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Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children (Review)

Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B

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[Intervention Review]

Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children

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ABSTRACT

Background

Respiratory syncytial virus (RSV) is one of the most important viral pathogens causing acute respiratory infections, resulting in about 3.4 million hospitalisations annually in children under five. Palivizumab is the only product approved for prevention of serious RSV disease, as motavizumab is no longer being developed for this condition. The efficacy and safety of palivizumab has been evaluated in randomized controlled trials (RCTs) and a large number of economic evaluations (EEs) have tested its cost-effectiveness.

Objectives

To assess the effectiveness and safety of palivizumab prophylaxis in reducing the risk of complications (hospitalization due to RSV infection) in high-risk infants and children. To assess the cost-effectiveness (or cost-utility) of palivizumab prophylaxis in infants and children in different risk groups.

Search methods

We searched CENTRAL (2012, Issue 7), MEDLINE (1996 to July week 4, 2012), EMBASE (1996 to August 2012), CINAHL (1996 to August 2012) and LILACS (1996 to August 2012) for RCTs. We searched the NHS Economic Evaluations Database (NHS EED 2012, Issue 4), Health Economics Evaluations Database (HEED, 9 August 2012), Paediatric Economic Database Evaluations (PEDE, 1980 to 2009), MEDLINE (1996 to July week 4, 2012) and EMBASE (1996 to August 2012) for EEs.

Selection criteria

We included RCTs comparing palivizumab prophylaxis with a placebo or another type of prophylaxis in preventing serious lower respiratory tract disease caused by RSV in paediatric patients at high risk. We included cost-effectiveness analyses and cost-utility analyses comparing palivizumab prophylaxis with no prophylaxis.

Data collection and analysis

Two review authors independently assessed risk of bias for the included studies and extracted data for both the RCTs and EEs. We calculated risk ratios (RRs) and their associated 95% confidence intervals (CIs) for dichotomous outcomes and for adverse events (AEs). For continuous outcomes, we provided a narrative summary of results due to missing data on standard deviations. We performed fixed-effect meta-analyses for the estimation of pooled effects whenever there was no indication of heterogeneity between included RCTs.

We summarised the results reported in included EEs, such as incremental costs, incremental effectiveness, and incremental cost-effectiveness and/or cost-utility ratios (ICERs), and we calculated ICER present values in 2011 Euros for all studies.

Main results

Of the seven available RCTs, three compared palivizumab with a placebo in a total of 2831 patients, and four compared palivizumab with motavizumab in a total of 8265 patients. All RCTs were sponsored by the drug manufacturing company. The overall quality of RCTs was good, but most of the outcomes assessed relied on data from only two studies. Palivizumab prophylaxis was associated with a statistically significant reduction in RSV hospitalisations (RR 0.49, 95% CI 0.37 to 0.64) and a statistically non-significant reduction in all-cause mortality (RR 0.69, 95% CI 0.42 to 1.15) when compared to placebo. When compared to motavizumab, palivizumab recipients showed a non-significant increase in the risk of RSV hospitalisations (RR 1.36, 95% CI 0.97 to 1.90) and a non-significant risk reduction in all-cause mortality (RR 0.74, 95% CI 0.38 to 1.43). In both cases, the proportion of children with any AE or any AE related to the study drug was similar between the two groups.

We included 34 studies that reported cost-effectiveness and/or cost-utility data for palivizumab prophylaxis in high-risk children with different underlying medical conditions. The overall quality of EEs was good, but the variations in modelling approaches were considerable across the studies, leading to large differences in the results. The cost-effectiveness of palivizumab prophylaxis depends on the consumption of resources taken into account by the study authors, and on the cost-effectiveness threshold set by the healthcare sector in each country.

Authors' conclusions

There is evidence that palivizumab prophylaxis is effective in reducing the frequency of hospitalisations due to RSV infection, i.e. in reducing the incidence of serious lower respiratory tract RSV disease in children with chronic lung disease, congenital heart disease, or those born preterm.

Results from economic evaluations of palivizumab prophylaxis are inconsistent across studies, ranging from highly cost-effective to not cost-effective, implying that economic findings must be interpreted with caution. The availability of low-cost palivizumab would reduce its inequitable distribution, so that RSV prophylaxis would be available to the poorest countries where children are at greatest risk.

PLAIN LANGUAGE SUMMARY

Palivizumab for reducing the risk of severe RSV infection in children

Respiratory syncytial virus (RSV) infection is a major cause of acute respiratory infections in children. RSV infection can lead to morbidity and mortality in children, resulting in hospitalization, admission to an intensive care unit, the need for intensive medical therapies and death.

Most infected children suffer little consequence. However, children who have other serious health problems are known to be at higher risk of complications from RSV infection. This review examined the use of a passive immunisation - palivizumab - to prevent and modify the severity of RSV infection in these children and to determine if it is cost-effective.

The results from this review are based on data from seven studies (all sponsored by the drug manufacturing company) involving 11,096 participants reporting on efficacy and safety of palivizumab, and 34 studies reporting on its cost-effectiveness.

