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Cost Effectiveness of Respiratory Syncytial Virus Prophylaxis

A Critical and Systematic Review

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Abstract

Respiratory syncytial virus (RSV) is the leading cause of infant hospitalization in the US. The economic burden of severe disease is substantial, including hospitalization costs and out-of-pocket expenses. RSV prophylaxis with either RSV immune globulin intravenous (RSV-IGIV) or palivizumab has been shown to be effective in reducing RSV-related hospitalizations. Motavizumab, a new enhanced-potency humanized RSV monoclonal antibody, is presently in clinical trials. RSV-IGIV and palivizumab are associated with high acquisition costs. Cost-effectiveness analyses are therefore of great importance in helping to determine who should receive RSV prophylaxis. Six studies have analysed the cost effectiveness of RSV-IGIV, 14 have analysed the cost effectiveness of palivizumab and five have analysed the cost effectiveness of both agents, two of which directly compared palivizumab with RSV-IGIV. The cost effectiveness of motavizumab has not been studied.

Significant variation exists in the modelling used in these analyses. Many studies have examined short-term benefits such as reducing hospitalizations and associated costs, while fewer studies have examined long-term benefits such as QALYs or life-years gained. The payer and society have been the most common perspectives used. The endpoints examined varied and

generally did not account for the potential impact of RSV prophylaxis on RSV-related complications such as asthma. While some studies have reported acceptable cost-effectiveness ratios for RSV prophylaxis, the majority failed to show cost savings or cost-effectiveness ratios below commonly accepted thresholds for either RSV-IGIV or palivizumab. Cost effectiveness of RSV prophylaxis tended to be more favourable in populations with specific risk factors, including premature infants ≤32 weeks' gestational age, and infants or children aged <2 years with chronic lung disease or congenital heart disease.

Comparing the results of economic analyses of the two agents suggests palivizumab may be the more cost-effective option in the population for which RSV prophylaxis is recommended. Over time, the acquisition cost of RSV prophylaxis agents, a major cost driver, may decrease, and more acceptable outcomes of economic analyses may result. Albeit important, the results of economic analyses are not the only tool that decision makers rely on, as population-specific risk factors, and efficacy and safety data must be considered when developing treatment guidelines and making clinical decisions.

Respiratory syncytial virus (RSV) is a common cause of serious respiratory tract infections in infants and young children, and is a leading cause of virus-related death among infants.[1,2] RSV prophylaxis has been shown to be effective in reducing RSV-related hospitalizations.[3-8] The significant costs of RSV prophylaxis has prompted extensive study into the cost effectiveness of these preventive treatments.

Our objective was to systematically review the literature on the cost effectiveness of RSV prophylaxis, identify the cost drivers associated with RSV prophylaxis, and discuss the modelling used in cost-effectiveness analyses conducted to date.

1. Respiratory Syncytial Virus (RSV) Prophylaxis

RSV infection rates follow a seasonal pattern in the US. The RSV season typically begins during November or December, peaks during January or February, and dissipates during March or April, after which the prevalence of RSV in the southern hemisphere increases.[9] The vast majority of infected infants and children will develop mild upper respiratory tract symptoms, while a subset of patients will progress to severe RSV disease (bronchiolitis and/or pneumonia).[1,10] Severe RSV disease often necessitates admission to the hospital, particularly among infants aged <1 year, resulting in more than 70 000 infant hospitalizations and 140–410 deaths per year in the US.[11-13] The estimated worldwide annual incidence of RSV is 64 million cases, resulting in an estimated 160 000 deaths per year.[14] Among hospitalized RSV-infected infants, 80% experience complications that result in an increased length of hospital stay and increased costs.[10,15] Following resolution of the acute phase of severe RSV infection in infants, a significant rise in subsequent utilization of inpatient and outpatient healthcare resources has been reported. This has been attributed to acute respiratory conditions such as asthma, clinical allergy and allergic sensitization, further adding to the burden of RSV on the healthcare system.[16]

Since the treatment of RSV infection is primarily supportive, prevention during seasonal peaks is critical to reducing RSV hospitalization. RSV prophylaxis targets high-risk patients in whom the risk of severe RSV disease is significantly increased, including premature infants, infants with chronic lung disease (CLD) and infants with congenital heart disease (CHD). In these high-risk populations, the RSV hospitalization rate ranges from 3% to 37%.[1,10,17-20] RSV prophylaxis has been shown to reduce morbidity, but not mortality, in prospective, randomized, double-blind, placebo-controlled trials.[3,4,7] RSV immune globulin intravenous (RSV-IGIV), a

hyperimmune polyclonal human antibody, was the first agent with proven benefit for passive immunization against RSV, reducing the incidence of RSV hospitalization among high-risk infants and children by 41–63%.[3,8,21] Although effective in high-risk patients, its inconvenient method of administration, potential to interact with live-attenuated vaccines and contraindication in infants with cyanotic CHD has prompted its replacement by palivizumab, a humanized murine monoclonal antibody, as the preferred agent for RSV prophylaxis.[20,22,23] Palivizumab, given once monthly during the RSV season (typically five doses), has been shown to be a well tolerated and effective option for the prevention of severe RSV disease in premature infants, and infants or children with CLD or haemodynamically significant CHD, reducing RSV hospitalization by 45–55%.[4,7] Premature infants without CLD, infants or children aged ≤24 months with CLD, and infants or children aged ≤24 months with CHD demonstrated a 78%, 39% and 45% reduction in RSV hospitalizations, respectively.[4,7] Furthermore, palivizumab has been reported to reduce subsequent recurrent wheezing in premature infants without CLD.[24] Motavizumab, a new enhanced-potency, humanized RSV monoclonal antibody currently in clinical trials, has demonstrated similar efficacy and safety to palivizumab in premature infants or infants with CLD.[5]

The American Academy of Pediatrics (AAP) recommends RSV prophylaxis be considered for the highest-risk patients: premature infants, infants or children aged <24 months with CLD, infants or children aged ≤24 months with haemodynamically significant CHD, and premature infants with congenital abnormalities of the airways or neuromuscular disease that compromises handling of respiratory secretions.[20,22,25] The population indications within these guidelines are similar to, but not the same as, those recommended in many other countries/regions, including the UK, Canada, Europe and Latin America, but are less conservative than those recommended in New Zealand.[26] Hence, there is clearly no consensus as to which populations to target for prophylaxis.

