

An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Cost-Effectiveness of Palivizumab Prophylaxis for
Respiratory Syncytial Virus (RSV): A Systematic
Review

PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH



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Conflict of Interest: The authors have no conflicts of interest relevant to this report to disclose.

Abbreviations: BPD, bronchopulmonary dysplasia; CAD, Canadian dollar; CE, cost-effective; CF, cystic fibrosis; CHD, congenital heart disease; CLD, chronic lung disease; GA, gestational age; HA, hospitalizations avoided; ICER, Incremental cost-effectiveness ratio; LYG, life years gained; OECD, Organisation for Economic Co-operation and Development; PPP, purchasing power parity; QALY, quality-adjusted life year; RSV, respiratory syncytial virus; RSVH, respiratory syncytial virus hospitalization; PVZ, palivizumab; UK, United Kingdom; US, United States; USD, United States dollar; wGA, weeks gestational age (GA)

Table of Contents Summary: This systematic review investigates the cost-effectiveness of palivizumab prophylaxis for respiratory syncytial virus, stratified by setting and infant population subgroups relevant to health policy decision-making.

EXECUTIVE SUMMARY

Background: Palivizumab (PVZ) prophylaxis is used as passive immunization for respiratory syncytial virus (RSV). However, due to its high acquisition costs, the value of this intervention is unclear. The objective of this study was to systematically review the cost-effectiveness of PVZ prophylaxis compared to no prophylaxis in infants under 24 months of age.

Methods: The systematic review followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Three databases were searched: Medline, Embase, and the Cochrane Library for terms related to RSV, PVZ, cost-effectiveness, health economics, and economic evaluations. The following were included: economic evaluations (e.g., cost-benefit, cost-effectiveness, and cost-utility analyses) conducted from Organization for Economic Co-operation and Development (OECD) countries, published between 2000 and 2018. Quality appraisal was completed using the Joanna Briggs Institute checklist for economic evaluations. Costs were adjusted to 2017 Canadian dollars (CAD), using purchasing power parity and inflation rates. Results were stratified based on outcomes used, study perspective and other risk factors (e.g., prematurity, chronic lung disease, and congenital heart disease) for RSV. Parameters affecting cost-effectiveness were summarized.

Results: A total of 28 economic evaluations met the inclusion criteria, of which 20 were cost-utility analyses, and 8 studies were cost-effectiveness analyses. Most studies were conducted in the United States (n=6), Canada (n=5), Netherlands (n=3), the United Kingdom (n=3) and Spain (n=3). Overall, included studies were considered good to high quality; 23 studies met over 80% of the checklist criteria. PVZ prophylaxis ranged from being a dominant strategy (i.e., less costly and more effective) to having an incremental cost-effectiveness ratio (ICER) of \$2,975,489/quality-adjusted life years (QALY) depending on the study setting, perspective, population (risk factors, weeks GA at birth), and key model input parameters such as reduction in RSV hospitalizations (39%-96%), RSV-related mortality (1%-8.1%), and PVZ costs (\$1,099-\$2,198 per 100-mg vial). From the payer perspective, the cost-effectiveness of PVZ prophylaxis was estimated for infants born prematurely at 29 to 35 weeks GA (ICER: \$6,216/QALY to \$938,623/QALY, n=21), with 82% of estimates below \$50,000/QALY. The top 3 influential parameters reported were: reduction in RSV hospitalization (RSVH) rates, PVZ cost, and the discounting rate.

Conclusions: Cost-effectiveness results of PVZ as a RSV prophylaxis were heterogeneous across studies, ranging from being dominant (i.e., less costly and more effective) to highly not cost-effective. Results varied due to study setting, population of interest, local RSV epidemiology, and healthcare setup, as well as key model parameters such as reduction in hospitalization rates, RSV acquisition costs, dosage schemes and vial usage. Palivizumab may be considered cost-effective in specific subgroups: infants with bronchopulmonary dysplasia / chronic lung disease, infants with congenital heart disease, term infants from specific remote communities with high baseline RSVH rates, and preterm infants with and without lung complications. No overall trends were detected between GA thresholds and cost-effectiveness results. No trends were seen either when stratified by perspective.

I. INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of lower respiratory tract infections in infants and young children worldwide ¹. It is a ubiquitous virus that nearly 100% of infants will contract within 2 years after birth ²⁻⁴. RSV is seasonal respiratory infection that is a significant cause of morbidity and mortality, with the virus estimated to cause up to 90% of pediatric bronchiolitis hospitalizations and up to 50% of pediatric hospitalizations for pneumonia ^{1,5}. Risk factors for severe RSV in infants include: preterm birth, congenital heart disease (CHD), bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD), cystic fibrosis (CF), Down syndrome, and a weakened immune system ⁶⁻⁸.

Although there is currently no vaccine available to prevent RSV infection, since 1998, passive prophylaxis has been available with palivizumab (PVZ) ⁹. PVZ is a humanized murine monoclonal antibody administered monthly as an intramuscular injection, and has shown a significant reduction in overall rate of RSVH infection ¹⁰. However, due to its high acquisition costs, there has been considerable debate surrounding the cost-effectiveness of this intervention. Since 2000, 8 reviews have summarized the cost-effectiveness of PVZ, of which half were completed over 10 years ago ¹¹⁻¹⁴. A recent study by Andabaka *et al.* in 2013 reported that the economic evaluation results are inconsistent across studies, ranging from highly cost-effective to not cost-effective depending on the scenario ¹⁵.

The objective of this study was to provide an update on the cost-effectiveness of PVZ passive immunization for prevention of RSV in infants and children up to 24 months of age, and where possible, to stratify results by risk populations to inform policy decisions for these groups. Economic evaluations conducted in high income countries from the Organization for Economic Co-operation and Development (OECD) after the year 2000 were included in order to limit heterogeneity in population baseline health, healthcare systems and quality of care. This review provides a much needed update to support health policy decision-making for PVZ prophylaxis with particular emphasis on cost-effectiveness results according to GA at birth for preterm infants, which has historically been an area of clinical and policy uncertainty ¹⁶⁻¹⁸.

II. METHODS

This systematic review was completed to inform the National Advisory Committee on Immunization's evidence-informed recommendations on PVZ prophylaxis for RSV, which are presented in the NACI Statement entitled "Recommended Use of Palivizumab to Reduce Complications of Respiratory Syncytial Virus Infection in Infants" published on June 1, 2022. The original systematic review was published in the journal of Pediatrics in 2019¹⁹. For the purposes of this NACI supplement, changes were made to the reporting and discussion of the original review to meet the needs of NACI's decision-making, including having currency reported in CAD, a section on Canadian studies, alternate subgroups reported, and additional commentary.

II.1 SEARCH STRATEGY

The systematic review followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (**Appendix 1**)²⁰. The search strategy was developed with a Public Health Agency of Canada librarian (LG). The scientific literature search included English and French language studies published in 3 electronic databases: Medline and E-pub Ahead of Print, In-Process & Other Non-Indexed Citations (Ovid interface), Embase (Ovid interface), and the Cochrane Library, which included the Health Technology Assessment Database (HTA), National Health Service Economic Evaluation Database Economic Evaluation Database (NHS EED) and Database of Abstracts of Reviews of Effects (DARE). The search used medical subject headings and text words related to the following concepts: respiratory syncytial virus, palivizumab, economic evaluations, and cost-effectiveness. The primary search strategy was developed in Medline and adapted to other databases for account for database-specific vocabulary and functionality. A complete list of search terms and the full search strategy for Medline are summarized in **Appendix 2**. Reference lists were manually searched from relevant articles and systematic reviews.

II.2 ELIGIBILITY CRITERIA

The protocol and eligibility criteria for studies are published on PROSPERO (CRD42018104977). The following were included: full economic evaluations (e.g., cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis) comparing palivizumab prophylaxis for RSV to any comparator (e.g., no prophylaxis) for infants up to 24 months of age, based on current NACI guidelines²¹. Economic evaluations were included if they were conducted in OECD countries between 2000 and 2018 (the time the review was conducted), and reported outcomes related to an incremental ratio of cost per unit of effect (e.g., cost per quality-adjusted life year (QALY), cost per cases avoided, cost per life year gained (LYG), and cost-benefit ratio). Cost-minimization studies, cost-of-illness studies, and budget impact analyses were excluded. Studies conducted outside of the OECD countries, studies published in a language other than English or French, and studies published prior to 2000 were also excluded.

II.3 DATA EXTRACTION AND ANALYSIS

All levels of screening, data extraction and quality appraisal were completed in duplicate. Conflicts were discussed and resolved through consensus. Data extraction was guided by CHEERS (Consolidated Health Economics Evaluation and Reporting Statement)²². The following were collected: study characteristics (publication year, country, study design, study perspective, time horizon, discounting, primary and secondary outcomes, use of cost-effectiveness thresholds, funding sources), study population characteristics (age range,

GA, health conditions, setting), key parameters (RSV incidence/hospitalization rates, mortality rates, sequelae, cost of PVZ, number of doses), and results (base-case incremental cost-effectiveness ratios (ICER), scenario analyses, type of sensitivity analysis, and influential parameters). The quality of included studies were assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Economic Evaluations ²³. A study was “high-quality” if it met over 80% of the JBI checklist criteria ²⁴. The World Health Organization checklist for immunization programmes to assess economic evaluations was not used since PVZ is not considered a vaccine.

Study and population characteristics were summarized descriptively. Cost-effectiveness outcomes were adjusted to 2017 CAD using purchasing power parity (PPP) rates from the OECD ²⁵ and inflation rates from the Bank of Canada. Unadjusted and adjusted ICERs were summarized. In this supplement, currency was not updated to the year 2022 to retain the prices upon which NACI had deliberated upon. Subgroup analyses were conducted to summarize the cost-effectiveness for studies conducted from a Canadian perspective, and studies reporting cost-effectiveness in costs/QALY for preterm infants. For studies that included preterm infants, ICERs were stratified based on GA at birth (weeks) and plotted to visually identify the spread of ICER estimates and possible trends related to GA. The number of estimates and the proportion of them being cost-effective at various thresholds were summarized. Meta-analysis of cost-effectiveness was not appropriate due to the heterogeneity of the study setting, model designs, parameters used, population, and perspective taken in the studies.

III. RESULTS

III.1 STUDY CHARACTERISTICS

The systematic literature search identified 237 unique records, of which 30 met the eligibility criteria and were included in this review (**Figure 1**)^{14,26–54}. Conclusions from 2 studies^{33,53} were updated using more recent data^{34,41}; hence, only the more recent studies were included in this review. The 28 studies included were published between 2000 and 2018, with most conducted from the United States (US) (n=6), Canada (n=5), Netherlands (n=3), United Kingdom (UK) (n=3), and Spain (n=3). The rest of the studies were conducted from: Austria (n=2), Germany (n=2), Italy (n=1), Mexico (n=1), New Zealand (n=1), and Sweden (n=1). Study characteristics are summarized in **Table 1**.

Of the 28 economic evaluations (20 cost-utility analyses, 8 cost-effectiveness analyses), 23 studies used decision-tree models, 4 used Markov cohort models, and 1 conducted a microsimulation. Two economic evaluations were piggy-backed with a clinical trial, and the rest were considered model-based. All studies conducted deterministic sensitivity analysis; 15 studies conducted probabilistic sensitivity analyses.

III.2 QUALITY APPRAISAL

Most studies (83%) met over 80% of the JBI quality appraisal checklist criteria (**Appendix 3**). The 2 checklist items that were least met were: (1) whether the study results included all issues of concerns to users (39%); and (2) whether all relevant costs and outcomes were identified (75%). Overall, studies included in this review were considered relatively high-quality (**Figure 2**).

III.3 STUDY POPULATION

In 14 studies, the chronological patient age was explicitly reported to be <24 months, while the other 14 studies were assumed to assess the cost-effectiveness of PVZ in infants <24 months of age based on their respective country guidelines on PVZ use. High-risk infant populations were often studied, and in some cases overlapped: preterm infants (\leq 35 weeks gestational age, wGA) (n=19), BPD or CLD (n=13), CHD (n=11), and other risk factors (n=6).

III.4 STUDY OUTCOMES

Base-case analyses were almost equally conducted from a societal perspective (n=13) or health system payer perspective (n=15). Eight of the 15 payer perspective studies performed additional analyses from a societal perspective. Time horizon ranged from 6 months to lifetime, and 1 study⁵⁰ did not report a time horizon (**Table 1**). Discount rates ranged between 3% and 5%; 5 studies did not discount due to time horizon of 1 year or less^{26,35,36,47,48}, and 3 studies did not report a discount rate^{43,50,51}. The majority of studies were industry sponsored (n=17, 61%). Cost-effectiveness was reported as ICERs, mostly represented as the incremental cost per additional QALY (n=20) and cost per hospitalization avoided (HA) (n=6). For the remainder of this review, results are reported as adjusted ICERs (2017 CAD); original unadjusted ICERs are summarized in **Table 2**.

