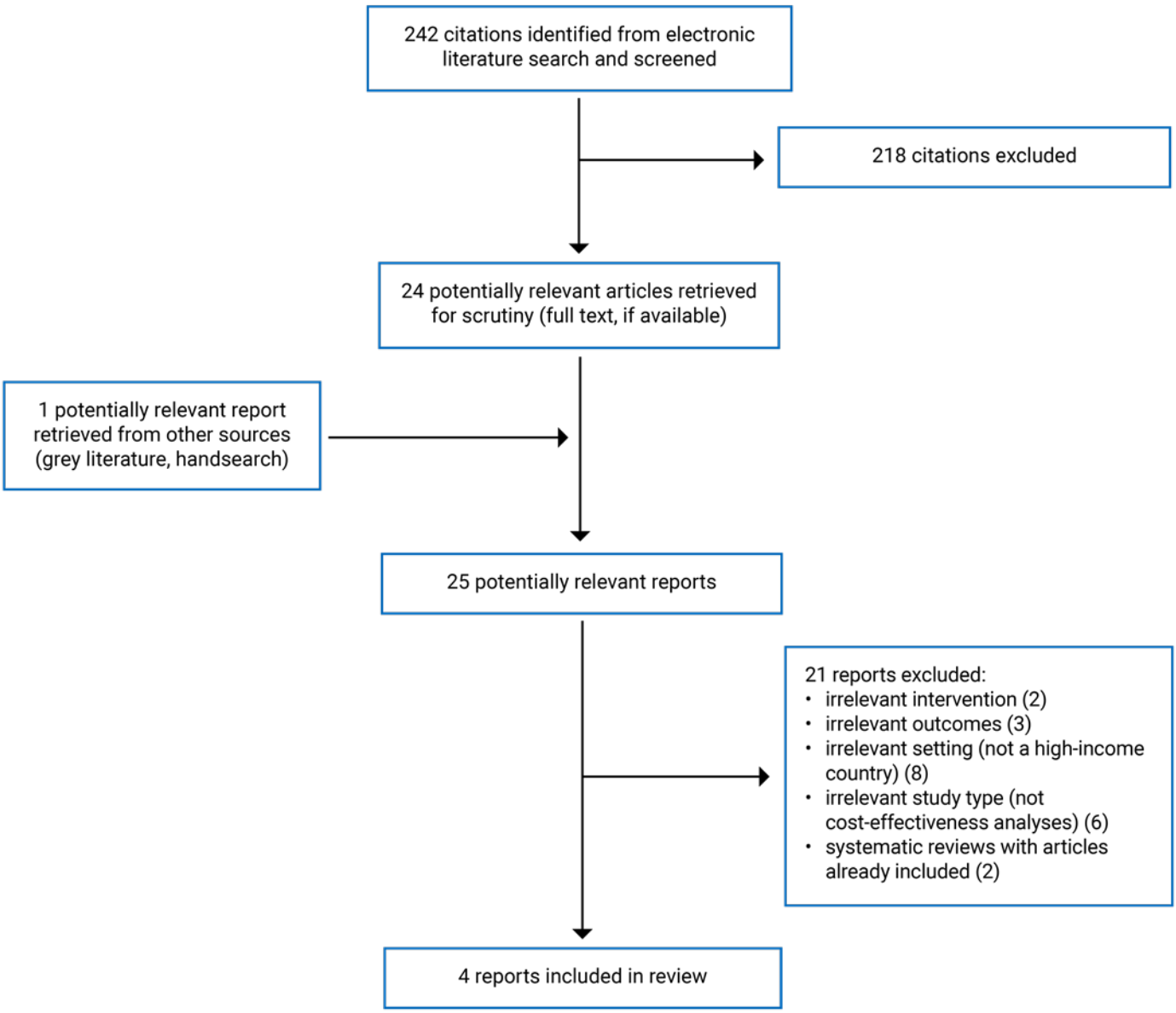

Table 2: Characteristics of Included Economic Evaluations

Authors, year	Country	Type of analysis, perspective	Time horizon, discount rate	Population	Intervention and comparator(s)	Modelling approach	Source of clinical efficacy and duration of protection[a]	Cost per dose	Industry funding
Getaneh et al. (2023)[19]	Denmark, Finland, England, Scotland, Italy (Venato region), the Netherlands	Cost-effectiveness analysis; health care payer perspective as base case. Abbreviated results also available from "partial societal" (includes caregiver productivity costs) and "full societal" (includes caregiver productivity costs and loss of leisure time) scenario analyses.	5 years; Rates vary by country; 3% to 4% for costs, 1.5% to 3.5% for effects	1-year cohort of infants	Year-round IP No intervention Seasonal long-acting mAb at birth (October to April) Seasonal long-acting mAb at birth (October to April) plus catch-up in October (for babies born May to September)	Static cohort model (adapted MCMARCEL)	**Base case** IP: 70%, 4 months (Source: WHO PPC[22]) mAb: medically attended RSV LRTI 74.5%, severe medically attended RSV LRTI 62.1%, 5 months. (Source: nirsevimab MELODY trial data[23]) **Scenario** IP: medically attended RSV LRTI 51.3%, severe medically attended RSV LRTI 69.4%, 6 months. (Source: RSVpreF MATISSE data.[11])	IP: €50, (CA$99 2023) Long-acting mAb: €50, (CA$99 2023)	RESCEU, which received funding from Innovative Medicines Initiative, a partnership between the EU and pharmaceutical companies. Authors specify funders had no role in the study.
Li et al. (2022)[20]	Norway	Cost-effectiveness analysis; health care payer perspective	5 years; 4% for costs and effects	1-year cohort of infants	Year-round IP No intervention 28 seasonal long-acting mAb strategies (single	Static cohort model (adapted MCMARCEL)	IP: 70% for both RSV primary care visits and hospitalization, 4 months (Source: WHO PPC[22])	IP: 500 NOK, (CA$73 2023) Long-acting mAb: 500	RESCEU, which received funding from Innovative Medicines Initiative, a

Authors, year	Country	Type of analysis, perspective	Time horizon, discount rate	Population	Intervention and comparator(s)	Modelling approach	Source of clinical efficacy and duration of protection[a]	Cost per dose	Industry funding