2. Economic Impact of RSV Infection

The medical management of infants and children infected with RSV is often provided in outpatient settings such as a paediatrician's office, urgent-care clinic and/or the ED.[27] However, hospitalization is often required in severe cases. This is particularly true among infants aged <1 year, in whom RSV infection (bronchiolitis and/or pneumonia) is the leading cause of hospitalization in the US, resulting in an estimated 73 000–126 000 infant hospitalizations per year.[12] This translates to a bronchiolitis hospitalization rate of 31.2 per 1000 infants.[12] In the UK, the incidences of RSV-related and bronchiolitis-associated hospitalization have been reported to be 24 and 31 per 1000 infants, respectively.[28] The mean length of hospital stay has been reported to be 3.4–3.9 days among US infants, while a median length of stay of 2 days has been observed among infants or children aged <2 years in the UK.[28-30] The economic burden of severe disease necessitating hospital admission among infants is substantial, costing between $US469 million and $US1.1 billion annually, based on data collected between 1997 and 2002.[29-31] In the UK, the direct costs of RSV-related and bronchiolitis-associated hospitalization have been estimated to be £180 734 and £140 646 per year, respectively, based on data collected between 1996 and 1999.[28] Costs per individual hospitalization depend upon patient-specific risk factors, such as premature birth at ≤35 weeks' gestational age (WGA).[32]

Following hospital discharge, follow-up with a paediatrician and/or pulmonary specialist is usually necessary.[27] In a study conducted in the UK,[33] children with a history of prematurity (<32 WGA) and CLD who were hospitalized for RSV infection during their first 2 years of life were found to have increases in hospitalization days, overall and respiratory-related outpatient visits, and prescription requirements (overall and for respiratory-related problems) between the ages of 2 and 4 years compared with matched controls without a history of RSV hospitalization. Those infants with a history of hospitalization due to RSV were also found to have a lower health-related quality of life (HR-QOL) score at

age 5 years. The median total cost of care (£2630 vs £1361; p = 0.0154), the median cost of outpatient visits (£756 vs £356; p < 0.0001) and the median cost of prescriptions (£40 vs £27; p = 0.0019) were significantly greater over the 3-year study period in those children with a history of RSV-related hospitalization (year of valuation not reported).

The true economic impact of RSV-related hospitalization extends beyond these direct costs, and has been associated with substantial out-of-pocket expenses and losses in time and productivity of affected families, both during admission and following hospital discharge.[34,35] In a 2000–1 US study,[34] the mean out-of-pocket expenses (travel, parking, meals, child care and other expenses) and total economic burden (out-of-pocket expenses plus the estimated value of losses in productivity) were reported to be $US644 and $US4517 per RSV-related hospitalization for premature infants, and $US214 and $US2135 per RSV-related hospitalization for full-term infants, respectively (year of valuation not reported). The mean out-of-pocket expenses were increased in infants admitted to the ICU ($US1192) compared with infants admitted to the acute care floor ($US252). The mean time spent by parents and visitors was 282 and 140 hours for premature and full-term infants, respectively. These monetary and time losses continued for at least 1 month following discharge from the hospital.

In a 1998–2000 study conducted in the Netherlands,[35] parents lost a median of 0.3 and 1.5 workdays prior to and during the RSV-related hospitalization, respectively. When the costs associated with this lost work time were added to costs associated with travel and consultation of the family physician, the total out-of-pocket expenses incurred equated to $US295 per child (year of valuation not reported).

Several long-term health consequences, including asthma, clinical allergy and allergic sensitization, have been attributed to RSV disease, but the economic burden of these has not yet been determined.

3. Method of Review

A MEDLINE search was performed, covering 1950 to 15 April 2009. The full MEDLINE search strategy was as follows: ('respiratory syncytial virus, human' OR 'bronchiolitis, viral' OR 'respiratory syncytial virus infections' OR 'respiratory syncytial viruses' OR 'bronchiolitis') AND ('palivizumab' OR 'motavizumab' OR 'immunoglobulins, intravenous') AND ('cost-benefit analysis' OR 'cost-effective' OR 'cost-effectiveness') AND ('limit to English language'). In order to perform a more complete search of the literature, the reference lists of relevant publications were searched. Thus, further studies detailing the cost effectiveness of RSV-IGIV, palivizumab or motavizumab were included. We excluded review articles, letters, research published as an abstract only and analyses that did not detail study methodology.

A total of 89 titles and abstracts were identified and screened, resulting in 40 studies retrieved in full-text format for distribution to the authors. Following independent screening by two investigators, 25 studies met the inclusion criteria and were included in the final review (figure 1). Six studies analysed the cost effectiveness of RSV-IGIV, 14 analysed the cost effectiveness of palivizumab, five analysed the cost effectiveness of both agents (two of which directly compared RSV-IGIV with palivizumab), while none analysed the cost effectiveness of motavizumab.

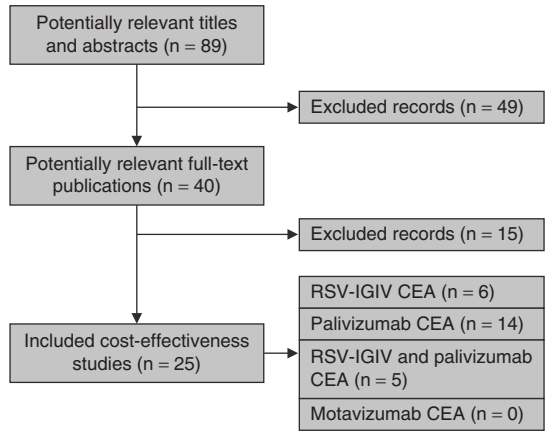

Fig. 1. Flow diagram of included studies. **CEA** = cost-effectiveness analysis; **n** = number of studies; **RSV-IGIV** = respiratory syncytial virus immune globulin intravenous.

4. Cost Effectiveness of RSV Prophylaxis

4.1 Economic Issues of RSV Prophylaxis: Modelling within Cost-Effectiveness Analyses and Cost Drivers

RSV prophylaxis with RSV-IGIV or palivizumab is associated with high medication acquisition costs. Although RSV-IGIV is no longer marketed in the US, it has an acquisition cost that is relatively similar to palivizumab. Palivizumab, now the most widely available RSV prophylactic agent, is supplied preservative-free in 50 mg and 100 mg single-use vials at an average wholesale price (AWP) of approximately $US1018 and $US1923 per vial,[36] respectively (the medication acquisition costs of palivizumab may be slightly less than the AWP and may vary across different nations). For a 4.8 kg infant (the mean weight within the IMpact-RSV trial),[4] this translates to an estimated cost of $US1923 per dose (15 mg per kg per dose = 72 mg per dose) and $US9615 per season (five doses), assuming the 100 mg vial is used in a single-dose fashion. A cost-saving method for palivizumab administration, wherein single-dose vials are used for multiple patients, has been shown to minimize drug wastage and therefore medication costs, without compromising safety.[37]

The total cost of RSV prophylaxis with palivizumab does extend beyond the acquisition cost of the medication, and includes time spent administering the medication, coordinating office visits and obtaining prior authorization from insurance carriers. A 2001–2 US study estimated these activities to cost $US300 per patient per season.[38] Data detailing the costs of palivizumab administration outside the US have not been published. RSV-IGIV has additional significant expenses associated with its use, including the need for infusion pumps and extensive personnel time devoted to administering the 4-hour intravenous infusion.