III.5 ECONOMIC EVALUATIONS WITH OUTCOMES EXPRESSED IN COST PER QALY

For studies reporting cost-effectiveness in incremental cost per QALY units, **Table 3** summarizes the number of estimates, the ICER ranges, and proportion of estimates under selected thresholds of \$50,000/QALY to \$200,000/QALY, stratified by population subgroups and study perspective. From a health system payer perspective, there were 22 variable cost-effectiveness estimates for preterm infants, ranging between \$6,216/QALY and \$938,623 per QALY^{14,29–31,34,38,39,41,49}. The subgroups with the next highest number of estimates were preterm infants with risk factors (n=14)^{27,39,41,42} where the ICER was between \$215/QALY and \$205,563/QALY, infants with CHD (n=10)^{14,29,31,32,34,37} where the ICER was between \$11,668/QALY and \$164,946/QALY, and infants with BPD/CLD (n=6)^{29,31,34,37,49} where the ICER was between \$4,786/QALY and \$46,821/QALY. At a \$100,000/QALY threshold, 86% of estimates for preterm infants, 86% of estimates for preterm infants with risk factors, 90% of estimates for infants with CHD, and 100% of estimates for infants with BPD/CLD were considered cost-effective. Other risk factors considered in preterm infants included chronological age at the beginning of the RSV season, school age siblings, day-care attendance, smoking during pregnancy, male sex, and CF (in term infants only)^{27,39,41,44,54}. From a societal perspective, PVZ prophylaxis was considered a dominant strategy (i.e., less costly and more effective) in some instances for preterm infants^{30,44,54}, term infants (with and without other risk factors)⁴², and infants with CHD³¹.

III.6 ECONOMIC EVALUATIONS WITH OUTCOMES EXPRESSED IN COST PER HOSPITALIZATION AVOIDED

There were 6 studies that reported cost-effectiveness as cost per hospitalization avoided (HA)^{14,26,35,36,43,50}, of which 3 were industry funded^{26,36,43}. The study by Banerji *et al.* studied healthy term infants from a payer perspective in different regions of the Canadian Arctic, and compared 2 scenarios of PVZ prophylaxis for infants who were <6 months of age. The ICER for PVZ prophylaxis ranged from being dominant (in specific Arctic regions) up to \$593,250/HA in the Northwest Territories²⁶. Also from the payer perspective, Hampp *et al.* was conducted in a Florida (US) setting, and studied cost-effectiveness in preterm infants (<32 wGA) and term infants with CHD, CLD and combinations of all 3 risk factors. The ICERs were between \$413,127/HA (preterm infants) and \$2,924,911/HA (healthy term infants without CLD or CHD)⁵⁰.

From a societal perspective, the study by Rietveld *et al.* in 2010 from southwest Netherlands studied preterm infants (< 28 wGA) with additional risk factors (male sex, birth weight < 2,500 grams, and BPD). The ICER ranged between \$24,875/HA and \$1,572,268/HA depending on the month of the prophylaxis. PVZ prophylaxis had the lowest ICER) during the month of December while October had the highest ICER (indicating poor value for money). This study recommended a restricted immunization policy based on their results³⁵. Roeckl-Wiedmann *et al.* conducted a study in 2003 from southern Germany on preterm infants (<35 wGA) with additional risk factors. ICERs ranged between \$11,821/HA and \$364,462/HA for preterm infants with CLD and preterm with risk factors (male, no CLD, no siblings in school), respectively. This study also recommended a restricted use of PVZ in preterm infants with CLD³⁶. In New Zealand, Vogel *et al.* studied preterm infants (<28, 29-31 wGA) and infants with CLD. The ICER ranged between \$33,376/HA for preterm infants discharged home on oxygen and \$193,859/HA for preterm (29-31 wGA) infants with CLD. The authors concluded that the intervention was more cost-effective for preterm infants discharged home on oxygen, followed by preterm infants of 28 weeks' gestation or less⁴³.

III.7 ECONOMIC EVALUATIONS WITH OUTCOMES EXPRESSED IN OTHER RATIOS

Three studies reported cost-effectiveness of PVZ prophylaxis in other units: cost to prevent 1 day of hospitalization⁵¹, cost per life-year gained (LYG)⁵², and cost per RSV infection episode avoided⁴⁷. Two of 3 studies conducted analyses from a societal perspective^{51,52}. Harris *et al.* conducted an economic evaluation on term infants with CHD in western Canada. The base-case ICER was \$18,155 per 1 day of hospitalization prevented⁵¹. Hascoet *et al.* studied preterm infants (< 32 wGA) with BPD and infants with significant CHD in France. The base-case ICER was \$43,856 per LYG and \$33,450/LYG for preterm infants with BPD, and preterm infants with cardiopathy (CHD), respectively. Originally, this study used a cost-effectiveness threshold (unadjusted) of 45,000 Euros/LYG, and considered prophylaxis cost-effective for both subgroups in France⁵². Lastly, a study by Lofland *et al.* studied preterm infants with CLD in the US. Their model used a reduction in incidence of RSV infection instead of a hospitalization reduction approach, ranging from 50% (\$66,494 per RSV infection episode avoided) to 83% reduction, where PVZ prophylaxis was considered a dominant strategy (i.e. less costly and more effective)⁴⁷.

III.8 ECONOMIC EVALUATIONS FROM A CANADIAN SETTING

From a Canadian setting, there were 5 studies included in this review^{26,27,41,42,51}. Three studies investigated cost-effectiveness of PVZ in term infants (1 with CF²⁷, 2 in Canadian Arctic settings)^{26,42}, 1 in preterm infants⁴¹, and 1 in infants with CHD⁵¹. Most studies used a lifetime horizon (60%), reported outcomes from a healthcare payer perspective (80%), in units of cost/QALY (60%), conducted scenario analysis (100%), and deterministic sensitivity analysis (100%). The study on term infants with CF by McGirr *et al.*, was the only study not funded by industry²⁷.

These studies assumed 4.5 to 6 doses of PVZ per RSV season at a cost of \$1,599 - \$1,718 (2017 CAD) per 100mg of PVZ. The effectiveness of PVZ was measured in reduction in RSVH, which ranged between 42% and 96%. Mortality rates were incorporated into only 2 models, at 1% and 8.1%^{41,42}. Sequelae was incorporated into 2 models (1 related to RSV, one associated with CF)^{27,41}. Study characteristics and conclusions are summarized in **Table 4**.

Overall, 4 of the 5 studies concluded that the use of PVZ passive immunization was cost-effective based on their models and target population^{26,41,42,51}. Tam *et al.* considered PVZ as cost-effective for all Baffin Island infants < 1 year chronological age (\$46,151/QALY), infants at high-risk for RSV (\$391/QALY), infants from remote areas (\$28,965/QALY), infants < 6 months of age from remote areas, or remote areas with high rates of RSV (dominant—that is, less costly and more effective). However, when compared to a \$100,000/QALY threshold, it was not cost-effective for infants < 6 months, or infants < 1 year of age residing in Iqaluit⁴². Similarly, Banerji *et al.* concluded that their proposed PVZ programs would be cost-effective in some but not all Arctic regions. Both studies attribute the likelihood of these results to the high costs of hospitalizations in these regions^{26,42}. From the payer perspective, PVZ was considered cost-effective for preterm infants (\$35,119/QALY)⁴¹, while from a societal perspective, PVZ yielded an ICER of \$18,155/day of HA in the study by Harris *et al.* Although no cost-effectiveness threshold was used, Harris *et al.* concluded that PVZ prophylaxis was likely cost-effective⁵¹. PVZ for high-risk infants with CF was determined to unlikely be cost-effective (\$167,107/QALY)²⁷.

The most influential parameters in the 5 Canadian studies were: RSVH rates ^{26,42}, cost of palivizumab ^{27,51}, and cost for hospitalization ^{26,42}, which includes inpatient medical costs and transportation costs to the medical centre.

III.9 COST-EFFECTIVENESS IN PRETERM INFANTS

The cost-effectiveness of PVZ prophylaxis compared to no PVZ prophylaxis ranged widely. Some studies found PVZ to be a dominant strategy (i.e., less costly and more effective than no PVZ), whereas one study found an ICER of \$2,975,489/QALY in preterm infants. Since studies estimated cost-effectiveness for varying ranges of wGA, not all estimates could be grouped into pre-defined intervals. For example, <29 wGA estimates were not grouped under the <32 wGA estimates as the breakdown of the wGA in each preterm group could not be inferred, or reasonably assumed. From the payer perspective, the ICER for PVZ prophylaxis for infants born < 29 wGA (n=3) ranged between \$6,216/QALY and \$24,009/QALY ^{37,38}. For infants born 29-32 wGA, the ICER (n=3) ranged between \$9,989/QALY and \$58,872/QALY ^{37,38}. At < 32 wGA and < 33 wGA, 2 estimates (\$12,710/QALY to \$25,065/QALY) ³⁰, and 3 estimates (\$16,434/QALY to \$42,730/QALY) were identified, respectively ^{34,49}. In the 32-35 wGA range (includes 2 estimates at 32-35 wGA and 4 estimates at 33-35 wGA), there were 6 ICER estimates for preterm infants (\$26,170/QALY to \$919,073/QALY) ^{34,37,39,41,49}, and 14 ICER estimates for preterm infants with additional risk factors (\$215/QALY to \$205,563/QALY) ^{39,41}. For preterm infants born < 35 wGA, there were 5 estimates between \$30,650/QALY and \$938,623/QALY ^{14,29,31,34}. In subgroup analyses of preterm infants born <35 wGA with BPD/ CLD, 4 estimates ranged between \$15,202/QALY and \$131,874/QALY ^{14,29,31,49}.

From a societal perspective, estimates of preterm infants born at 26-28 wGA were entirely extracted from El-Hassan *et al.* with ICERs between \$165,301/QALY and \$2,406,619/QALY ⁴⁶. For preterm infants born < 29 wGA, there were 5 ICER estimates between \$22,765/QALY and \$1,359,641/QALY ²⁸. PVZ cost-effectiveness from a societal perspective varied across studies for preterm infants born between 29 and 35 wGA, with ICER estimates between \$449,264/QALY and \$1,083,976/QALY (29-30 wGA) ⁴⁶, being a dominant strategy (i.e., less costly and more effective for < 32 wGA) ^{30,44,54}, \$32,390/QALY and \$338,823/QALY (32-35 wGA) ^{39,48}, and \$25,678/QALY and \$983,064/QALY (<35 wGA) ^{14,34}. In preterm infants (< 35 wGA) with lung complications, 3 studies reported separate ICER estimates between \$18,717/QALY and \$138,282/QALY ^{14,29,31}. Six estimates were reported for preterm infants with risk factors between \$21,931/QALY and \$635,172/QALY (\$21,931/QALY to \$61,229/QALY for 2 32-34 wGA estimates, \$52,299/QALY to \$635,172/QALY for 4 32-35 wGA estimates) ^{44,54}.

ICERs were stratified and plotted for PVZ prophylaxis expressed in cost/QALY in preterm infants by wGA and **Figure 3** presents 57 of 72 ICER estimates, stratified by study perspective, that were estimated under \$200,000/QALY ^{14,28-31,33,34,37-39,41,44,46,49,53,54}. In **Figure 3**, 50 of the 56 (89%) ICER estimates for preterm infants (with or without other health conditions) were below the \$100,000 per QALY threshold. Of the 16 ICER estimates excluded from Figure 3, 8 (i.e., half of all estimates) were from a single study by El-Hassan *et al.* ⁴⁶. while the rest were single estimates from other studies ^{28,37,41,44,48,54,55}.

III.10 KEY MODEL PARAMETERS

Reduction in RSVH used in models ranged between 39% for infants with CLD in the UK ³⁷, and 96% in healthy infants in a Canadian Arctic setting ²⁶. Mortality was reported in 19 studies, ranging between 1% ^{42,52} and 8.11% ³⁴ for various infant populations. Number of PVZ doses per season were between an average of 3.88 doses in a 5-month season in Spain ³⁹, and 6 doses in a 6-month RSV season in the Canadian Arctic ²⁶. Most studies evaluated cost-effectiveness assuming 5 PVZ doses per RSV season (n=17), while 3 studies did not report the

dose schedule^{37,48,50}. The cost of a 100-mg vial of PVZ in 2017 CAD ranged between \$1,099 (from UK study)³⁷ and \$2,198 (from US study)⁴⁶.