					month, multiple consecutive months) Seasonal long-acting mAb at birth (October to April) plus catch-up in October (for babies born May to September)		mAb: 74.5% RSV primary care visits, 62.1% RSV hospitalization, 5 months. (Source: nirsevimab MELODY trial data[23])	NOK, (CA$73 2023)	partnership between the EU and pharmaceutical companies.
Nourbakhsh et al. (2021)[2]	Canada (Nunavik)	Cost-effectiveness analysis; perspective unstated, appears to be health care payer	1 year; No discounting due to time horizon	1-year cohort of infants	Seasonal IP given to pregnant persons due November through June Seasonal IP plus long-acting mAb for preterm/chronically ill infants No intervention[b]	Discrete-event agent-based simulation	IP[c]: Derived from ResVax PREPARE trial data[24] Short-acting mAb: palivizumab data from the literature[28-30] Long-acting mAb assumed same as palivizumab	IP: $1,560 (CA$1,736 2023)[d] Long- or short-acting mAb: $1,065 (CA$1,185 2023)	CIHR and PHAC through CIRN, the latter of which reports some industry funding. Authors specify funders had no role in the study.
Regnier (2013)[21]	US	Cost-effectiveness analysis; health care system and societal perspective (includes nondirect medical costs, loss of caregiver	5 years; 3% costs and effects	1-year cohort of infants	Year-round IP or infant vaccine effective from birth No intervention	Decision analysis model	IP: 50% for all outcomes, 12 month half-life (Source: assumption)	IP: US$196 (CA$316 2023)	Funding received from Novartis for editorial assistance.

Authors, year	Country	Type of analysis, perspective	Time horizon, discount rate	Population	Intervention and comparator(s)	Modelling approach	Source of clinical efficacy and duration of protection[a]	Cost per dose	Industry funding
		income per RSV event, and lifetime income loss due to premature death of infant)							

CIHR = Canadian Institutes of Health Research; CIRN = Canadian Immunization Research Network; EU = European Union; IP = immunization during pregnancy; LRTI = lower respiratory tract infection; mAb = monoclonal antibody; MCMARCEL = Multi-Country Model Application for RSV Cost-Effectiveness policy; PAHC = Public Health Agency of Canada; PPC = Preferred Product Characteristic; RESCEU = Respiratory Syncytial virus Consortium in Europe; RSV = respiratory syncytial virus.