A vast number of patients qualify for prophylaxis under the AAP recommendations. However, the AAP has stated in its RSV prophylaxis guidelines[22] that although many infants will qualify for prophylaxis, the risk of hospitalization for severe RSV disease will be low, and the potential benefits may be outweighed by the costs and logistical issues associated with providing prophylaxis. They have thus revised their guidelines in an effort to ensure optimal balance of benefit and cost.[25] Cost-effectiveness analyses are therefore of great importance in helping the medical community determine who should receive RSV prophylaxis.

Significant variation exists in the modelling used in analyses assessing the cost effectiveness of RSV prophylaxis. Many studies have examined short-term benefits such as reducing hospitalizations and associated costs, while fewer studies have examined long-term benefits such as QALYs or life-years gained. Analyses of hypothetical cohorts based on published reports were more likely to identify cost per QALY as an outcome than those based on reviews of a specific population.

Although discounting was included appropriately in studies where long-term outcomes were analysed, the discount rates varied. Discounting most significantly reduced benefits associated with avoided asthma; however, all long-term clinical and economic benefits were greatly moderated because of the extended time over which these benefits were realized.

The payer and society were the most common perspectives used among the analyses, and serve to represent primary decision makers in coverage choices within most nations. Interestingly, one study,[39] which examined the cost effectiveness of palivizumab, provided analysis from the provider's perspective with the goal of imparting providers with guidance for directed prescribing.

Significant differences were found in the results of these economic analyses. The direct and indirect costs of the agents used to prevent RSV are not trivial, and should be reviewed before implementing guidelines for their use. Like many other anti-infective agents, appropriate use provides the best value regardless of the perspective. Accordingly, determining appropriate use of RSV prophylaxis at the local level is a key cost driver. Local factors, such as regional RSV infection incidence rates and health status of the infant population, must be taken into consideration. Given similar efficacy, higher direct medical costs associated with the method of drug administration, and more limited availability of RSV-IGIV compared with palivizumab, a substantial

reduction in drug acquisition costs would have to be realized in order to identify RSV-IGIV as the preferred agent. Acquisition cost and administration cost, which were rarely delineated in the published analyses, appear to be the primary drivers that increase costs in individuals receiving prophylaxis. This is highlighted in one study,[40] which identified the cost of the prophylaxis agent (palivizumab) as the only cost component that was significantly different in individuals who did and did not receive prophylaxis. When identified, hospitalization expenses, including decreases in the number of admissions and length of stay, were the primary drivers responsible for reducing cost.

In cases where asthma prevention was considered, this was not identified as a primary driver of cost effectiveness.[41] In another analysis,[42] rational selection of the population receiving prophylaxis was reported to greatly influence the costs and outcomes of RSV prophylaxis. Decision makers must consider the relative cost of services and the prophylaxis agents as well as the acceptable cost-effectiveness threshold in their respective nation when assessing the cost and outcomes of prophylaxis against RSV. Given all of this information, the primary driver of cost effectiveness is the population eligible to receive prophylaxis in which the study was conducted.

4.2 RSV-Immune Globulin Intravenous

RSV-IGIV is a solution of immune globulin G (IgG) from pooled human plasma selected for high titers of neutralizing antibody against RSV. Because RSV-IGIV is a pooled immune globulin, it is also likely to contain IgG for other respiratory and non-respiratory pathogens, a potential advantage compared with other preventive measures. This widened spectrum of activity may therefore extend the effectiveness of this agent beyond RSV to a variety of infectious diseases that would further impact the utilization of healthcare resources, making the overall cost effectiveness difficult to determine. When specifically evaluated for RSV prophylaxis, several studies have compared RSV-IGIV with no prophylaxis or with palivizumab in a variety of paediatric populations including infants at different gestational ages with and without additional risk factors for severe RSV disease.[43-50] Although RSV-IGIV has largely been replaced by palivizumab in many countries, it is still a clinically viable option for the prevention of RSV, and its cost effectiveness is therefore worth consideration. Several studies, all of which were set in the US, have evaluated the cost effectiveness of RSV-IGIV prophylaxis compared with a historical, non-prophylaxis cohort (table I).

In a retrospective analysis,[43] the severity of illness and cost of RSV-related care for premature infants ≤32 WGA was compared during the two winter seasons before (n = 159) and after (n = 195) the implementation of RSV prophylaxis in 1996. Of the 195 premature infants included in the RSV prophylaxis group, only 100 actually received RSV-IGIV. Following the initiation of RSV prophylaxis, the incidence of RSV hospitalization was significantly reduced (8.7% vs 22%; p = 0.00049). The length of hospital admission was reduced by 83.8% (p = 0.00055), the length of paediatric ICU admission by 92.7% (p = 0.00029) and the days of intubation by 95.6% (p = 0.00024). The amount spent on RSV-related care (hospitalizations and prophylaxis) in infants at risk for RSV was reduced by 65% in the cohort of infants born after implementation of a policy to provide prophylaxis was initiated ($US234 596 vs $US670 590 per 100 infants at risk; p = 0.00056; year of valuation not reported).

Four studies were performed using decision-analysis methodologies,[44-47] of which only one found RSV-IGIV to be cost effective in the general high-risk population: premature infants and infants or children with CLD or CHD.[45] Three analyses determined RSV-IGIV to be not cost effective in the general high-risk population as a whole, of which one included premature infants ≤32 WGA,[46] two included premature infants ≤35 WGA,[44,47] three included infants or children with CLD aged ≤24 months[44,46,47] and one included infants or children with severe immunodeficiency.[46] Analysis of these high-risk groups revealed RSV-IGIV prophylaxis to be most cost effective in infants with CLD.[44,46,47] In the fourth study, decision analysis using data from a

Table I. Economic analyses of respiratory syncytial virus immune globulin intravenous (RSV-IGIV) prophylaxis