III.11 INFLUENTIAL PARAMETERS

The most influential parameters reported across the 28 studies (**Figure 4**) were: RSVH rates (43%)^{26,29,31,32,35-37,41,42,44,50,54}, cost of PVZ (36%)^{27,32,35,36,44,46,47,50,51,54}, discount rate (32%)^{28-32,34,37,38,40}, and efficacy of PVZ (29%)^{35-37,43,44,48,50,54}. Other parameters that were influential in multiple studies included: mortality rate reduction, incidence of RSV (and/or sequelae), drug wastage resulting from vial usage, utility values (health-related quality of life) and dosage scheme.

IV. DISCUSSION

IV.1 SUMMARY OF RESULTS

The systematic review identified 28 relevant economic evaluations from OECD countries assessing the cost-effectiveness of PVZ prophylaxis compared to no prophylaxis. The most cost-effectiveness estimates were for preterm infants, consistent with their higher risk for RSV^{6,8}. Almost all categories of infants (term, preterm, with and without additional risk factors) had a majority (>50%) of their cost-effectiveness estimates below the \$100,000/QALY threshold. The only exception to this was the estimates for preterm infants from the societal perspective, where only 48% of the estimates were below \$100,000/QALY. This exception was likely a result of a large group of estimates (n=8, 35% of all for this subgroup) extracted from one study that were between \$347,803/QALY and \$2,975,489/QALY⁴⁶. Possible reasons for the higher ICERs in this study may be having used the highest adjusted cost for a 100-mg vial of PVZ at \$2,198, following infants only up to 8 years of age, and as suggested by the authors, overestimating the impact of subsequent asthma onset on health-related quality of life (utility). Sensitivity analysis reducing the PVZ cost by 25%, or reducing the impact of asthma on utility afforded ICERs under \$200,000/QALY (USD), and under \$100,000/QALY (USD), respectively⁴⁶.

Based on this review, PVZ prophylaxis cost-effectiveness varies depending on the population and setting. In order to facilitate comparisons and summarize the findings, all ICERs were adjusted to 2017 CAD per QALY, and stratified based on GA at birth and risk-factors for RSV in **Figure 3**. For term and preterm infants with BPD/CLD, the ICER was under \$50,000/QALY in 9 of the 10 estimates from a payer perspective. All other subgroups of infants (term, preterm, CHD, other risk factors) resulted in inconsistent results for PVZ prophylaxis with the intervention being dominant at times (i.e., less costly and more effective), and having an ICER up to \$938,623/QALY in other scenarios. When stratifying for preterm births by wGA, evidence was lacking for infants born < 28 wGA, especially from the payer perspective. No specific trend was depicted between the wGA and the ICER, overall or stratified by perspective. However, while preterm estimates were available across 26-35 wGA, preterm infants with additional risk factors or BPD/CLD were limited to 33-35 wGA. Generally, one would expect ICERs from a societal perspective to be lower than those from a payer perspective, but based on this review, this trend does not exist for 2 reasons: 1) payer and societal perspective estimates were coming from different studies and; 2) due to the heterogeneity in model designs and differences between setting-specific costs, and RSV epidemiology.

IV.2 ECONOMIC EVALUATIONS FROM A CANADIAN SETTING

There were 5 economic evaluations conducted from a Canadian setting. While 4 of 5 studies used a healthcare payer perspective, the time horizon, discount rate and cost-effectiveness outcome report varied. Populations were different between all studies: term infants with CF, term infants from the Canadian Arctic, preterm infants, and infants with CHD. The studies by Tam *et al.* and Banerji *et al.* similarly concluded that PVZ prophylaxis was cost-effective for most subgroups of infants in the Canadian Arctic due to high costs of hospitalizations (e.g., transportation). Study conclusions from Tam *et al.* were for Baffin region infants, while Banerji *et al.* included populations from 8 Arctic regions: the Northwest Territories, Nunavut, Nunavut without Iqaluit, the 3 sub-regions of Nunavut (Kitikmeot, Kivalliq and Qikiqtaaluk), the Qikiqtaaluk Region without Iqaluit, and Nunavik (northern Quebec). Both studies were conducted from a healthcare payer perspective, used similar PVZ costs (\$220 - \$226 per kilogram weight of the infant, original cost). Given the study populations, clinical settings, and costing of drugs and resources, the studies by Tam *et al.* and Banerji *et al.* can be considered generalizable to other territories or remote areas in Canada for infants at high-risk for RSV.

The remaining 3 studies are also considered generalizable to most Canadian provinces given that they used similar PVZ costs (\$1,468 - \$1,505 per 100 mg vial, original costs) available to Canadian provinces, used dosing schedules close to 5 injections per season (4.5 to 5.39 vials per season), used healthcare costs from British Columbia and Ontario, and included model parameters of relevance to the Canadian healthcare system. While there was evidence for varying subpopulations from large provinces and territories, cost-effectiveness of PVZ prophylaxis for infants from smaller Canadian provinces (e.g., Maritimes provinces) were lacking.

IV.3 HETEROGENEITY IN RESULTS: KEY PARAMETERS

Since PVZ prophylaxis was determined to be cost-effective in some settings but not cost-effective in others, this review summarized the most frequently reported influential parameters affecting the ICER. They included RSVH rates and cost of PVZ used. Reduction in RSVH varied drastically between 39% and 96% depending on the population of interest and the data source. The cost of a 100mg vial of PVZ also ranged between \$1,099 and \$2,198 (2017 CAD). Both parameters' influential nature was expected given the reduction in RSV and RSVH is essential to reduction in costs, and future sequelae, while the costs of PVZ is directly related to the ICER. However, it was interesting to note that vial usage and dosage scheme only affected the ICER in 4^{29,30,40,43}, and 3 studies^{39,43,49}, respectively.

In studies addressing drug wastage through vial usage, ICERs fluctuated up to 50% depending on the assumed vial usage. In a New Zealand study, assuming no vial sharing (entire 100mg vial is used per injection) increased costs of up to 50%⁴³, while another study in Spain concluded a lower ICER when 50-mg vials were used instead of 100mg³⁰. It has been suggested in the literature and by physicians that vial usage efficiency can be achieved for PVZ⁵⁶. Many studies did not assess scenarios in which the vial usage becomes more efficient or the number of assumed doses is reduced, which remains a question that should be addressed in future studies.

IV.4 COMPARISON TO THE LITERATURE

The cost-effectiveness of PVZ prophylaxis has been explored in multiple reviews in the past 2 decades^{11,12,14}, but only 4 have been published between 2010 and 2013^{15,57-59}. These results and conclusions are consistent with other reviews, and are most comparable to a systematic review by Smart *et al.* published in 2010, where

the authors reported a range of ICERs (in 2009 CAD) for PVZ prophylaxis: from being dominant (i.e., less costly and more effective), up to being \$3,365,768/QALY depending on the study population, outcomes, and model parameters⁵⁹. This present work added onto the Smart review by capturing studies from 2010 to mid-2018, but limited the scope to OECD countries, and adjusted for inflation differences by using the PPP rates from the OECD. Reviews by Andabaka *et al.* and Prescott *et al.* similarly concluded that cost-effectiveness of PVZ was inconsistent^{15,58}. Hussman *et al.* conducted a review on RSV prophylaxis overall and included studies comparing PVZ and other interventions (e.g., Respiratory syncytial virus immune globulin (RSV-IGIV)⁵⁷. This present review is the first to update PVZ prophylaxis cost-effectiveness compared to no prophylaxis since the 2014 American Academy of Pediatrics (AAP) guideline update⁶⁰.

IV.5 GENERALIZABILITY OF INCLUDED STUDIES TO CANADIAN SETTING

Most study results may be broadly generalizable to the Canadian healthcare system since the eligibility criteria screened for economic evaluations conducted from OECD countries, of which all members except for the US and Switzerland have healthcare components similar to Canada⁶¹. The only exception were the 6 studies from the US. The remaining studies from the Netherlands, UK, Spain, Austria, Germany, Italy, New Zealand and Sweden have public system financing in parts by general tax revenue⁶¹. However, choice of payer or societal perspective may influence the included costs in the analysis. For example, cost-effectiveness from a societal perspective includes possible indirect, out-of-pocket, or productivity loss costs, which can vary across different countries regardless of healthcare system financing.

From 3 Canadian studies, the cost per 100-mg vial of PVZ used in models were between \$1,599 and \$1,718 (2017 CAD). Models from the UK used a lower PVZ cost of \$1,099 to \$1,240 per 100-mg vial, and the remaining studies (with the exception of US studies) scattered between \$1,386 and \$2,035 (2017 CAD). The number of doses per season assumed or calculated in these economic evaluations ranged between 3.88 and 6 doses. The Canadian Pediatric Society recommends up to 5 doses of PVZ per season for infants up to 24 months of age⁶². In the subset of countries with similar healthcare structure to Canada, almost all models assumed 5 doses of PVZ per season, except for Resch *et al.* (Austria)³⁴, Banerji *et al.* (Canada)²⁶, Nuijten *et al.*, Sanchez-Luna *et al.*, and Schmidt *et al.* (all from Spain), where the average number of doses was 4 per season^{30,39,40}. Additionally, the RSV risk factors modeled are consistent with those published in the Canadian literature: preterm birth, CHD, BPD/CLD, male sex⁸.

Despite the similarities in PVZ prophylaxis cost and dosage schedule, reduction rates of RSVH varied from 39% to 96% depending on the infant population, and literature referenced. Many studies cited the IMPact-RSV trial for their model parameters, a trial that included Canada and concluded that reduction in RSVH was 78% for preterm infants, 39% for children with BPD/CLD and 55% overall. The subgroup of Canadian subjects in the IMPact-RSV trial reportedly showed a 40% overall reduction in RSVH. The trend was similar to that seen in US (56%), and UK subjects (64%)⁶³. Question 11 of the JBI quality appraisal checklist gauges for transferability in which 2 independent reviewers concluded that 24 of 28 studies were generalizable based on their model attributes (structure, parameters) and reported outcomes. Results from the US may have limited generalizability when evaluating this part of the checklist.

IV.6 STUDY LIMITATIONS

This review has several limitations. Differences in model designs, RSVH rates used, disease progress, perspectives and settings prevented us from providing definitive conclusions on the value of this intervention.

The review attempted to summarize cost-effectiveness of this intervention from 2000 to 2018, but changes in American Academy Pediatrics recommendations in the US (and decision-makers in other respective countries) over time can affect model design and input data. Lastly, the review may be subject to publication and language bias since it did not search the grey literature or include articles not in English or French.

IV.7 STUDY STRENGTHS

Despite these limitations, this review provides a comprehensive summary of the cost-effectiveness of PVZ prophylaxis from OECD countries to inform decision-makers of the estimated value for this intervention in term infants, preterm infants, and infants at high-risk for RSV (e.g., CHD, BPD/CLD). Figure 3 shows all base-case results and scenario analyses, which gives a sense of the number of studies (and estimates) that fall under specific cost-effectiveness thresholds from both payer and societal perspectives. All estimates were standardized to 2017 CAD, which allowed us to group, stratify and compare the cost-effectiveness estimates. These adjusted ICERs should be useful for program decision-makers where costs can be significantly underestimated if not appropriately adjusted.

V. CONCLUSION

Cost-effectiveness results of PVZ as a RSV prophylaxis were heterogeneous across studies, ranging from being dominant (i.e., less costly and more effective) to highly not cost-effective. Results varied due to study setting, population of interest, local RSV epidemiology, and healthcare setup, as well as key model parameters such as reduction in hospitalization rates, RSV acquisition costs, dosage schemes and vial usage. Based on several authors' conclusions, PVZ prophylaxis for RSV may be considered cost-effective in certain subgroups of infants. From a payer perspective, authors concluded PVZ was considered cost-effective in infants with BPD/CLD, infants with CHD, term infants from specific remote communities, and preterm infants with and without lung complications. No overall trends were detected between specific GA thresholds and cost-effectiveness results, overall or stratified by perspective. Among the 2 studies in the Canadian North, authors concluded PVZ was considered cost-effective for some settings where baseline RSVH rates were very high, thus preventing high hospitalization and medical evacuation costs.