[a]Modelled efficacy of all active interventions dropped to 0% at the end of the specified duration (i.e., an all-or-nothing approach),[2,19,20] with the exception of Regnier et al. (2013), where duration of efficacy was described as having a 12-month half-life in the base case.[21]

[b]Other interventions were included within the study but not compared to IP, with some only compared to each other rather than to no treatment. These included: short-acting mAb for preterm /chronically ill infants, long-acting mAb given to pre-term/chronically ill infants, short-acting mAb as above and seasonally for healthy infants born October to May, long-acting mAb as above and seasonally for healthy infants born October to May.[2]

[c]Efficacy varies by outcome, age, and health of infant. In healthy or preterm/chronically ill infants for the first 3 months, IP was assumed to reduce the risk of RSV-related outpatient visits by 14%, pediatric ward admissions by 24.7% to 61.9%, and ICU stays by 31.9% to 75%. See publication for mAb efficacy rates.[2]

[d]Based on "same age-specific cost as palivizumab per kilogram for a specific dose."[2] Whether administration, transportation, or other costs were included was unclear.

Table 3: Quality Appraisal Results

Critical appraisal: Joanna Briggs Institute checklist questions[16]	Getaneh et al. (2023)[19]	Li et al. (2022)[20]	Nourbakhsh et al. (2021)[2]	Regnier (2013)[21]
1. Is there a well-defined question?	Yes	Yes	Yes	No
2. Is there comprehensive description of alternatives?	Yes	Yes	Yes	Yes
3. Are all important and relevant costs and outcomes for each alternative identified?	Yes	Yes	Yes	Yes
4. Has clinical effectiveness been established?	No[a]	No[a]	No[a]	No[a]
5. Are costs and outcomes measured accurately?	Yes	Yes	Unclear	Yes
6. Are costs and outcomes valued credibly?	Unclear	Yes	Unclear	Yes
7. Are costs and outcomes adjusted for differential timing?	Yes	Yes	NA	Yes
8. Is there an incremental analysis of costs and consequences?	Yes	Yes	Yes	Yes
9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences?	Yes	Yes	Yes	Yes
10. Do study results include all issues of concern to users?	No	No	No	No
11. Are the results generalizable to the setting of interest in the review?	Unclear	Unclear	No	No

NA = not applicable.

[a]Clinical effectiveness assumptions regarding RSV IP were well described in each study but were not reflective of data specific to RSVpreF except for a partially reported scenario analysis in Getaneh et al. (2023).[19]

Table 4: Main Results of Included Economic Evaluations

Author (year)	Country, currency	ICER IP vs. no intervention (original)	ICER IP vs. no intervention (2023 CA$)[a]	ICER IP vs. long-acting mAb	Cost-effectiveness frontier (original)	Cost-effectiveness frontier (2023 CA$)	Pricing threshold
Getaneh et al. (2023)[19]	Denmark 2021 Euro	€71,684/QALY[b]	$141,471/QALY	IP was dominated by seasonal mAb and seasonal mAb plus catch-up	WTP < €9,129: no intervention €9,129 ≤ WTP < €24,664: seasonal mAb €24,664 ≤ WTP: seasonal mAb plus catch-up[c]	WTP < $18,016: no intervention $18,016 ≤ WTP < $48,675: seasonal mAb $48,675 ≤ WTP: seasonal mAb plus catch-up	Year-round IP became a cost-effective option when priced at least 50% lower per dose than long-acting mAb.[cd]
	England 2021 Euro	€35,333/QALY[b]	$69,731/QALY	IP was dominated by seasonal mAb plus catch-up	WTP < €4,444: no intervention €4,444 ≤ WTP < €8,864: seasonal mAb €8,864 ≤ WTP: seasonal mAb plus catch-up[c]	WTP < $8,770: no intervention $8,770 ≤ WTP < $17,493: seasonal mAb $17,493 ≤ WTP: seasonal mAb plus catch-up	
	Finland 2021 Euro	Dominant; −€16,626/QALY[b]	Dominant; −$32,812/QALY	IP was dominated by seasonal mAb and seasonal mAb plus catch-up	WTP < €13,373: seasonal mAb €13,373 ≤ WTP: seasonal mAb plus catch-up[c]	WTP < $26,392: seasonal mAb $26,392 ≤ WTP: seasonal mAb plus catch-up	
	Italy (Venato) 2021 Euro	€51,200/QALY[b]	$101,045/QALY	IP was dominated by seasonal mAb plus catch-up	WTP < €23,814: no intervention €23,814 ≤ WTP < €42,245: seasonal mAb €42,245 ≤ WTP:	WTP < $46,998: no intervention $46,998 ≤ WTP < $83,372: seasonal mAb $83,372 ≤ WTP:	