Study, year (year of valuation),[a] country	Population (perspective)	Methodology	Outcome measure	Results
Atkins et al.,[43] 2000, US	Premature infants ≤32 WGA (payer)	Retrospective analysis comparing severity of illness and cost of RSV-related care during the two winter seasons before and after prophylaxis	RSV-related expenditures	RSV-related expenditures per 100 infants at risk for RSV were reduced by 65% in the cohort of infants born after implementation of a policy to provide prophylaxis was initiated: $US234 596 vs $US670 590 per 100 infants at risk ($p = 0.00056$)
Barton et al.,[44] 2001 (1997), US	Various populations from multiple studies (payer)	Decision analysis comparing costs, outcomes and cost effectiveness of administering RSV-IGIV vs no treatment in different paediatric populations	Cost per RSV hospitalization avoided	If only infants at high risk of severe RSV infections received treatment with RSV-IGIV, a calculated cost saving of about $US27 000 per hospitalization prevented. If the US FDA indications for RSV-IGIV were followed, the cost to prevent one hospitalization due to RSV bronchiolitis was >$US53 000
Hay et al.,[45] 1996 (1993), US	Various populations from multiple studies (societal)	Decision analysis with the main endpoint of cost per life-year saved	Cost per life-year saved	Overall cost per life-year saved was $US24 305. If all high-risk infants were given prophylaxis in the US, total cost of care would decrease from $US628 million to $US178 million
Oelberg et al.,[46] 1998, US	From multiple studies[b,c] (payer)	Decision analysis comparing the cost benefit of (three groups) high-risk infants without RSV-IGIV, all high-risk infants with RSV-IGIV and infants with CLD with RSV-IGIV	RSV-related expenditures	RSV-IGIV prophylaxis was only cost effective when limited to prophylaxis in high-risk infants with active CLD
Robbins et al.,[50] 1998, US	High-risk infants and young children[d] (payer)	NNT analysis to determine how many high-risk infants would require RSV treatment to avoid one hospital admission using data taken from three RCTs and willingness-to-pay data from 39 healthcare professionals	Cost per RSV hospitalization avoided	Overall NNT was ≥16. As low as NNT = 12 with CLD and as high as NNT = 63 for premature infants without CLD
O'shea et al.,[47] 1998 (1996), US	Preterm very low birth weight infants with and without CLD[e] (payer)	Economic model comparing benefits of prophylaxis with RSV-IGIV in preterm infants and infants with CLD using 30-month period encompassing three RSV seasons	Cost/benefit of prophylaxis	The estimated net cost of prophylaxis per infant ranged between $US5415 for a 6 kg infant without CLD to $US1689 for an infant with CLD and age ≤3 months

a Not all studies reported the year of valuation.

b High-risk infants with CLD.

c Children aged <2 years with history of CLD or <32 WGA.

d Children aged <2 years with diagnosis of CLD, aged <4 years with CLD or CHD, <35 WGA and aged <6 months, infants with cardiomyopathy.

e Birth weight <1500 g and <36 WGA.

CHD = congenital heart disease; **CLD** = chronic lung disease; **NNT** = number needed to treat; **RCT** = randomized controlled trial; **WGA** = weeks' gestational age.

Table II. Economic analyses of palivizumab prophylaxis; analyses using hypothetical cohorts based on published data

Study, year (year of valuation),[a] country	Population (perspective)	Methodology	Outcome measure	Results
Marchetti et al.,[55] 1999, US	IMpact trial[b] (payer)	Identify and compare expected RSV-related healthcare expenditures incurred by preterm infants who received prophylaxis with palivizumab vs preterm infants who did not receive such prophylaxis	RSV-related expenditures	Expenditure changes for each infant if all infants at risk of LRTI received prophylaxis ranged from an increase of $US3459 to savings of $US39 107
Lofland et al.,[39] 2000, US	From multiple studies[c] (provider)	CEA based on IMpact study; decision-analytic model included costs to the healthcare system (rather than charges or payments) such as acquisition cost and physician/home healthcare visits; sensitivity analysis performed for cost of therapy, cost of hospitalization and no. of visits (ED, office and home health)	Cost per RSV infection avoided	Incremental cost per avoided RSV infection ranged from $US2702 (prophylaxis reduces infection rate from 38% to 5%, prophylaxis costs $US4500) to $US79 706 (reduction from 10% to 5%, $US4500)
Roeckl-Wiedmann et al.,[42] 2003, Germany	Premature infants ≤35 WGA (societal)	Decision-tree analysis of multiple scenarios; clinical outcomes were modelled after the IMpact study, while costs (direct and indirect) consisted of administration costs of palivizumab, the cost for a RSV-related hospitalization and work-loss costs (for one parent)	Costs and benefits of avoided RSV hospitalization	Prophylaxis was more costly than no prophylaxis and was associated with a range of costs per hospitalization avoided from €6639 (high-risk infants ≤35 WGA with siblings in day care discharged between Oct and Dec with CLD) to €204 684 (male infants ≤35 WGA). The NNT ranged from 4 to 54
Yount and Mahle,[57] 2004, US	Infants and children with CHD per AAP guidelines[22][d] (provider and societal [authors state both])	Decision analysis/cost utility for a hypothetical cohort of 10 000 paediatric CHD patients. Direct costs included medical costs (medicine costs), medication costs (administration costs including wages) and hospitalization costs. Indirect costs included missed work (parent) and mortality value. Discounting of costs and benefits was applied at 3% per year	Cost per QALY	After discounting at a rate of 3% per year, 203.33 life-years were saved, with a cost per QALY of $US114 337
Elhassan et al.,[54] 2006 (2002), US	Premature infants ≤32 WGA (societal)	Decision tree assessing hypothetical cohorts based on published data; included asthma and associated QOL outcomes. Discounting applied at 3% annually with an ICER of $US200 000 per QALY considered cost effective	Cost per QALY	The ICER ranged from $US675 780 per QALY (infants 29–30 WGA) to $US1 855 000 per QALY (infants 32 WGA). Gestational age and ICER did not exhibit a strong relationship; however, the cohort examined was not described in detail
Nuijten et al.,[41] 2007 (2003), UK	IMpact trial[b] (payer/societal [UK NHS])	Cost-utility/cost-benefit study. Decision tree based on published literature, clinical trials and UK price/tarif lists as well as national population statistics. Costs included prophylaxis costs, hospitalization costs and clinical complications (i.e. asthma treatment costs). Lifetime outcomes were considered, with discounting employed at 3.5% annually	Cost per QALY	The ICER was calculated at £7042 per QALY without discounting and £16 720 with discounting at 3.5%

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Table II. Contd

Study, year (year of valuation),[a] country	Population (perspective)	Methodology	Outcome measure	Results
Resch et al.,[56] 2008, Austria	Premature infants ≤35 WGA and infants and children with CLD or CHD[b,d] (payer/societal [Austrian national health insurer])	Decision tree, hypothetical cohort. Costs analysed included those associated with treatment of sequelae (asthma), drug administration and hospital care associated with RSV infection in the base case. Discounting was applied at 5% in the base case (range 3–10%). Indirect costs included lost productivity. A value of €30 000 per QALY was chosen as the cost-effectiveness threshold	Cost per QALY	Palivizumab use increased medical costs by €3159. Including direct costs of asthma reduced the additional costs for palivizumab to €2336. A total of 0.13 (discounted) and 0.42 (non-discounted) QALYs were gained when palivizumab was used. The discounted base-case ICER per QALY was calculated as €31 867 in subjects with CLD, €20 704 in subjects born pre-term, and €11 390 in those with CHD

a Not all studies reported the year of valuation.

b Premature infants ≤35 WGA and aged ≤6 months; or infants and children aged ≤24 months with CLD.

c Premature infants ≤32 WGA; or premature infants ≤35 WGA and aged ≤6 months; or premature infants ≤35 WGA; or infants and children aged ≤24 months with CLD; or infants with birth weight <1500 g.

d Infants and children aged ≤24 months with haemodynamically significant cyanotic and acyanotic CHD.