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FIGURES AND TABLES

Figure 1. Literature Search and Study Selection

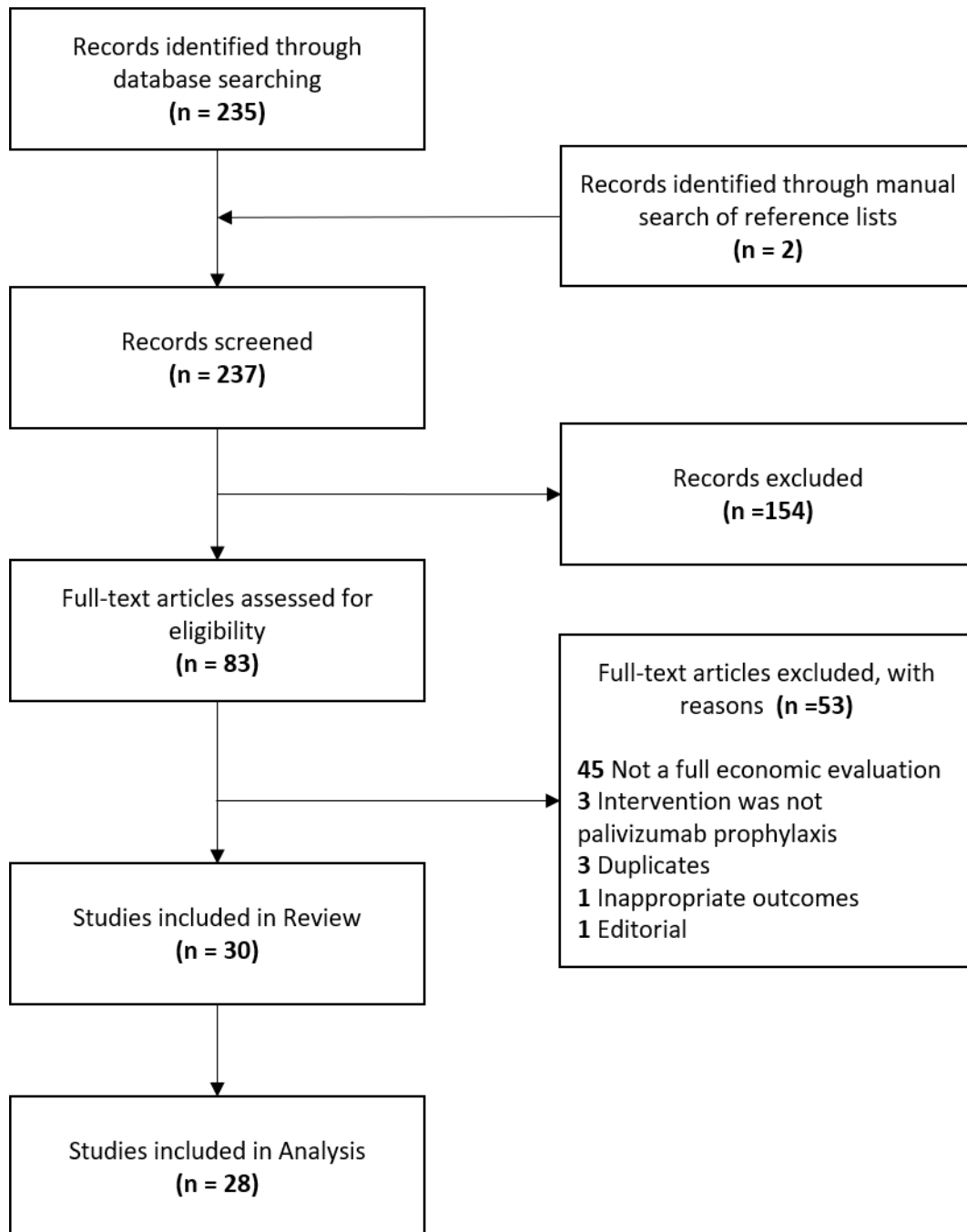


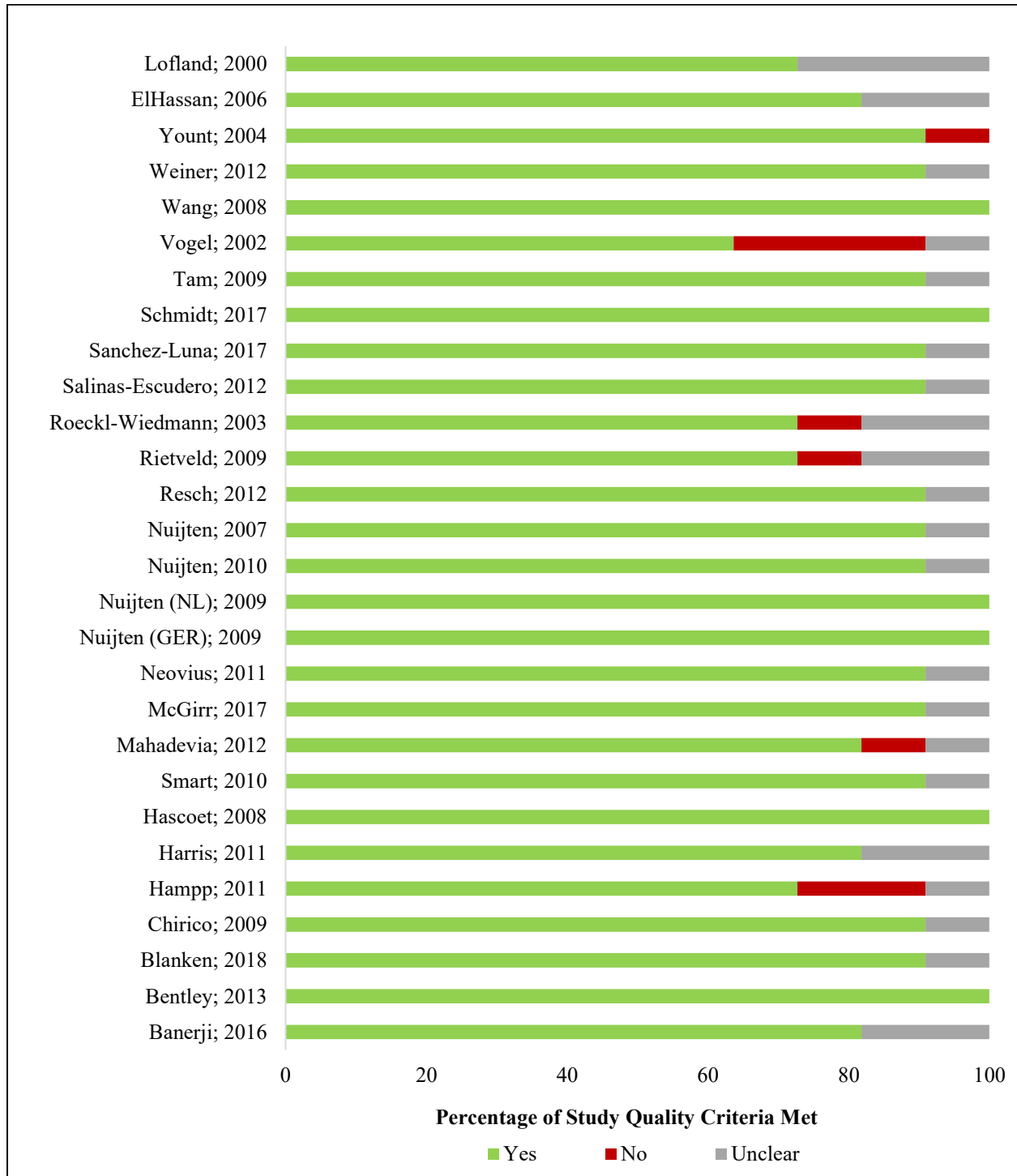
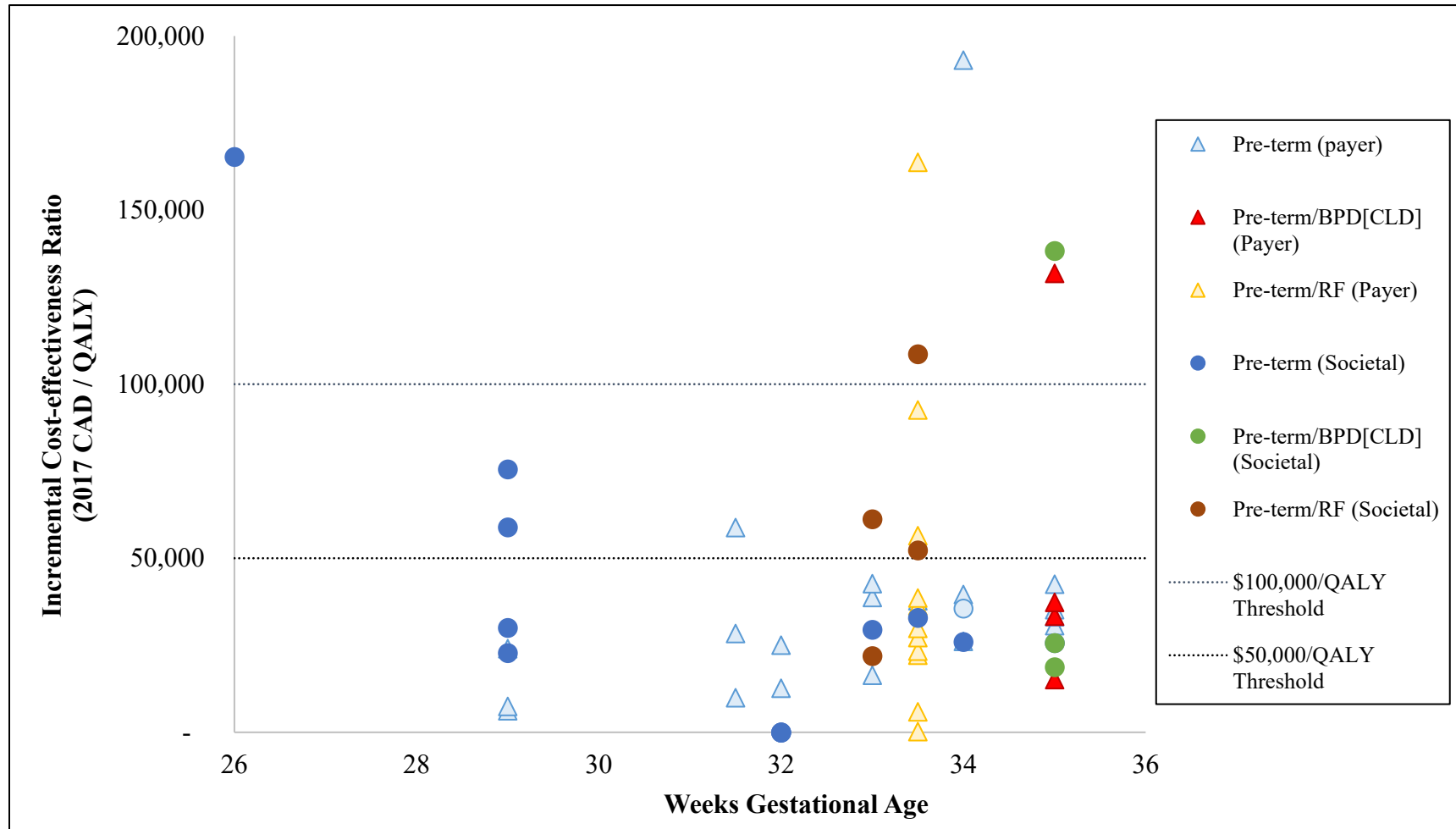
Figure 2. Quality Appraisal Results

Figure 3. Cost-Effectiveness of PVZ in Preterm Infants Where the ICER was Less than \$200,000 per QALY*



* Estimates included (n=56), ICERs > \$200,000/QALY were not captured (n=16). Payer perspective: preterm (32-35 wGA) w/RF: \$205,563/QALY,⁴¹ preterm (<35 wGA): \$938,623/QALY,¹⁴ preterm (32-35 wGA): \$919,073/QALY.⁴¹ Societal: preterm (26 wGA): \$1,331,595/QALY,⁴⁶ preterm (27 wGA): \$2,078,481/QALY,⁴⁶ preterm (28 wGA): \$2,406,619/QALY,⁴⁶ preterm (28 wGA): \$347,803/QALY,⁴⁶ preterm (<29 wGA): \$1,359,641/QALY,²⁸ preterm (29-30w GA): \$1,083,976/QALY,⁴⁶ preterm (29-30 wGA): \$449,264/QALY,⁴⁶ preterm (31w GA): \$1,944,890/QALY,⁴⁶ preterm (32 wGA): \$2,975,489/QALY,⁴⁶ preterm (32-35 wGA): \$338,823/QALY,⁴⁸ preterm (<35 wGA): \$983,064/QALY,¹⁴ preterm (32-35 wGA) w/RF: \$635,172/QALY⁵⁴ and \$385,488/QALY.⁴⁴