Author (year)	Country, currency	ICER IP vs. no intervention (original)	ICER IP vs. no intervention (2023 CA$)[a]	ICER IP vs. long-acting mAb	Cost-effectiveness frontier (original)	Cost-effectiveness frontier (2023 CA$)	Pricing threshold
					seasonal mAb plus catch-up[c]	seasonal mAb plus catch-up	
	The Netherlands 2021 Euro	€197,429/QALY[b]	$389,257/QALY	IP was dominated by seasonal mAb and seasonal mAb plus catch-up	WTP < €21,187: no intervention €21,187 ≤ WTP < €130,308: seasonal mAb €130,308 ≤ WTP: seasonal mAb plus catch-up[c]	WTP < $41,813: no intervention $41,813 ≤ WTP < $257,167: seasonal mAb $257,167 ≤ WTP: seasonal mAb plus catch-up	
	Scotland 2021 Euro	€28,600/QALY[b]	$56,443/QALY	IP was dominated by seasonal mAb plus catch-up	Seasonal mAb plus catch-up across all WTP[c]	Seasonal mAb plus catch-up across all WTP	
Li et al. (2022)[20]	Norway 2019 NOK	1,377,667[b] NOK/QALY	$202,040/QALY	IP was dominated by various seasonal mAb strategies	WTP < 390,000NOK: November to February mAb 390,000NOK < WTP ≤ 500,000: October to February mAb 500,000NOK < WTP: October to March mAb	WTP < $57,195: November to February mAb $57,195 < WTP ≤ $73,327: October to February mAb $73,327 < WTP: October to March mAb	Year-round IP became a cost-effective option when priced 2 to 5 times lower than the long-acting mAb[e]
Nourbakhsh et al. (2021)[2]	Canada (Nunavik) 2021 CA$	Mild season: $227,286/QALY[f] Moderate season: Dominant; −$587,402 Severe season:	Mild: $252,856/QALY[f] Moderate: Dominant; −$587,402/QALY Severe: Dominant; −$900,382/QALY	Not compared[g]	No sequential analysis	Not applicable	No pricing threshold

Author (year)	Country, currency	ICER IP vs. no intervention (original)	ICER IP vs. no intervention (2023 CA$)[a]	ICER IP vs. long-acting mAb	Cost-effectiveness frontier (original)	Cost-effectiveness frontier (2023 CA$)	Pricing threshold
		Dominant; –$809,332					
Regnier (2013)[21]	US 2011 US$	Health care system perspective: US$93,401/QALY US$216,120/LY US$19,172 per hospitalization averted Societal perspective: US$65,115/QALY	Health care system perspective: $150,643/QALY $348,573/LY $30,921 per hospitalization averted Societal perspective: $105,022/QALY	mAbs not considered	No sequential analysis	Not applicable	A vaccine priced at US$100 (CA$161 2023) per dose with 50% effectiveness and a 12-month half-life would be cost-saving. The ICER would be less than US$50k at US$200 per dose, and be about US$100k at US$300 per dose.

ICER = incremental cost-effectiveness ratio; IP = immunization during pregnancy; LY = life-year; mAb = monoclonal antibody; NOK = Norwegian krone; QALY = quality-adjusted life-year; WTP = willingness to pay.

[a]Conversion to Canadian dollars conducted using OECD Purchasing Price Parity rates for the year of the original currency,[17] and then inflated to 2023 using Bank of Canada inflation calculator.[18]

[b]ICER calculated by CADTH from incremental costs (reported rounded to nearest 1,000) and incremental QALYs (reported rounded to nearest 1).