AAP = American Academy of Pediatrics; **CEA** = cost-effectiveness analysis; **CHD** = congenital heart disease; **CLD** = chronic lung disease; **ICER** = incremental cost-effectiveness ratio; **LRTI** = lower respiratory tract infection; **NNT** = number needed to treat; **QOL** = quality of life; **RSV** = respiratory syncytial virus; **WGA** = weeks' gestational age.

multicentre randomized trial of RSV-IGIV and annual RSV incidence rates determined the overall costs of prophylaxis with RSV-IGIV in the US in premature infants (≤35 WGA and <6 months old) and infants or children with CLD or CHD aged <48 months.[45] The estimated median cost per life-year saved of $US24 305 if all high-risk infants received prophylaxis in the US compares favourably with other standard medical interventions (year 1993 values). In another study,[50] the number needed to treat (NNT) in order to prevent one RSV-related hospital admission was reported to be 16, but was population dependent, since NNTs as low as 12 in premature infants with CLD and as high as 63 for premature infants without CLD were reported.

4.3 Palivizumab

The efficacy of palivizumab, a monoclonal antibody specific to RSV, has been established.[4] However, the cost effectiveness of this agent has been widely debated.[51-53] Numerous economic analyses using hypothetical cohorts based solely on published data have been conducted.[39,41,42,54-57] The details of these analyses (i.e. those using hypothetical cohorts based solely on published data) are summarized in table II.

Furthermore, several studies have utilized hypothetical cohorts based on retrospective analysis.[26,58-61] Three analyses of palivizumab cost effectiveness have included premature infants with and without CLD. One analysis, based on a retrospective case review set in Australia, found that providing prophylaxis with palivizumab to high-risk infants (identified as premature infants ≤32 WGA, infant birth weight <2500 g, and all indigenous infants [Aboriginal or Torres Strait Islander]) was expected to require 11–16 patients to be treated at a cost of Australian dollars ($A)69 861–98 818 to prevent one hospitalization (year of valuation not reported).[61]

An analysis in Argentina estimated the costs incurred by premature infants (≤35 WGA and ≤6 months old, or ≤28 WGA and ≤12 months old) and infants or children aged ≤24 months with CLD in a neonatal ICU (NICU) provided with palivizumab. The NNT was estimated to be 7.9 patients

at a cost of $US15 358 (year 2000 values) to prevent one hospitalization.[58] Another report[62] submitted by a co-author of that study described the results of a retrospective and prospective cohort study examining expenditures in infants or children with or without CLD in Argentina. The analysis found that the NNT was lowest among infants or children without CLD who have older siblings (NNT = 4.5, cost per hospitalization avoided $US13 198), and was highest among infants and children without CLD or older siblings (NNT = 25, cost per hospitalization avoided $US89 902; year 2007 values). The NNT among infants or children with CLD ranged from 6.6 to 12.5, while the cost per hospitalization avoided ranged from $US21 152 to $US43 027.

An analysis based on premature infants <32 WGA in a New Zealand hospital examined the cost per case averted. The NNT to prevent one RSV hospitalization can be calculated from the authors' report that 3.51 cases would have been prevented had 40 infants been treated (NNT = 11.4). The cost per case averted was reported to be New Zealand dollars ($NZ)65 305 (year 2000 values).[26]

Two analyses of the cost effectiveness of palivizumab have included infants or children with CHD. An analysis set in Norway[59] reviewed 500 cases of RSV in infants or children aged <2 years with CHD to assess the NNT to prevent a single RSV-related hospitalization. Based on a hospitalization rate of 9.2% in individuals with severe CHD, it was reported that 24 individuals must be treated at an expected expense of $US195 000 to avoid one hospitalization (year of valuation not reported). An analysis[60] that included infants in the UK aged <1 year with CHD reported that each admission averted would have been associated with an additional cost of £17 700 or $US34 100 (year of valuation not reported).

Only a few studies performed economic analyses based on individuals that actually received palivizumab. While these analyses are subject to the strengths and weaknesses traditionally associated with observational studies (e.g. prescriber guided rather than protocol guided, etc.), they do provide insight into the costs and outcomes in a real-world setting. One cohort study from the US,[40] which examined 374 Medicaid-enrolled premature infants 32–35 WGA in North Carolina, reported that RSV-related hospitalization was reduced from 6.6% to 2.7% with palivizumab prophylaxis ($p = 0.078$). After controlling for co-variates, the odds ratio of admission was found to be 0.27 ($p = 0.058$) with a cost per patient of $US5436 in the cohort receiving prophylaxis compared with $US505 in the comparator cohort ($p < 0.0001$; year 2003 values). The only cost component found to be significantly different was the cost of palivizumab.

Another retrospective cohort study from the US[63] examined Medicaid-enrolled premature infants or infants with CLD aged <10 months in Kansas receiving either palivizumab (n = 136) or RSV-IGIV (n = 1), and compared these subjects with 137 matched controls. This analysis sought to determine the cost-benefit ratio of providing prophylaxis. Total prophylaxis-related expenditures were $US4687 per treated individual, while hospitalization costs were reduced by $US703 per admission (year of valuation not reported), providing a cost-benefit ratio (cost per unit of benefit, as reported by the authors) of 6.67 (e.g. for every $6.67 spent on prophylaxis, hospitalization costs were reduced by $1). These analyses further support the theory that prophylaxis with palivizumab is not cost saving.