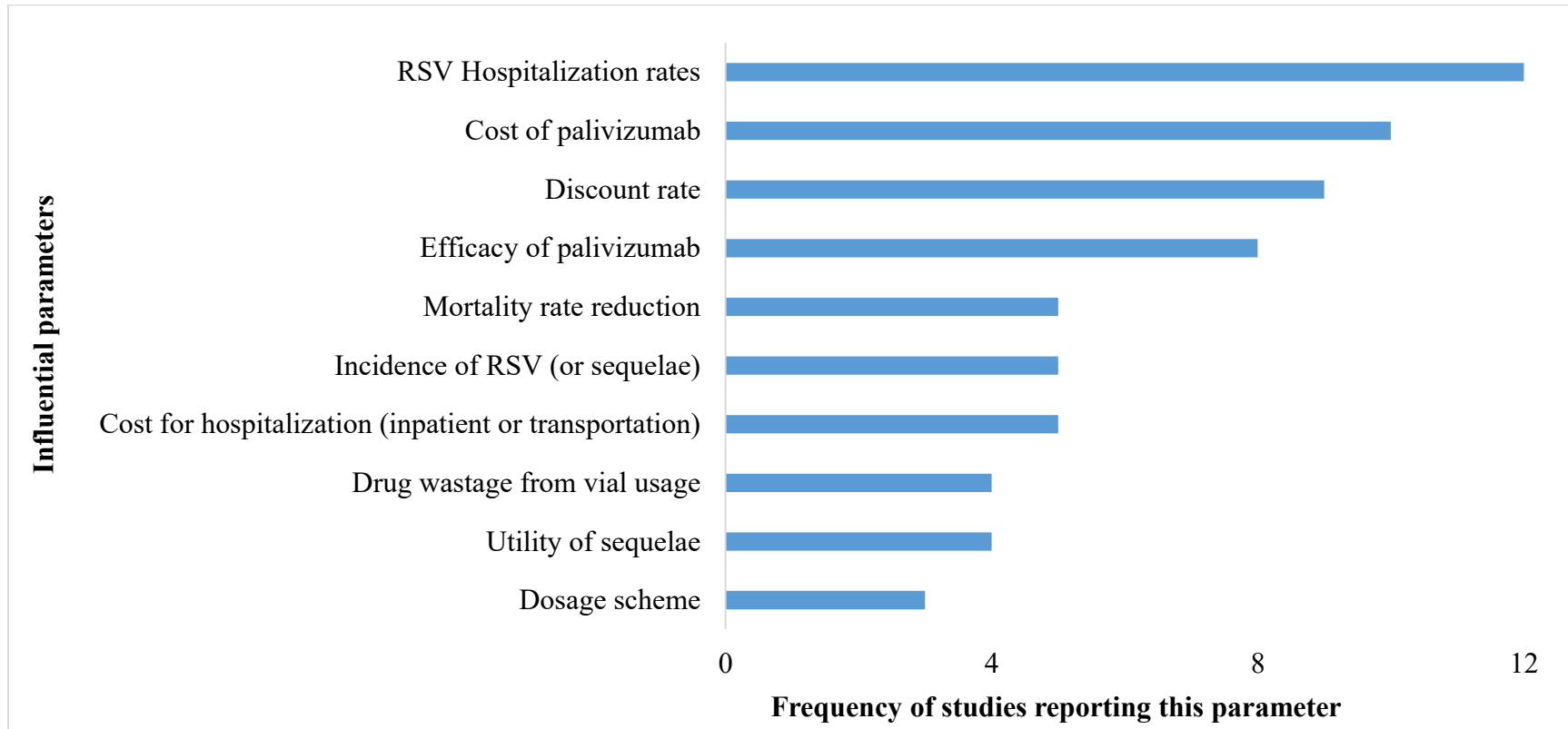
Figure 4. Most Influential Parameters Reported

Table 1. Summary of Study and Model Characteristics

Authors, Year	Country	Perspective	Type of analysis	Piggy-back or model-based?; Type of model	Outcome Measure	Population	Time Horizon	Discount Rate	Industry Funding
Banerji 2016 ²⁶	Canada	Payer	CEA	Model-based; Decision-analysis	Cost per HA	Term infants	6-month	N/Ap	Abbott/MedImmune (Grants)
Bentley 2011 ³⁷	UK	Payer	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm, CHD, CLD infants	Lifetime	3.5%	AbbVie
Blanken 2018 ⁴⁸	Netherlands	Societal	CUA	Piggy-back; Decision-analysis	Cost per QALY	Preterm infants	1-year	N/Ap	Unknown: Grants for investigator-initiated studies from MedImmune and AbbVie
Chirico 2009 ⁴⁹	Italy	Payer	CUA	Model-based; Simulation	Cost per QALY	Preterm, BPD infants	Lifetime	3%	Abbott
ElHassan 2006 ⁴⁶	US	Societal	CUA; CBA	Model-based; Markov cohort	Cost per QALY	Preterm infants without CLD	8 years	3%	None
Hampp 2011 ⁵⁰	US	Payer	CEA	Model-based; Decision-analysis	Cost per HA	Preterm and term infants (both with and without CHD, CLD)	NR	NR	None
Harris 2011 ⁵¹	Canada	Societal	CEA; CBA	Model-based; Decision-analysis	Cost per day of HA	CHD infants	5-year**	NR	Unknown: Honorarium (< \$1,000) from Abbott
Hascoet 2008 ⁵²	France	Societal (BC) and payer	CEA; CBA	Model-based; Decision-analysis	Cost per LYG	Preterm infants with CHD or BPD	Lifetime	3%	Abbott France
Lofland 2000 ⁴⁷	US	Payer	CEA	Piggy-back; Decision-analysis	Cost per RSV infection avoided	Preterm infants with CLD	6 months	N/Ap	MedImmune, Inc.
Mahadevia 2012 ⁵⁴	US	Societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm infants	Lifetime	3%	MedImmune LLC
McGirr 2017 ²⁷	Canada	Payer	CUA	Model-based; Markov cohort	Cost per QALY	Term infants with CF	Lifetime	5%	None
Neovius 2011 ²⁸	Sweden	Societal	CUA	Model-based;	Cost per QALY	Preterm infants	Lifetime	3%	Abbott Scandinavia

				Markov cohort					
Nuijten 2009 ³²	Germany	Societal (BC), and payer	CUA	Model-based; Decision-analysis	Cost per QALY	CHD infants	Lifetime	5%	Abbott
Nuijten 2009 ³¹	Netherlands	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm, BPD, CHD infants	Lifetime	4%, 1.5%**	Abbott GmbH & Co. Germany
Nuijten 2010 ³⁰	Spain	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm infants	Lifetime	3%	Abbott GmbH & Co. Germany
Nuijten 2007 ²⁹	UK	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY; Cost per HA	Preterm, BPD, CHD infants	Lifetime	3.5%	Abbott GmbH & Co. Germany
Resch 2012 ^{33,34}	Austria	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm, BPD, CHD infants	Lifetime	5%	None
Rietveld 2010 ³⁵	Netherlands	Societal	CEA	Model-based; Decision-analysis	Cost per HA	Preterm, BPD infants	1-year	N/Ap	None
Roeckl-Wiedmann 2003 ³⁶	Germany	Societal	CEA	Model-based; Decision-analysis	Cost per HA	Preterm infants with RF	1-year	N/Ap	Abbott Laboratories, Germany.
Salinas-Escudero 2012 ³⁸	Mexico	Payer	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm infants	Lifetime	3%	Abbott Laboratories of Mexico
Sanchez-Luna 2017 ³⁹	Spain	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm infants with RF	6-year	3%	None
Schmidt 2017 ⁴⁰	Spain	Societal	CUA	Model-based; Markov state (Decision-tree structure in first year and Markov structure in later years)	Cost per QALY	CHD infants	Lifetime	3%	AbbVie (Grant)
Smart 2010 ^{41,53}	Canada	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm infants with RF	Lifetime	5%	Unknown: Other relationships with Abbott

Tam 2009 ⁴²	Canada	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY	NR	Lifetime	5%	Abbott Laboratories/ Abbott International (Grant)
Vogel 2002 ⁴³	New Zealand	Societal	CEA; CBA	Model-based; Decision-analysis	Cost per case averted	Preterm, CLD infants	3-year*	NR	Abbott (Grant)
Wang 2008 ¹⁴	UK	Payer (BC) and societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm, BPD, CHD, CLD, term infants with RF	Lifetime	3.5%	None
Weiner 2012 ⁴⁴	US	Societal	CUA	Model-based; Decision-analysis	Cost per QALY	Preterm infants with RF	Lifetime	3%	MedImmune LLC
Yount 2004 ⁴⁵	US	Societal	CUA; CBA	Model-based; Decision-analysis	Cost per QALY	CHD infants	Lifetime	3%	None

BC, base-case; BPD, bronchopulmonary dysplasia; CBA, Cost-benefit analysis; CEA, Cost-effectiveness analysis; CF, Cystic fibrosis; CHD, congenital heart disease; CLD, chronic lung disease; CUA, Cost-utility analysis; LYG, life years gained; N/Ap, not applicable; NR, not reported; QALY, quality-adjusted life years; UK, United Kingdom; US, United States

*Not clearly reported, assumed based on data used for cohorts

** 4% for economic outcomes, 1.5% for clinical outcomes

Table 2. Summary of Study Cost-Effectiveness (Unadjusted and Adjusted to 2017 Canadian Dollars) Outcomes

Author Year	Original Currency, WTP Used	ICER (Original)	ICER (Adjusted, 2017 CAD)	Results (Context)	Sensitivity Analysis	Study Conclusions	
Banerji 2016 ²⁶	CAN 2011; \$50,000 per hospital admission	4,633	5,042	Cost per hospitalization avoided	Scenario B ^a Nunavut without Iqaluit	Deterministic	PVZ was CE in the Kitikmeot and Kivalliq regions and Nunavik. Scenario B (compared to Scenario A) was more CE in all regions except the Kitikmeot region.
		14,545	15,829		Scenario B ^a , Nunavut		
		15,601	16,979		Scenario B ^a , Nunavik		
		22,954	24,981		Scenario A ^p , Kivalliq Region		
		28,580	31,104		Scenario A ^p , Nunavut without Iqaluit		
		30,230	32,899		Scenario A ^p , Nunavik		
		41,404	45,060		Scenario A ^p , Nunavut		
		105,259	114,554		Scenario B ^a , Qikiqtaaluk Region w/o Iqaluit		
		133,407	145,187		Scenario B ^a , Qikiqtaaluk Region		
		166,600	181,311		Scenario A ^p , Qikiqtaaluk Region w/o Iqaluit		
		211,444	230,115		Scenario A ^p , Qikiqtaaluk Region		
		326,441	355,267		Scenario B ^a , NWT		
		545,115	593,250		Scenario A ^p , NWT		
		Dominant	Dominant		Scenario A ^p , Kitikmeot Region		
		Dominant	Dominant		Scenario B ^a , Kitikmeot Region		
Dominant	Dominant	Scenario B ^a , Kivalliq Region					
Bentley 2011 ³⁷	GBR 2010; £20,000 per QALY and £30,000 per QALY	3,845	7,494	Cost per QALY gained	Preterm infants (<29 wGA)	Deterministic ; probabilistic	Prophylactic PVZ represents an economically viable use of NHS resources for infants (aged under 24 months) with CHD, infants (aged under 24 months) with CLD and preterm infants born at 32 wGA or below and preterm infants born 33–35 wGA when additional RF are considered.
		19,168	37,360		CLD infants		
		30,205	58,872		Preterm infants (29-32 wGA)		
		33,216	64,741		CHD Infants		
		99,056	193,068		Preterm infants (33-35 wGA)		
Blanken 2018 ⁴⁸	NLD 2015; €80,000 per QALY	214,748	338,823	Cost per QALY gained	Preterm (32-35 wGA)	Deterministic ; probabilistic	
Chirico 2009 ⁴⁹	ITA 2007; €50,000 per QALY	2,732	4,786	Cost per QALY gained	BPD	Deterministic	Compared with no prophylaxis, PVZ is CE in the prevention of RSV infection among high risk preterm infants.
		8,677	15,202		Preterm (<35 wGA, mix) with BPD		
		9,380	16,434		Preterm (<33 wGA)		
		14,937	26,170		Preterm (33-35 wGA)		
ElHassan 2006 ⁴⁶	USA 2002; \$200,000 per QALY	103,053	165,301	Cost per QALY gained	BC, preterm (26 wGA), targeted use policy	Deterministic	Our model supports implementing more restrictive guidelines for PVZ prophylaxis. PVZ was CE for some infants in
		216,830	347,803		BC, preterm (28 wGA), targeted use policy		
		280,083	449,264		BC, preterm (29-30 wGA), targeted use policy		