[c]Represents base-case results where IP efficacy was 70% for 4 months. Scenario analysis using RSVpreF data from the MATISSE trial did not substantially differ as the longer duration (6 months) was offset by lower efficacy for young infants (medically attended RSV: 51.3%; severe medically attended RSV: 69.4%).

[d]Two-way pricing scenarios were conducted across a range of willingness-to-pay thresholds (€0 to €100,000 per QALY gained) for each included country/region. For example, in Finland, when the willingness to pay was €25,000 (CA$49,448 2023), IP was the cost-effective strategy when it cost up to €25 (2023 CA$49) and mAb was at or above €50 (2023 CA$99), or when IP cost €50 (2023 CA$99) and the long-acting mAb was at least €100 (2023 CA$197). However, when the modelled country was the Netherlands and at the same willingness to pay of €25,000, the price of IP needed to be at or below €10 (2023 CA$20) and mAb at least €50 (2023 CA$99) for IP to be considered cost-effective. Results for these 2-way pricing scenarios for each country can be found in Figure 3 as well as Section 2.4 of the supplementary information of Getaneh et al. (2023).[19]

[e]Two-way pricing scenarios were conducted across a range of willingness-to-pay thresholds (NOK100,000 to NOK900,000; 2023 CA$14,665 to $131,988). When the willingness to pay was NOK300,000 (2023 CA$43,996), IP was the cost-effective option when priced at NOK100 (2023 CA$15) if the long-acting mAb was at least NOK300 (2023 CA$44), and when IP was priced at NOK300 (2023 CA$44) if the mAb cost at least NOK700 (2023 CA$103). Further results for other prices and willingness-to-pay thresholds can be found in Supplementary Figure 7 of Li et al. (2022).[20]

[f]Severity of season was defined by the proportion of modelled households having at least 1 infant under 1 year of age infected with RSV: Mild = 30% to 50%; Moderate = 50% to 70%; Severe = 70% to 90%. While seasonal IP was not cost-effective at traditional thresholds in a mild season, when seasonal IP was combined with immunization of preterm and chronically ill infants using a long-acting mAb, the combination was dominant (more effective, less costly) compared to no intervention in mild, moderate, and severe seasons.

[g]ICERs for long-acting mAb for preterm/chronically ill infants vs. no intervention were lower than seasonal IP vs. no intervention. The included long-acting mAb intervention for all infants was not compared to no intervention or to IP.

Appendix 2: Literature Search Strategy

Economic Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946 to present)
- Embase (1974 to present)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: March 24, 2023

Alerts: Biweekly search updates until May 8, 2023.

Search filters applied: Systematic reviews; meta-analyses; network meta-analyses; health technology assessments; economic evaluations; costs and cost analysis studies, and quality of life studies.

Limits: None

Table 5: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Keyword heading word
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.mp	Mapped term
.jw	Journal title word (MEDLINE)
freq = #	Requires terms to occur # number of times in the specified fields

Medline Database Strategy

1. Respiratory Syncytial Virus Vaccines/
2. ("Respiratory syncytial virus prefusion F*" or RSVPreF* or RSV-PreF* or RSV-PRE-F*).ti,ab,kf.
3. ((Respiratory syncytial or RSV) adj5 ("prefusion F*" or "pre-fusion F*" or "PRE-F*" or PREF?)).ti,ab,kf.
4. (Ad26RSVpreF* or "Ad26 RSV preF*" or mRNA-1345* or mRNA1345* or "Ad26.RSV.preF*" or ABRYSVO* or "PF-06928316*").ti,ab,kf.
5. ((Respiratory syncytial or RSV) and (vaccine? or vaccinat* or immunis* or immuniz*)).ti,kf.
6. or/1-5
7. Economics/
8. exp "Costs and Cost Analysis"/
9. Economics, Nursing/
10. Economics, Medical/
11. Economics, Pharmaceutical/
12. exp Economics, Hospital/
13. Economics, Dental/
14. exp "Fees and Charges"/
15. exp Budgets/
16. budget*.ti,ab,kf.
17. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
18. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq = 2
19. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
20. (value adj2 (money or monetary)).ti,ab,kf.
21. exp models, economic/
22. economic model*.ab,kf.
23. markov chains/
24. markov.ti,ab,kf.
25. monte carlo method/
26. monte carlo.ti,ab,kf.
27. exp Decision Theory/
28. (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.