4.4 RSV-Immune Globulin Intravenous and Palivizumab

Five studies compared the cost advantages and disadvantages of both RSV-IGIV and palivizumab with no prophylaxis in infants (table III).[48,49,63-65] Two retrospective studies directly compared the relative cost effectiveness of RSV-IGIV versus palivizumab.[48,49] In one US study,[49] both prophylaxis agents increased the net cost of care among premature infants born at ≤32 WGA when examined from a payer perspective (although the perspective was not stated specifically by the authors). Palivizumab was found to be more cost effective in preventing RSV hospitalization for infants <36 weeks' post-conceptional age (PCA) requiring respiratory support, especially among those <26 WGA. In

Table III. Economic analyses of both respiratory syncytial virus immune globulin intravenous (RSV-IGIV) and palivizumab prophylaxis

Study, year (year of valuation),[a] country	Population (perspective)	Methodology	Outcome measure	Results
Joffe et al.,[48] 1999 (1995), US	Premature infants[b] (societal)	Decision analysis comparing projected societal cost effectiveness of three strategies: RSV-IGIV, palivizumab and no prophylaxis among a hypothetical cohort of premature infants	Cost per RSV infection avoided	In specific pts,[c] palivizumab was predicted to cost $US12 000 per hospitalization averted or $US33 000 per LY saved vs $US25 000 and $US70 000 for RSV-IGIV; NNT to avoid one hospitalization estimated at 7.4 for palivizumab and 8.5 for RSV-IGIV
Numa,[64] 2000, Australia	High-risk infants[d] (payer)	Retrospective study comparing costs and outcomes using data from Australian hospital and intensive care databases over a 3-year period	Cost/benefit	Cost of prophylaxis was estimated to be between 7.2- and 65.3-fold the cost saved in hospital care, depending on the weight of the pt and choice of drug
Schrand et al.,[65] 2001 (1999), US	High-risk infants[e] (hospital)	Decision analysis comparing pts who received either RSV-IGIV or palivizumab during the 1998–9 RSV season with pts identified from the 1994–5 RSV season who would have been eligible to receive prophylaxis had either agent been available	Cost/benefit	The average costs for the RSV prophylaxis group were less per pt: $US3733 vs $US4258 in pts who did not receive prophylaxis; benefit/cost ratio was 1.15 : 1
Shireman and Braman,[63] 2002, US	At-risk infants[f] (payer)	Retrospective cohort study of Kansas Medicaid pts from the 1999–2000 RSV season aged <10 months, and born premature or with CLD	Hospital admissions and costs	Reduced odds of hospitalization to 0.47 and hospitalization costs by $US703; cost/benefit ratio was 6.67
Stevens et al.,[49] 2000, US	Premature infants[b] (payer)	Historical cohort assessing risk of hospitalization with RSV and economic impact of RSV prophylaxis in infants born ≤32 WGA	Cost per hospitalization prevented	The cost per hospitalization prevented and NNT decreased with lower WGA in the prophylaxis groups; palivizumab was more cost effective than RSV-IGIV in infants who required respiratory support at <36 weeks' PCA, while RSV-IGIV was more cost effective than palivizumab in infants who required respiratory support at ≥36 weeks' PCA

a Not all studies reported the year of valuation.

b Infants <32 WGA.

c Infants ≤32 WGA who required ≥28 days of oxygen in the NICU, and who were discharged from the NICU from September through November.

d Children aged <2 years with CLD, immune deficiency or CHD.

e Children aged <2 years with prematurity <28 WGA, CLD, interstitial pulmonary fibrosis of prematurity, Wilson-Mikity syndrome, or unspecified respiratory condition of foetus/newborn.

f Infants aged <10 months who were born premature or with CLD.

CHD = congenital heart disease; **CLD** = chronic lung disease; **LY** = life-year; **NICU** = neonatal ICU; **NNT** = number needed to treat; **PCA** = postconceptional age; **pt** = patient; **WGA** = weeks' gestational age.

contrast, RSV-IGIV was found to be more cost effective for infants ≥36 weeks' PCA requiring respiratory support.

In a second US study,[48] palivizumab was found to be more effective and less costly than RSV-IGIV among premature infants when examined from a societal perspective. Among infants ≤32 WGA who required ≥28 days of oxygen in the NICU, and who were discharged from the NICU from September through November, palivizumab was predicted to cost $US12 000 per hospitalization averted, or $US33 000 per life-year saved (year 1995 values), with an NNT in order to avoid one hospitalization estimated at 7.4. In this same patient population, RSV-IGIV was much more costly, at $US25 000 per hospitalization averted, and $US70 000 per life-year saved, with an NNT in order to avoid one hospitalization estimated at 8.5. The cost effectiveness of these agents in other patient populations (month of NICU discharge between December and August and/or <28 days of oxygen treatment in the NICU and/or 33–35 WGA) was variable; for palivizumab it ranged from $US38 000 to $US420 000 per hospitalization averted, or $US110 000 to $US1 200 000 per life-year saved, with an NNT to avoid one hospitalization estimated at 17–152, while for RSV-IGIV it ranged from $US67 000 to $US690 000 per hospitalization averted, or $US190 000 to $US1 900 000 per life-year saved, with an NNT in order to avoid one hospitalization estimated at 19–170.

The studies evaluating both palivizumab and RSV-IGIV do not provide a consensus. Two studies reported favourable cost effectiveness,[48,65] whereas three studies reported the cost effectiveness to be non-favourable.[49,63,64] Where cost effectiveness was noted, it was maximized among infants of younger gestational age and among infants with CLD. These mixed results are similar to what was noted in a previous review of the literature.[52]

5. Discussion

RSV prophylaxis is expected to have only a minor impact on the total economic burden of RSV disease. However, RSV prophylaxis has been shown to reduce the incidence of hospitalization related to severe RSV disease in high-risk infants.[3,4,7,8] The high acquisition cost of RSV prophylaxis has prompted extensive study into the costs and benefits associated with use of these agents.

Comparison of the results for the two RSV prophylaxis agents suggests palivizumab may be the more cost-effective option in the population for which RSV prophylaxis is recommended. However, although some studies have reported acceptable cost-effectiveness ratios for RSV prophylaxis, the majority of analyses have failed to show cost savings or cost-effectiveness ratios below commonly accepted thresholds for either RSV-IGIV or palivizumab. It should be noted that the year of valuation for cost data was not reported in some studies. While each payer and each nation must decide the investment that they are willing to make to obtain an additional life-year, QALY or avoided hospitalization, these analyses reinforce the notion that RSV prophylaxis does not lead to cost savings and is associated with a high cost per benefit gained among high-risk infants and children, e.g. premature infants and infants or children with CLD or CHD. Some nations or payers may have formal incremental cost-effectiveness ratios (such as the 'traditional' threshold of $US50 000 per QALY) that are considered acceptable and are likely based on the local economy; however, others will evaluate both the cost effectiveness and social justice of a treatment option when considering reimbursement.

In order to optimize cost benefit for either RSV-IGIV or palivizumab, RSV prophylaxis should be restricted to high-risk populations during peak outbreak months. Delaying prophylaxis until after the season has begun may result in high-risk infants not receiving the full benefit of RSV prophylaxis, while too-early initiation or continuation of prophylaxis following the termination of the RSV season is not cost effective and yields little benefit to recipients. Using the strictest criteria, it appears that providing guided 'in-season' prophylaxis focused on premature infants, especially those ≤32 WGA, and infants or children with CLD or CHD, provides a more favourable clinical and economic benefit.