		675,780	1,083,976		BC, preterm (29-30 wGA)		an analysis that accounted for increased risk of severe asthma following RSV infection. We found evidence that long-term health consequences of RSV are central to the determination of the CEness of the intervention.
		830,152	1,331,595		BC, preterm (26 wGA)		
		1,212,497	1,944,890		BC, preterm (31 wGA)		
		1,295,781	2,078,481		BC, preterm (27 wGA)		
		1,500,351	2,406,619		BC, preterm (28 wGA)		
		1,855,000	2,975,489		BC, preterm (32 wGA)		
Hampp 2011 ⁵⁰	USA 2010; NR (compared to \$8,910 per hospitalization)	302,103	413,127	Cost per hospitalization avoided	Preterm (<32 wGA)	Deterministic ; probabilistic	The cost of immunoprophylaxis with PVZ far exceeded the economic benefit of preventing hospitalizations, even in infants at highest risk for RSV infection.
		361,727	494,663		Preterm (<32 wGA) and CHD		
		368,048	503,307		Preterm (<32 wGA) and CLD		
		522,490	714,507		Term, CLD and CHD		
		823,868	1,126,642		Term, CHD only		
		920,033	1,258,148		Any risk factor (indication)		
		1,322,422	1,808,416		Term, CLD only		
		2,138,870	2,924,911		No risk factor (indication)		
Harris 2011 ⁵¹	CAN 2007; NR	8,292	9,704	Cost to treat 1 child per RSV season	BC	Deterministic	Our study contributes to the growing body of literature that suggests PVZ is not CE in children < 2 years old with hsCHD.
		15,513	18,155	Cost to prevent 1 day of hospitalization	BC		
Hascoet 2008 ⁵²	FRA 2006; €45,000 per QALY	10,172	16,368	Cost per LYG	Preterm (<32 wGA) with BPD (healthcare)	Deterministic ; probabilistic	RSV prophylaxis using PVZ in premature children with BPD or hsCHD can be considered CE in France.
		20,788	33,450		Preterm (<32 wGA) with cardiopathy (societal)		
		27,255	43,856		Preterm (<32 wGA) with BPD (Societal)		
Lofland 2000 ⁴⁷	USA 2000; NR	1,008	1,693	Cost per RSV infection episode avoided	BC, preterm (NR wGA), 81% reduction incidence of RSV infection (5% vs. 26%)	Deterministic	The incremental Cost per RSV infection episode avoided ranged from \$0 (cost savings) to \$39,591 for PVZ prophylaxis costs of \$2,500 and from \$2,702 to \$79,706 for PVZ prophylaxis costs of \$4,500. Clinicians may use this information to help determine whether prophylactic PVZ therapy is CE in their clinical practice setting.
		39,591	66,494		Preterm (NR wGA), 50% reduction incidence of RSV infection (5% vs. 10%)		
		Dominant	Dominant		Preterm (NR wGA), 83% reduction incidence of RSV infection (5% vs. 28%)		
Mahadevia 2012 ⁵⁴	USA 2010; NR (Compared to \$157,000 per QALY, from meningococcal vaccine)	44,774	61,229	Cost per QALY gained	Group 2, preterm (32-35 wGA) with RF ^c	Deterministic	PVZ remained CE for guideline-eligible high-risk infants across both public and private sectors. Guideline-eligible infants included infants of <32 wGA, 32–34 wGA with 2009 AAP RF, and 32–35 wGA with 2006 AAP RF. PVZ was not CE in infants of 32– 35 wGA with 1 RF.
		79,477	108,685		Group 3, preterm (32-35 wGA) with RF ^d		
		464,476	635,172		Group 4, preterm (32-35 wGA) with RF ^e		
		Dominant	Dominant		Group 1, preterm (<32 wGA) ^f		

McGirr 2017 ²⁷	CAN 2013; \$50,000 per QALY	157,332	167,107	Cost per QALY gained	High risk CF < 2 yrs. (high risk for severe RSV disease)	Deterministic	PVZ is not CE in CAD by commonly used thresholds. However, given the rarity of CF and relatively small budget impact, consideration may be given.
		652,560	693,105		All CF < 2 yrs.		
Neovius 2011 ²⁸	SWE 2009; 500,000 SEK per QALY	148,293	22,765	Cost per QALY gained	Preterm (<29 wGA) adding wheezing to asthma	Deterministic ; probabilistic	Based on a WTP of 500 000 SEK /QALY, PVZ was found to be cost-effective compared with no prophylaxis for infants born at <29 weeks if severe RSV infection was assumed to increase subsequent asthma or mortality risk.
		195,420	30,000		BC, Preterm (<29 wGA)		
		383,825	58,922		Preterm (<29 wGA) excluding indirect effect on asthma		
		492,430	75,595		Preterm (<29 wGA) excluding indirect effect on mortality		
		8,856,829	1,359,641		Preterm (<29 wGA) excluding the indirect effect of mortality and asthma		
Nuijten 2009_DEU ³²	DEU 2006; €20,000 per QALY	2,221	3,772	Cost per QALY gained	BC, CARDIAC Study parameters, societal	Deterministic ; probabilistic	This analysis showed that PVZ represents a CE means of prophylaxis against severe RSV infection requiring hospitalisation in infants with hsCHD.
		9,528	16,184		BC, CARDIAC Study parameters, including asthma, payer		
		9,529	16,185		BC, societal		
		11,126	18,898		BC, CARDIAC Study parameters, excluding asthma, payer		
		16,673	28,320		BC, direct medical costs (including asthma), payer		
		18,266	31,025		BC, direct medical costs (excluding asthma), payer		
		123,439	209,666		BC, excluding mortality, societal		
		Nuijten 2009_NLD ³¹	NLD 2006; €30,000 per QALY		7,067		
11,336	18,717			BC – preterm (<35 wGA, mix) with BPD (total costs, societal)			
18,563	30,650			Preterm (<35 wGA, mix)			
20,236	33,412			BC, preterm (<35 wGA, mix) with BPD			
23,461	38,737			BPD sub-populations			
Dominant	Dominant			BC - CHD (total costs, societal)			
Nuijten 2010 ³⁰	ESP 2006; €30,000 per QALY			6,498	12,710	Cost per QALY gained	BC, preterm (<32 wGA) inclusion of costs of sequelae treatment
		12,814	25,065	BC, preterm (<32 wGA)			
		Dominant	Dominant	BC, preterm (<32 wGA), societal perspective			
Nuijten 2007 ²⁹	GBR 2003; £25,000 per QALY	6,664	14,891	Cost per QALY gained	CHD	Deterministic ; probabilistic	This study suggests that PVZ prophylaxis against severe RSV infection in children at high risk may be CE from the NHS perspective.
		11,494	25,684		BC, preterm (<35 wGA) with indirect costs (societal)		
		14,883	33,257		Preterm (<35 wGA)		
		16,720	37,362		BC, preterm (<35 wGA) with BPD		
		20,953	46,821		BPD only		

Resch 2012 ^{33,34}	AUT 2010; €40,693 per QALY (based on the £30,000 per QALY from NICE in 2010)	3,045	4,949	Cost per QALY gained	BC, CHD, including recurrent wheezing treatment, societal	Deterministic	Our results based on nationwide long-term epidemiologic data suggest that PVZ is CE in prevention of RSV disease in high-risk infants.
		7,818	12,706		BC, CHD, including recurrent wheezing treatment		
		8,484	13,788		BC, CHD		
		15,800	25,678		BC, for all preterm (<35 wGA, mix), including recurrent wheezing treatment, societal		
		15,992	25,990		BC, preterm (33-35 wGA), including recurrent wheezing treatment, societal		
		17,554	28,529		BC, BPD, including recurrent wheezing treatment, societal		
		18,133	29,470		BC, preterm (<33 wGA), including recurrent wheezing treatment, societal		
		21,669	35,216		BC, for all preterm (<35 wGA, mix), including recurrent wheezing treatment		
		21,862	35,530		BC, preterm (33-35 wGA), including recurrent wheezing treatment		
		22,515	36,591		BC, BPD, including recurrent wheezing treatment		
		23,833	38,733		BC, preterm (<33 wGA), including recurrent wheezing treatment		
		24,392	39,642		BC, preterm (33-35 wGA)		
		24,654	40,068		BC, BPD		
		26,212	42,600		BC, for all preterm (<35 wGA, mix)		
		26,292	42,730		BC, preterm (<33 wGA)		
Rietveld 2010 ³⁵	NLD 2000; NR (\$1325 to \$8700, mean of \$5,787 per hospitalization)	13,190	24,875	Cost per hospitalization avoided	Male infant, preterm (< 28 wGA), birth weight < 2,500g, with BPD (December)	Deterministic	Every month costs per hospitalisation avoided were higher for children without BPD and children with higher GAs. Incremental costs per hospitalisation avoided were always high. Passive immunisation was always most cost effective in December. A restrictive immunisation policy only immunising children with BPD in high-risk months is therefore recommended. The costs of passive immunisation would have to be considerably reduced to achieve cost-effectiveness.
		30,795	58,076		Male infant, preterm (< 28 wGA), birth weight < 2,500g, with BPD (January)		
		31,055	58,567		Male infant, preterm (< 28 wGA), birth weight < 2,500g, with BPD (November)		
		47,145	88,911		Male infant, preterm (< 28 wGA), birth weight < 2,500g, with BPD (February)		
		105,120	198,246		Male infant, preterm (< 28 wGA), birth weight < 2,500g, with BPD (March)		
		395,860	746,554		Male infant, preterm (< 28 wGA), birth weight < 2,500g, with BPD (April)		
		833,695	1,572,268		Male infant, preterm (< 28 wGA), birth weight < 2,500g, with BPD (October)		
		Roeckl-Wiedmann 2003 ³⁶	DEU 2000; NR		6,639		
25,288	45,028			Group B, preterm (<35 wGA) with RF ^h			
52,838	94,084			Group C, preterm (<35 wGA) with RF ⁱ			
204,684	364,462			Group D, preterm (<35 wGA) with RF ⁱ			

							PVZ was most cost-effective among male infants with CLD who had siblings visiting day-care groups, and who were discharged between October and December.
Salinas-Escudero 2012 ³⁸	USA 2009; \$50,000 per QALY, and 3x GDP per capita	4,539	6,216	Cost per QALY gained	Partial coverage, preterm (< 29 wGA)	Deterministic ; probabilistic	PVZ prophylaxis for preterm newborn patients born ≤ 32 weeks of age resulted in a CE alternative. When evaluating the ICER per QALY and LYG against the USD \$50,000 threshold, all age groups within the prophylaxis group are CE.
		7,294	9,989		Partial coverage, preterm (29-32 wGA)		
		17,532	24,009		Full coverage, preterm (<29 wGA)		
		20,760	28,429		Full coverage, preterm (29-32 wGA)		
Sanchez-Luna 2017 ³⁹	ESP 2016; €30,000 per QALY	11,550	22,173	Cost per QALY gained	Subgroup A (payer), preterm (32-35 wGA) with RF: 2 major 2 minor ^k	Deterministic ; probabilistic	Out of 1,000 Monte Carlo simulations, 85.70% of the cases presented an ICUR under a €30,000/QALY. PVZ is efficient for preventing from RSV infections in preterm infants 32-35 wGA in Spain, including specific high risk subgroups.
		14,177	27,216		Subgroup B (payer), preterm (32-35 wGA) with RF: 2 major 1 minor ^l		
		17,153	32,930		BC (societal), preterm (32-35 wGA)		
		18,938	36,356		Subgroup C (payer), preterm (32-35 wGA) with RF: 2 major RF ^m		
		19,698	37,815		BC (payer), preterm (32-35 wGA)		
Schmidt 2017 ⁴⁰	ESP 2016; €30,000 per QALY	15,748	30,232	Cost per QALY gained	BC	Deterministic ; probabilistic	PSA demonstrated that the probability of PVZ prophylaxis being CE at a € 30,000 per QALY threshold was 92.7%. The ICER remained below this threshold for most extreme scenario analyses. PVZ prophylaxis was shown to be a CE health care intervention according to the commonly accepted standards of CEness in Spain (ICER below the threshold of € 30,000 per QALY).
Smart 2010 ^{41,53}	CAN 2010; \$50,000 per QALY	192	215	Cost per QALY gained	Preterm (32-35 wGA), 4 or more RF	Deterministic ; probabilistic	PVZ ICERs remained fairly stable from 2007 to 2010. The original recommendation stating that PVZ is cost effective in infants born between 32 and 35 wGA with 2 or more RF, or who are at moderate-to-high risk based on a risk assessment model, does not change.
		5,274	5,906		Preterm (32-35 wGA), Risk scoring tool, high risk (65-100)		
		20,814	23,309		BC Preterm (32-35 wGA), (including asthma)		
		26,701	29,901		Preterm (32-35 wGA), 3 RF		
		31,360	35,119		BC Preterm (32-35 wGA), (excluding asthma)		
		34,438	38,566		Preterm (32-35 wGA), Risk scoring tool, medium risk (49-64 score)		
		48,495	54,308		Base case, Preterm (32-35 wGA), mortality rate (1.2%)		
		50,434	56,479		Base case, Preterm (32-35 wGA), mortality rate (1.0%)		
		82,732	92,649		Preterm (32-35 wGA), 2 RF		
		146,218	163,744		Preterm (32-35 wGA), 1 RF		