29. or/7-28
30. “Value of Life”/
31. Quality of Life/
32. quality of life.ti,kf.
33. ((instrument or instruments) adj3 quality of life).ab.
34. Quality-Adjusted Life Years/
35. quality adjusted life.ti,ab,kf.
36. (qaly* or qald* or qale* or qtime* or life year or life years).ti,ab,kf.
37. disability adjusted life.ti,ab,kf.
38. daly*.ti,ab,kf.
39. (sf36 or sf 36 or short form 36 or shortform 36 or short form36 or shortform36 or sf thirtysix or sfthirtysix or sfthirty six or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab,kf.
40. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six or shortform6 or short formsix).ti,ab,kf.
41. (sf8 or sf 8 or sf eight or sfeight or shortform 8 or shortform 8 or shortform8 or short form8 or shortform eight or short form eight).ti,ab,kf.
42. (sf12 or sf 12 or short form 12 or shortform 12 or short form12 or shortform12 or sf twelve or sftwelve or shortform twelve or short form twelve).ti,ab,kf.
43. (sf16 or sf 16 or short form 16 or shortform 16 or short form16 or shortform16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab,kf.
44. (sf20 or sf 20 or short form 20 or shortform 20 or short form20 or shortform20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab,kf.
45. (hql or hqol or h qol or hrqol or hr qol).ti,ab,kf.
46. (hye or hyes).ti,ab,kf.
47. (health* adj2 year* adj2 equivalent*).ti,ab,kf.
48. (pqol or qls).ti,ab,kf.
49. (quality of wellbeing or quality of well being or index of wellbeing or index of well being or qwb).ti,ab,kf.
50. nottingham health profile*.ti,ab,kf.
51. sickness impact profile.ti,ab,kf.
52. exp health status indicators/
53. (health adj3 (utilit* or status)).ti,ab,kf.
54. (utilit* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or weight)).ti,ab,kf.

55. (preference* adj3 (valu* or measur* or health or life or estimat* or elicit* or disease or score* or instrument or instruments)).ti,ab,kf.
56. disutilit*.ti,ab,kf.
57. rosser.ti,ab,kf.
58. willingness to pay.ti,ab,kf.
59. standard gamble*.ti,ab,kf.
60. (time trade off or time tradeoff).ti,ab,kf.
61. tto.ti,ab,kf.
62. (hui or hui1 or hui2 or hui3).ti,ab,kf.
63. (eq or euroqol or euro qol or eq5d or eq 5d or euroqual or euro qual).ti,ab,kf.
64. duke health profile.ti,ab,kf.
65. functional status questionnaire.ti,ab,kf.
66. dartmouth coop functional health assessment*.ti,ab,kf.
67. or/30-66
68. 29 or 67
69. 6 and 68
70. (systematic review or meta-analysis).pt.
71. meta-analysis/ or systematic review/ or systematic reviews as topic/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
72. ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf.
73. ((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf.
74. ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf.
75. (data synthes* or data extraction* or data abstraction*).ti,ab,kf.
76. (handsearch* or hand search*).ti,ab,kf.
77. (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf.
78. (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf.
79. (meta regression* or metaregression*).ti,ab,kf.
80. (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
81. (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
82. (cochrane or (health adj2 technology assessment) or evidence report).jw.

83. (comparative adj3 (efficacy or effectiveness)).ti,ab,kf.
84. (outcomes research or relative effectiveness).ti,ab,kf.
85. ((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf.
86. (meta-analysis or systematic review).md.
87. (multi* adj3 treatment adj3 comparison*).ti,ab,kf.
88. (mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf.
89. umbrella review*.ti,ab,kf.
90. (multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
91. (multiparamet* adj2 evidence adj2 synthesis).ti,ab,kf.
92. (multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kf.
93. or/70-92
94. 6 and 93
95. 69 or 94

Authors: Samantha Verbrugghe, Quenby Mahood, Sean Tiggelaar

ISSN: 2563-6596

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **requests@cadth.ca**