The endpoints examined in the studies were variable and generally did not account for the potential impact of RSV prophylaxis on RSV-related complications such as asthma. Inclusion of other outcomes should positively impact the cost effectiveness of the agents; however, when long-term outcomes such as asthma were considered, economic analyses did not have substantially improved outcomes. While this may be the appropriate conclusion, it may also be due to gaps in understanding of the true cost of the disease, and is influenced by discounting. Over time, pending the establishment of regulatory pathways for biosimilars, the acquisition cost of these RSV prophylaxis agents may decrease, and more acceptable outcomes of economic analyses may result.

Cost-effectiveness analyses are important tools that help decision makers allocate resources rationally and effectively in order to optimize health outcomes for populations while considering available resources. However, the results of economic analyses are not the only tool that decision makers rely upon when developing treatment guidelines and making clinical decisions. Efficacy and safety (including side effect and adverse event profiles) must be considered primarily, and when making clinical decisions, consideration of the needs of vulnerable populations, such as those who cannot champion their own cause, is imperative.

6. Conclusion

Overall, from the various economic analyses of RSV prophylaxis, it appears that palivizumab may be more cost effective than RSV-IGIV, although the majority of studies found neither agent to have favourable cost effectiveness. RSV prophylaxis needs to be targeted to both high-risk patients and the RSV season in order to optimize cost benefit.

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References

1. Black CP. Systematic review of the biology and medical management of respiratory syncytial virus infection. Respir Care 2003 Mar; 48 (3): 209-33
2. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA 2003 Jan 8; 289 (2): 179-86
3. Reduction of respiratory syncytial virus hospitalization among premature infants and infants with bronchopulmonary dysplasia using respiratory syncytial virus immune globulin prophylaxis. The PREVENT Study Group. Pediatrics 1997 Jan; 99 (1): 93-9
4. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. The IMpact-RSV Study Group. Pediatrics 1998 Sep; 102 (3 Pt 1): 531-7
5. Carbonell X, Losonsky G, Hultquist M, et al. Phase 3 trial of motavizumab (MEDI-524), an enhanced potency respiratory syncytial virus (RSV) specific monoclonal antibody (Mab) for the prevention of serious RSV disease in high risk infants [abstract 8220.9]. The Pediatric Academic Societies Annual Meeting; 2007 May 8; Toronto (ON)
6. Chandran A, Millar EV, Weatherholtz R, et al. Safety and efficacy of motavizumab in the prevention of RSV disease in healthy infants [abstract no. 4460.5]. The Pediatric Academic Societies Annual Meeting; 2008 May 4; Honolulu (HI)
7. 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 Oct; 143 (4): 532-40
8. Groothuis JR, Simoes EA, Levin MJ, et al. Prophylactic administration of respiratory syncytial virus immune globulin to high-risk infants and young children. The Respiratory Syncytial Virus Immune Globulin Study Group. N Engl J Med 1993 Nov 18; 329 (21): 1524-30
9. Forbes M. Strategies for preventing respiratory syncytial virus. Am J Health Syst Pharm 2008 Dec 1; 65 (23 Suppl. 8): S13-9
10. Checchia P. Identification and management of severe respiratory syncytial virus. Am J Health Syst Pharm 2008 Dec 1; 65 (23 Suppl. 8): S7-12
11. Leader S, Kohlhase K. Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999. Pediatr Infect Dis J 2002 Jul; 21 (7): 629-32
12. Shay DK, Holman RC, Newman RD, et al. Bronchiolitis-associated hospitalizations among US children, 1980–1996. JAMA 1999 Oct 20; 282 (15): 1440-6
13. Shay DK, Holman RC, Roosevelt GE, et al. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979–1997. J Infect Dis 2001 Jan 1; 183 (1): 16-22
14. World Health Organization. Respiratory syncytial virus and parainfluenza viruses [online]. Available from URL: http://www.who.int/vaccine_research/diseases/ari/en/index2.html [Accessed 2009 Sep 2]
15. Willson DF, Landrigan CP, Horn SD, et al. Complications in infants hospitalized for bronchiolitis or respiratory