		183,561	205,563		Preterm (32-35 wGA), Risk scoring tool, low risk (0-48 score)		
		820,701	919,073		Preterm (32-35 wGA), Zero RF (Preterm only)		
Tam 2009 ⁴²	CAN 2007; \$50,000 to \$75,000 per QALY	334	391	Cost per QALY gained	High risk <1 year	Deterministic ; probabilistic	PVZ is a CE option for the prevention of RSV for Inuit infants on Baffin Island, is highly cost effective in Arctic infants <1 year of age specifically residing outside of Iqaluit and is a dominant strategy for those under 6 months of age in remote areas. However, PVZ is not cost effective compared to no treatment for infants of all ages residing in Iqaluit.
		7,822	9,154		Baffin < 6 mo., societal		
		10,190	11,925		Baffin < 6 mo.		
		22,383	26,195		Outside of Iqaluit (remote areas) <1 year, societal		
		24,750	28,965		Outside of Iqaluit (remote areas) <1 year		
		37,070	43,383		All Baffin Island infants <1 year, societal		
		39,435	46,151		All Baffin Island infants < 1 year		
		100,872	118,052		Residing in Iqaluit <6 mo., societal		
		103,235	120,817		Residing in Iqaluit <6 mo.		
		149,782	175,291		Residing in Iqaluit <1 year, societal		
		152,145	178,057		Residing in Iqaluit <1 year		
		Dominant	Dominant		remote infants < 6 mo.		
		Dominant	Dominant		high risk < 6 mo.		
		Dominant	Dominant		High risk < 1 year, societal		
Dominant	Dominant	remote infants < 6 mo., societal					
Dominant	Dominant	high risk < 6 mo., societal					
Vogel 2002 ⁴³	NZL 2000; NR	28,700	33,376	Cost per case avoided	Preterm (32-35 wGA) with CLD, discharged home on oxygen	Deterministic	If value is placed on preventing morbidity, the priority groups for PVZ prophylaxis are preterm infants discharged home on oxygen, followed by preterm infants of 28 wGA or less.
		32,000	37,213		Preterm (<=28 wGA), no CLD		
		60,000	69,775		Total cohort, Preterm (32-35 wGA) with CLD, societal		
		65,000	75,590		Preterm (<=28 wGA) with CLD		
		98,000	113,966		Preterm (29-31 wGA), no CLD		
		166,700	193,859		Preterm (29-31 wGA) with CLD		
Wang 2008 ¹⁴	GBR 2006; £30,000 per QALY	51,800	107,070	Cost per hospitalization avoided	Preterm infants (<35 wGA) with children without CLD	Deterministic	According to this model, prophylaxis with PVZ is not a CE strategy for preterm infants and children with CHD compared with no prophylaxis from both an NHS perspective and societal perspective. These findings are robust to probabilistic and other sensitivity analyses. Prophylaxis with PVZ is also not a CE strategy for preterm infants or infants with CLD who have no other RF. Subgroup analyses
		63,800	131,874	Cost per QALY gained	Preterm infants (<35 wGA) and children with CLD		
		66,900	138,282	Cost per hospitalization avoided	Preterm infants (<35 wGA) and children with CLD (societal)		
		67,600	139,729	Cost per hospitalization avoided	Preterm infants (<35 wGA) and children with CLD		
		78,600	162,466	Cost per hospitalization avoided	CHD		
		79,800	164,946	Cost per QALY gained	CHD		
		83,200	171,974	Cost per QALY gained	CHD (societal)		

		454,100	938,623		Preterm infants (<35 wGA) and children without CLD		showed that prophylaxis with PVZ for children with CLD may be CE, at a WTP threshold of £30,000/QALY.
		475,600	983,064		Preterm infants (<35 wGA) and children without CLD (societal)		
Weiner 2012 ⁴⁴	USA 2010; \$157,000 per QALY (highest ICER for vaccine - meningococcal vaccine)	16,037	21,931	Cost per QALY gained	BC Group 2, preterm (32-34 wGA) with RF ⁿ	Deterministic ; probabilistic	PVZ, when dosed consistent with the FDA-approved labeling, was either cost-saving or CE among current guideline-eligible infants in the Medicaid population. PVZ did not demonstrate CEness in 32–35 wGA infants with ≤1 RF.
		38,244	52,299		BC Group 3, preterm (32-35 wGA) with RF ^o		
		281,892	385,488		BC Group 4, preterm (32-35 wGA) with RF ^p		
		Dominant	Dominant		BC Group 1, preterm (<32 wGA) ^q		
Yount 2004 ⁴⁵	USA 2002; NR	114,337	183,401	Cost per QALY gained	BC, term, CHD	Deterministic	The cost of PVZ prophylaxis was high relative to benefits realized. Given the large number of CHD patients who might be considered candidates for RSV prophylaxis (>6000 patients per year in the US) routine use of PVZ in young children with CHD needs to be evaluated further.

AUT, Austria; BC, base-case; BPD, bronchopulmonary dysplasia; CA, chronological age; CAD, Canadian dollar; CAN, Canada; CE, cost-effective; CHD, congenital heart disease; CLD, chronic lung disease; DEU, Germany; ESP, Spain; EUR, Euros; FRA, France; GA, gestational age; GBP, Great Britain Pounds; GBR: Great Britain; HA, hospitalization avoided; hsCHD, hemodynamically significant heart disease; ICER, incremental cost-effectiveness ratio; ITA, Italy; LYG, life years gained; NLD, Netherlands; NR, not reported; NWT, Northwest Territories; NZD, New Zealand dollars; NZL, New Zealand; PVZ, palivizumab; QALY, quality-adjusted life years; RF, risk factors; RSV, respiratory syncytial virus; SEK, Swedish Krona; SWE, Sweden; wGA, weeks' gestation age; USA, United States of America; USD, US dollars; WTP, Willingness-to-pay

^a**Scenario B:** palivizumab prophylaxis for infants up to 5 months of age only (for 6 months of protection) was compared to no prophylaxis;

^b**Scenario A²⁶:** universal palivizumab prophylaxis for all healthy term infants who were <6 months of age as of Jan. 1, 2009 was compared to no prophylaxis;

^c**Group 2:** 32–34 wGA, ≤3 months CA, with 2009 American Academy of Pediatrics (AAP) risk factors;

^d**Group 3:** 32–35 wGA, ≤6 months CA, with 2006 AAP risk factors;

^e**Group 4:** 32–35 wGA, ≤6 months CA, with ≤1 risk factor;

^f**Group 1⁵⁴:** < 32 weeks GA (wGA) and <6 months chronologic age (CA);

^g**Group A³⁶:** Male, Siblings in day-care, discharged between Oct and Dec, CLD;

^h**Group B:** Male, Siblings in day-care, discharged between Oct and Dec;

ⁱ**Group C:** Male, Siblings in day-care;

^j**Group D:** Male;

^k**Subgroup A:** 2 major risk factors (e.g., chronological age less than 10 weeks at the beginning of RSV season or being born during the first 10 weeks of the season; school-age siblings or day-care attendance) and 2 minor risk factors (e.g., mother smoking during pregnancy, male gender) associated with RSV infection requiring hospitalization;

^l**Subgroup B:** 2 major risk factors and 1 minor risk factors associated with RSV infection requiring hospitalization;

^m**Subgroup C:** 2 major factors associated with RSV infection requiring hospitalization;

ⁿ**BC Group 2:** 32–34 wGA and < 3 months CA with 2009 AAP risk factors (i.e., having siblings 55 years of age and/or attending day care);

^o**BC Group 3:** 32–35 wGA, < 6 months CA with 2006 AAP risk factors (any 2 of the following: exposure to environmental air pollutants, congenital abnormalities of the airways, severe neuromuscular disease, school-age siblings, day care attendance);

^p**BC Group 4:** 32–35 wGA, <6 months CA with <1 risk factor;

^q**BC Group 1⁴⁴:** <32 wGA and < 6 months CA.

Table 3. Summary of Cost-Effectiveness Estimates by Health Condition and Perspective

	Health Conditions							
	BPD/CLD	CHD	Preterm	Preterm with BPD/CLD	Preterm with risk factors*	CF	Canadian Artic**	
							All infants	High risk areas
Payer perspective								
Number of estimates	6	10	22	4	14	2	6	2
ICER (Minimum)	4,786	11,668	6,216	15,202	215	167,107	Dominant	Dominant
ICER (Maximum)	46,821	164,946	938,623	131,874	205,563	693,105	178,057	391
Proportion of estimates that are cost saving	0.0	0.0	0.0	0.0	0.0	0.0	0.17	0.50
Proportion of estimates CE below \$50,000/QALY	1.00	0.80	0.82	0.75	0.64	0.0	0.67	1.00
Proportion of estimates CE below \$100,000/QALY	1.00	0.90	0.86	0.75	0.86	0.0	0.67	1.00
Proportion of estimates CE below \$200,000/QALY	1.00	1.00	0.91	1.00	0.92	0.50	1.00	1.00
Societal perspective								
Number of estimates	1	8	23	3	6	0	6	2
ICER (Minimum)	28,529	Dominant	Dominant	18,717	21,931	N/A	Dominant	Dominant
ICER (Maximum)	28,529	209,666	2,975,489	138,282	635,172	N/A	175,291	Dominant
Proportion of estimates that are cost saving	0.0	0.13	0.13	0.0	0.0	N/A	0.17	1.00
Proportion of estimates CE below \$50,000/QALY	1.00	0.63	0.39	0.67	0.17	N/A	0.67	1.00
Proportion of estimates CE below \$100,000/QALY	1.00	0.63	0.48	0.67	0.50	N/A	0.67	1.00
Proportion of estimates CE below \$200,000/QALY	1.00	0.88	0.52	1.00	0.67	N/A	1.00	1.00

All ICERs are reported in 2017 Canadian dollars per QALY.

BPD, Bronchopulmonary dysplasia; CE, Cost-effective; CHD, Congenital heart disease; CLD, Chronic lung disease; CF: cystic fibrosis; ICER, Incremental cost-effectiveness ratio; N/Ap, not applicable; QALY, Quality-adjusted life years.

* major risk factors: chronological age < 10 weeks at beginning of RSV season, being born during first 10 weeks of the season; school age siblings; day-care attendance, minor risk factors: mother smoking during pregnancy, male gender

** Infants <1 year of age living in Baffin Island and infants <1 year of age living in high risk areas of Baffin Island (defined as having hospitalization rates over 500 per 1,000 live births). Effectiveness estimate in the model is from a study of preterm infants.

Table 4. Characteristics and Conclusions from Canadian-Context Studies

Authors, Year	Dosage	Cost per unit (Unadjusted)	Hospitalization			Mortality	RSV-Sequelae	Conclusions
			PVZ	No PVZ	Reduction (%)			
Tam <i>et al.</i> , 2009	5 (per season)	Vial unit cost: NR; \$220/kg infant	1.4 - 11.4%	6.3 - 51.2%	78%	1% (both groups)	N	From the payer perspective, PVZ is CE for all Baffin Island infants <1 year CA (ICER: \$46,151/QALY), infants at high-risk for RSV (\$391/QALY), infants from remote areas (\$28,965/QALY), infants < 6 months of age from remote areas, or at high-risk for RSV (dominant). It was not CE for infants < 12 mos residing in Iqaluit.
Smart <i>et al.</i> , 2010	5.39 vials (per season)	50mg: \$752 100mg: \$1,505	1.8%	10.0%	NR (82% back calculation)	3.9% (both groups) ²	Y	From the payer perspective, PVZ is CE for preterm infants when excluding asthma (\$35,119/QALY), and when including asthma (\$23,309/QALY).
Harris <i>et al.</i> , 2011	4.5 (per season)	100mg: \$1,468	1.7%	2.9%	NR (42% back calculation)	NR; 0.2% (1/41, no PVZ); 0% (0/292, PVZ)	N	From a societal perspective, PVZ in CHD infants: ICER of \$18,155/day of hospitalization avoided. No threshold was used but the study concluded this strategy was CE for the CHD infant population.
Banerji <i>et al.</i> , 2016	6; (per mo, max assump.)	Vial unit cost: NR; \$226/kg infant	NR	NR	96%	NR	N	From a payer perspective, 2 PVZ program scenarios proposed were both CE in some, but not all, Canadian Arctic regions (ICER range, dominant to \$45,060/QALY). PVZ is CE in these regions for term infants due to high costs of hospitalizations.
McGirr <i>et al.</i> , 2017	5 (monthly over 5-mo season)	100mg: \$1,505	1.7% (assuming 55% reduction) ¹	3.8%	55%	NR (Used CF-related death)	Y (CF)	PVZ is unlikely to be CE for all infants with CF (ICER: \$693,105/QALY) and for high-risk infants with CF (ICER: \$167,107/QALY).

¹ Hospitalization rates x 3.6 RR (for high-risk CF infants)² Annual mortality rate based on a Canadian sample of premature infants (33-35 wGA) hospitalized with RSV

CE, cost-effective; CF, cystic fibrosis; CHD, congenital heart disease; ICER, incremental cost-effectiveness ratio; mo, months; N, noNR, Not reported; PVZ, Palivizumab; QALY, quality-adjusted life years; RSV, respiratory syncytial virus; Y, yes

SUPPLEMENTARY MATERIALS

APPENDIX 1. PRISMA CHECKLIST

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	4-5
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Supplementary 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7-8

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I ²) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/Ap
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group; (b) effect estimates and confidence intervals, ideally with a forest plot.	8-13
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/Ap
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/Ap
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	3

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097
For more information, visit: www.prisma-statement.org

APPENDIX 2. SEARCH STRATEGY

Database(s): Ovid MEDLINE(R) ALL 1946 to August 08, 2018

#	Searches	Results
1	exp Antibodies, Monoclonal/ or exp antiviral agents/ or exp immunoglobulins/ or (antibody protein or anti viral agent* or anti viral drug* or antiviral agent* or antiviral drug* or antiviral substance or antivirals or antiviral agent* or antiviral drug* or anti-RSV or clonal antibody or endobulin or flebogamma or flebogammadif or gamastan or gamimmune n or gamimmune or gamma globulin* or gamma-globulin* or gammaglobulin* or gammar or gamulin or globuman or humanized antibody or humanized monoclonal antibody or hybridoma antibody or Ig or igam or igc or immune gamma globulin or immune globin or immune globulin* or immune serum globulin* or immuno gamma globulin* or immuno globulin* or immunogammaglobulin* or immunoglobulin* or immunoglobulin* or immunoprotein* or intragam or intraglobin f or isiven or iveegam or ivega or mAbs or MEDI 493 or monoclonal antibodies or monoclonal antibody or palivizumab or panglobulin* or passive immunization or sandoglobin* or sandoglobulin* or synagis or tegelin* or veinoglobulin* or venoglobulin* or viral inhibitor or virostatic agent* or virucidal agent* or virucide agent* or virustatic agent* or vivaglobin).tw,kf,nm.	1043332
2	respiratory syncytial virus infections/pc	1417
3	respiratory syncytial virus infections/ or Respiratory Syncytial Virus, Human/ or Respiratory Syncytial Viruses/ or (respiratory syncytial vir* or RSV*).tw.	18025
4	prophylaxis/ or (control or health protection or immunoprophylaxis or prevention or preventive measures or preventive medication or preventive therapy or preventive treatment or prophylactic institution or prophylactic management or prophylactic medication or prophylactic therapy or prophylactic treatment or prophylaxis).tw.	2762004
5	2 or (3 and 4)	4221
6	and/1,5	1760
7	exp Infant/ or exp Child/ or GA/ or exp Pediatrics/ or Schools, Nursery/ or (infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur* or preemie* or gestation* or GA or child or children or preschool* or kid or kids or toddler* or pediatric* or paediatric* or peadiatric* or nursery school*).tw.	3053948
8	Economics/	26937
9	exp "Costs and Cost Analysis"/	217482

10	Economics, Nursing/	3981
11	Economics, Medical/	8964
12	Economics, Pharmaceutical/	2794
13	exp Economics, Hospital/	23019
14	Economics, Dental/	1897
15	exp "Fees and Charges"/	29368
16	exp Budgets/	13335
17	budget*.ti,ab,kf.	26174
18	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.	202619
19	(economic* or cost or costs or costly or costing or price or prices or pricing or pharmaco-economic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2	246788
20	(cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.	138081
21	(value adj2 (money or monetary)).ti,ab,kf.	2025
22	exp models, economic/	13464
23	economic model*.ab,kf.	2837
24	markov chains/	12909
25	markov.ti,ab,kf.	19178
26	monte carlo method/	25573
27	monte carlo.ti,ab,kf.	43481
28	exp Decision Theory/	11145
29	(decision* adj2 (tree* or analy* or model*)).ti,ab,kf.	19525
30	or/8-29	647482
31	and/6-7,30	230
32	exp australia/ or austria/ or exp baltic states/ or exp belgium/ or exp canada/ or chile/ or czech republic/ or exp "scandinavian and nordic countries"/ or exp france/ or exp germany/ or greece/ or hungary/ or exp ireland/ or israel/ or exp italy/ or exp japan/ or exp republic of	4128242

korea/ or luxembourg/ or mexico/ or exp netherlands/ or exp new zealand/ or poland/ or exp portugal/ or slovakia/ or slovenia/ or exp spain/ or exp switzerland/ or turkey/ or exp united kingdom/ or exp united states/ or (australia* or new south wales or queensland or tasmania or victoria or sydney or melbourne or brisbane or austria* or vienna or viennese* or belgium* or belgian* or brussels or flemish* or canad* or ottawa* or british columbia* or colombie britannique* or vancouver* or alberta* or edmonton* or calgar* or saskatchewan* or regina* or saskatoon* or manitoba* or winnipeg* or ontari* or toronto* or quebec* or montreal* or new brunswick* or nouveau brunswick* or fredericton* or nova scotia* or nouvelle ecosse* or halifax* or haligonian* or prince edward island* or ile du prince edouard* or pei or charlottetown* or newfoundland* or terre neuve* or labrador* or nfld or yukon* or whitehorse* or northwest territor* or territoires du nord ouest* or nwt or yellowknife* or nunavut* or iqaluit* or chile* or santiago or czech* or prague or denmark* or danish or dane* or faroe* or copenhagen or estonia* or tallinn or finland* or finnish* or helsinki* or france* or french* or paris* or marseille or lyon or lille or nice or toulouse or bordeaux or german* or deutschland* or berlin* or hamburg or munich or cologne or frankfurt or stuttgart or dusseldorf or greece* or hellenic* or greek* or athens or macedonia* or hungary* or hungarian* or budapest or iceland* or reykjavik or ireland* or irish* or dublin* or israel* or jerusalem or tel aviv or italy or italian* or rome or milan or naples or turin or sicily or japan* or tokyo or yokohama or osaka or nagoya or sapporo or kobe or kyoto or korea* or seoul or busan or daegu or daejeon or gwangju or incheon or ulsan or latvia* or riga or lithuania* or vilnius or luxembourg* or netherland* or holland* or dutch* or amsterdam or rotterdam or hague or new zealand* or aotearoa or wellington or auckland or maori or mexic* or norway* or norwegian* or oslo or poland* or polish or warsaw or krakow or wroclaw or lodz or portug* or lisbon or slovak* or bratislava or slovenia* or slovene* or ljubljana or spain* or spanish* or spaniard* or madrid or barcelona or catalonia* or valencia* or seville or zaragoza or malaga or basque or scandinavia* or sweden or swedish or swede* or stockholm or switzerland* or swiss* or zurich or geneva or bern or turkey or turkish or istanbul or constantinople or britain* or british* or united kingdom* or scotland* or scottish or wales* or welsh or england* or belfast or london or manchester or glasgow or birmingham or leeds or bradford or liverpool or alabama* or alaska* or arizona* or arkansas* or california* or colorado* or connecticut* or delaware* or florida* or georgia* or hawaii* or idaho* or illinois* or indiana* or iowa* or kansas* or kentucky* or louisiana* or maine* or maryland* or massachusetts* or michigan* or minnesota* or mississippi* or missouri* or montana* or nebraska* or nevada* or new hampshire* or new jersey* or new mexico* or new york* or north carolina* or north dakota*

	or ohio* or oklahoma* or oregon* or pennsylvania* or rhode island* or south carolina* or south dakota* or tennessee* or texas* or utah* or vermont* or virginia* or washington* or west virginia* or wisconsin* or wyoming* or montgomery* or juneau* or anchorage* or phoenix* or little rock* or sacramento* or los angeles* or san diego* or san francisco* or denver* or hartford* or dover* or tallahassee* or miami* or orlando* or atlanta* or honolulu* or boise* or springfield* or chicago* or des moines* or topeka* or frankfort* or baton rouge* or new orleans* or augusta* or annapolis* or boston* or lansing* or detroit* or st?paul* or jackson* or jefferson city* or helena* or lincoln* or carson city* or reno* or las vegas* or concord* or trenton* or santa fe* or albany* or raleigh* or bismarck* or columbus* or oklahoma city* or salem* or harrisburg* or providence* or columbia* or peirre* or nashville* or austin* or dallas* or salt lake city* or montpelier* or richmond* or olympia* or seattle* or charleston* or madison* or cheyenne* or district of columbia* or usa or united states).tw,kf.	
33	31 and 32	117
34	limit 33 to (yr="2000 -Current" and (english or french))	104
35	(comment or editorial or letter or news).pt.	1825216
36	34 not 35	91

APPENDIX 3. QUALITY APPRAISAL RESULTS

	Critical Appraisal - Joanna Briggs Institute Checklist										
Author; Year	1	2	3	4	5	6	7	8	9	10	11
Banerji; 2016	Y	U	Y	Y	Y	Y	Y	Y	Y	U	Y
Bentley; 2013	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Blanken; 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Chirico; 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Hampp; 2011	Y	Y	N	Y	U	Y	N	Y	Y	Y	Y
Harris; 2011	Y	Y	U	Y	Y	Y	U	Y	Y	Y	Y
Hascoet; 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Smart; 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Mahadevia; 2012	Y	Y	N	Y	Y	Y	Y	Y	Y	U	Y
McGirr; 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Neovius; 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Nuijten; 2009_DEU	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nuijten; 2009_NLD	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nuijten; 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Nuijten; 2007	Y	Y	Y	Y	Y	U	Y	Y	Y	Y	Y
Resch; 2012	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y
Rietveld; 2009	Y	Y	N	Y	Y	Y	Y	Y	Y	U	U
Roeckl-Wiedmann; 2003	Y	Y	N	Y	Y	Y	Y	Y	Y	U	U
Salinas-Escudero; 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Sanchez-Luna; 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Schmidt; 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tam; 2009	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Vogel; 2002	Y	Y	N	Y	Y	Y	N	Y	Y	U	N
Wang; 2008	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Weiner; 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Yount; 2004	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N
ElHassan; 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y
Lofland; 2000	Y	Y	U	Y	U	U	Y	Y	Y	U	Y

DEU, Germany; NLD, Netherlands

Y, Yes; N, No; U, Unclear

Questions²³: 1. Is there a well-defined question? 2. Is there comprehensive description of alternatives? 3. Are all important and relevant costs and outcomes for each alternative identified? 4. Has clinical effectiveness been established? 5. Are costs and outcomes measured accurately? 6. Are costs and outcomes valued credibly? 7. Are costs and outcomes adjusted for differential timing? 8. Is there an incremental analysis of costs and consequences? 9. Were sensitivity analyses conducted to investigate uncertainty in estimates of cost or consequences? 10. Do study results include all issues of concern to users? 11. Are the results generalizable to the setting of interest in the review?