syncytial virus pneumonia. J Pediatr 2003 Nov; 143 (5 Suppl.): S142-9

16. Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr 2003 Nov; 143 (5 Suppl.): S150-6
17. Boyce TG, Mellen BG, Mitchel Jr EF, et al. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000 Dec; 137 (6): 865-70
18. Holman RC, Shay DK, Curns AT, et al. Risk factors for bronchiolitis-associated deaths among infants in the United States. Pediatr Infect Dis J 2003 Jun; 22 (6): 483-90
19. Thomas M, Bedford-Russell A, Sharland M. Prevention of respiratory syncytial virus infection with palivizumab. Monaldi Arch Chest Dis 2000 Aug; 55 (4): 333-8
20. Diagnosis and management of bronchiolitis. Pediatrics 2006 Oct; 118 (4): 1774-93
21. Respiratory syncytial virus immune globulin intravenous: indications for use. American Academy of Pediatrics Committee on Infectious Diseases, Committee on Fetus and Newborn. Pediatrics 1997 Apr; 99 (4): 645-50
22. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003 Dec; 112 (6 Pt 1): 1442-6
23. Meissner HC, Long SS. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003 Dec; 112 (6 Pt 1): 1447-52
24. Simoes EA, Groothuis JR, Carbonell-Estrany X, et al. Palivizumab prophylaxis, respiratory syncytial virus, and subsequent recurrent wheezing. J Pediatr 2007 Jul; 151 (1): 34-42
25. Committee on Infectious Diseases. Policy statement: modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. Pediatrics 2009 Dec; 124 (6): 1694-701
26. Vogel AM, McKinlay MJ, Ashton T, et al. Cost-effectiveness of palivizumab in New Zealand. J Paediatr Child Health 2002 Aug; 38 (4): 352-7
27. Peralta M, Johnson SE, Preskitt J. Respiratory syncytial virus (RSV) infections in a children's hospital: who were they and how much did they cost? [abstract]. 4th International Congress on Pediatric Pulmonary Disease; 2000 Feb 21-24; Nice
28. Deshpande SA, Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. Arch Dis Child 2003 Dec; 88 (12): 1065-9
29. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr 2003 Nov; 143 (5 Suppl.): S127-32
30. Pelletier AJ, Mansbach JM, Camargo Jr CA. Direct medical costs of bronchiolitis hospitalizations in the United States. Pediatrics 2006 Dec; 118 (6): 2418-23
31. McLaurin KK, Leader S. Growing impact of RSV hospitalizations among infants in the US, 1997–2002 [abstract no. 936]. The Pediatric Academic Societies Annual Meeting; 2005 May 41; Washington, DC
32. Horn SD, Smout RJ. Effect of prematurity on respiratory syncytial virus hospital resource use and outcomes. J Pediatr 2003 Nov; 143 (5 Suppl.): S133-41
33. Greenough A, Alexander J, Burgess S, et al. Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. Arch Dis Child 2004 Jul; 89 (7): 673-8
34. Leader S, Yang H, DeVincenzo J, et al. Time and out-of-pocket costs associated with respiratory syncytial virus hospitalization of infants. Value Health 2003 Mar-Apr; 6 (2): 100-6
35. Miedema CJ, Kors AW, Tjon ATWE, et al. Medical consumption and socioeconomic effects of infection with respiratory syncytial virus in the Netherlands. Pediatr Infect Dis J 2001 Feb; 20 (2): 160-3
36. Redbook™ for Windows®. Version 61127 (updated 2009 Feb). Greenwood Village (CO): Thompson PDR, 2009
37. Gooding J, Millage A, Rye AK, et al. The cost and safety of multidose use of palivizumab vials. Clin Pediatr (Phila) 2008 Mar; 47 (2): 160-3
38. Helm EA, Cummings GE, Keane V, et al. Administration of palivizumab: a medical provider's perspective. Clin Pediatr (Phila) 2003 Nov-Dec; 42 (9): 821-6
39. Lofland JH, O'Connor JP, Chatterton ML, et al. Palivizumab for respiratory syncytial virus prophylaxis in high-risk infants: a cost-effectiveness analysis. Clin Ther 2000 Nov; 22 (11): 1357-69
40. Wegner S, Vann JJ, Liu G, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. Pediatrics 2004 Dec; 114 (6): 1612-9
41. Nuijten MJ, Wittenberg W, Lebmeier M. Cost effectiveness of palivizumab for respiratory syncytial virus prophylaxis in high-risk children: a UK analysis. Pharmacoeconomics 2007; 25 (1): 55-71
42. Roeckl-Wiedmann I, Liese JG, Grill E, et al. Economic evaluation of possible prevention of RSV-related hospitalizations in premature infants in Germany. Eur J Pediatr 2003 Apr; 162 (4): 237-44
43. Atkins JT, Karimi P, Morris BH, et al. Prophylaxis for respiratory syncytial virus with respiratory syncytial virus-immunoglobulin intravenous among preterm infants of thirty-two weeks gestation and less: reduction in incidence, severity of illness and cost. Pediatr Infect Dis J 2000 Feb; 19 (2): 138-43
44. Barton LL, Grant KL, Lemen RJ. Respiratory syncytial virus immune globulin: decisions and costs. Pediatr Pulmonol 2001 Jul; 32 (1): 20-8
45. Hay JW, Ernst RL, Meissner HC. Respiratory syncytial virus immune globulin: a cost-effectiveness analysis. Am J Man Care 1996; 2: 851-61
46. Oelberg D, Reininger M, Van Eeckhout J. A cost-benefit analysis of respiratory syncytial virus hyperimmune globulin (RSV-IVIG) in high-risk infants. Neonatal Intensive Care 1998; 11: 29-33
47. O'Shea TM, Sevick MA, Givner LB. Costs and benefits of respiratory syncytial virus immunoglobulin to prevent hospitalization for lower respiratory tract illness in very low birth weight infants. Pediatr Infect Dis J 1998 Jul; 17 (7): 587-93

48. Joffe S, Ray GT, Escobar GJ, et al. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. Pediatrics 1999 Sep; 104 (3 Pt 1): 419-27
49. Stevens TP, Sinkin RA, Hall CB, et al. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. Arch Pediatr Adolesc Med 2000 Jan; 154 (1): 55-61
50. Robbins JM, Tilford JM, Jacobs RF, et al. A number-needed-to-treat analysis of the use of respiratory syncytial virus immune globulin to prevent hospitalization. Arch Pediatr Adolesc Med 1998 Apr; 152 (4): 358-66
51. Embleton ND, Harkensee C, McKean MC. Palivizumab for preterm infants: is it worth it? Arch Dis Child Fetal Neonatal Ed 2005 Jul; 90 (4): F286-9
52. Kamal-Bahl S, Doshi J, Campbell J. Economic analyses of respiratory syncytial virus immunoprophylaxis in high-risk infants: a systematic review. Arch Pediatr Adolesc Med 2002 Oct; 156 (10): 1034-41
53. Strutton DR, Stang PE. Prophylaxis against respiratory syncytial virus (RSV), varicella, and pneumococcal infections: economic-based decision-making. J Pediatr 2003 Nov; 143 (5 Suppl.): S157-62
54. Elhassan NO, Sorbero ME, Hall CB, et al. Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. Arch Pediatr Adolesc Med 2006 Oct; 160 (10): 1070-6
55. Marchetti A, Lau H, Magar R, et al. Impact of palivizumab on expected costs of respiratory syncytial virus infection in preterm infants: potential for savings. Clin Ther 1999 Apr; 21 (4): 752-66
56. Resch B, Gusenleitner W, Nuijten MJ, et al. Cost-effectiveness of palivizumab against respiratory syncytial viral infection in high-risk children in Austria. Clin Ther 2008 Apr; 30 (4): 749-60
57. Yount LE, Mahle WT. Economic analysis of palivizumab in infants with congenital heart disease. Pediatrics 2004 Dec; 114 (6): 1606-11
58. Farina D, Rodriguez SP, Bauer G, et al. Respiratory syncytial virus prophylaxis: cost-effective analysis in Argentina. Pediatr Infect Dis J 2002 Apr; 21 (4): 287-91
59. Meberg A, Bruu AL. Respiratory syncytial virus infections in congenital heart defects: hospitalizations and costs. Acta Paediatr 2006 Apr; 95 (4): 404-6
60. Rackham OJ, Thorburn K, Kerr SJ. The potential impact of prophylaxis against bronchiolitis due to the respiratory syncytial virus in children with congenital cardiac malformations. Cardiol Young 2005 Jun; 15 (3): 251-5
61. Reeve CA, Whitehall JS, Buettner PG, et al. Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab. J Paediatr Child Health 2006 May; 42 (5): 253-8
62. Rodriguez SP, Farina D, Bauer G. Respiratory syncytial virus prophylaxis in a high-risk population in Argentina: a cost-effectiveness analysis. Pediatr Infect Dis J 2008 Jul; 27 (7): 660-1
63. Shireman TI, Braman KS. Impact and cost-effectiveness of respiratory syncytial virus prophylaxis for Kansas medicaid's high-risk children. Arch Pediatr Adolesc Med 2002 Dec; 156 (12): 1251-5
64. Numa A. Outcome of respiratory syncytial virus infection and a cost-benefit analysis of prophylaxis. J Paediatr Child Health 2000 Oct; 36 (5): 422-7
65. Schrand LM, Elliott JM, Ross MB, et al. A cost-benefit analysis of RSV prophylaxis in high-risk infants. Ann Pharmacother 2001 Oct; 35 (10): 1186-93

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