Our findings suggest a favorable effect of preventive use of palivizumab in children who are at higher risk of acquiring severe RSV infection, when compared to placebo. Children treated with palivizumab were less often hospitalised, spent fewer days in the hospital, were admitted to an intensive care unit less often, and had fewer days of oxygen therapy than children who received a placebo.

Considering the underlying health problems in this population of infants and children, high rates of adverse events are quite expected. Our findings showed that children treated with palivizumab experienced adverse events similarly as often as children treated with placebo.

Palivizumab was shown to be effective in reducing the hospitalisations, but whether it is also cost-effective is not easy to determine. This review found large differences in cost-effectiveness results across the studies. Due to the high costs of the drug, in many countries palivizumab prophylaxis might not be available as a standard treatment.

Summary of findings for the main comparison. Palivizumab compared to placebo for high risk of severe respiratory syncytial virus infection

Palivizumab compared to placebo for high riskof severe respiratory syncytial virus infection						
Patient or population: patients at high risk of severe respiratory syncytial virus infection **Settings:** hospital **Intervention:** palivizumab **Comparison:** placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Palivizumab**				
Hospitalisation for RSV infection	**Study population**		**RR 0.49** (0.37 to 0.64)	2831 (3 studies)	⊕⊕⊕⊕ **high**	
	101 per 1000	**50 per 1000** (37 to 65)				
	Moderate					
	100 per 1000	**49 per 1000** (37 to 64)				
All-cause mortality	**Study population**		**RR 0.69** (0.42 to 1.15)	2831 (3 studies)	⊕⊕⊕⊖ **moderate**[1]	
	28 per 1000	**19 per 1000** (12 to 32)				
	Moderate					
	42 per 1000	**29 per 1000** (18 to 48)				
Total RSV hospital days per 100 children	See comment	See comment	Not estimable	2789 (2 studies)	⊕⊕⊕⊖ **moderate**[2]	Data on standard deviations missing; meta-analysis not possible.

Admission to ICU	**Study population**		**RR 0.5** (0.3 to 0.81)	2789 (2 studies)	⊕⊕⊕⊕ **high**	
	34 per 1000	**17 per 1000** (10 to 28)				
	Moderate					
	34 per 1000	**17 per 1000** (10 to 28)				
Mechanical ventilation for RSV infection	**Study population**		**RR 1.1** (0.2 to 6.09)	2789 (2 studies)	⊕⊖⊖⊖ **very low**[1,3]	
	13 per 1000	**14 per 1000** (3 to 80)				
	Moderate					
	12 per 1000	**13 per 1000** (2 to 73)				
Supplemental oxygen therapy for RSV infection	**Study population**		Not estimable	0 (0)	See comment	Numbers not reported in any of the three studies
	See comment	See comment				
	Moderate					
Number of children reporting any SAE	**Study population**		**RR 0.88** (0.8 to 0.96)	1287 (1 study)	⊕⊕⊕⊕ **high**	
	631 per 1000	**555 per 1000** (505 to 606)				
	Moderate					
	631 per 1000	**555 per 1000** (505 to 606)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **ICU:** intensive care unit; **RR:** risk ratio; **RSV:** respiratory syncytial virus; **SAE:** serious adverse event

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No statistical significance in results and very wide 95% CIs around estimates of effect.
[2]Data on standard deviations missing in both studies.
[3]Substantial heterogeneity across the two studies; point estimates of effect on opposite sides.

Summary of findings 2. Palivizumab compared to motavizumab for high risk of severe respiratory syncytial virus infection

Palivizumab compared to motavizumab for high riskof severe respiratory syncytial virus infection

Patient or population: patients at high risk of severe respiratory syncytial virus infection
Settings: hospital
Intervention: palivizumab
Comparison: motavizumab

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Motavizumab	Palivizumab				
Hospitalisation for RSV infection	**Study population**		**RR 1.36** (0.97 to 1.9)	7870 (2 studies)	⊕⊕⊕⊖ **moderate**[1]	
	15 per 1000	**20 per 1000** (14 to 28)				
	Moderate					
	17 per 1000	**23 per 1000** (16 to 32)				
All-cause mortality	**Study population**		**RR 0.74** (0.38 to 1.43)	8265 (4 studies)	⊕⊕⊕⊖ **moderate**[1]	
	5 per 1000	**4 per 1000** (2 to 7)				
	Moderate					
	15 per 1000	**11 per 1000** (6 to 21)				

Total RSV hospital days per 100 children		The mean total RSV hospital days per 100 children in the intervention groups was **24.95 higher** (21.59 lower to 71.49 higher)		7870 (2 studies)	⊕⊕⊝⊝ **low**[2,3]
Admission to ICU	**Study population**		**RR 1.68** (0.89 to 3.19)	7870 (2 studies)	⊕⊕⊕⊝ **moderate**[1]
	4 per 1000	**6 per 1000** (3 to 12)			
	Moderate				
	6 per 1000	**10 per 1000** (5 to 19)			
Mechanical ventilation for RSV infection	**Study population**		**RR 3.79** (1.26 to 11.42)	7870 (2 studies)	⊕⊕⊕⊕ **high**
	1 per 1000	**4 per 1000** (1 to 12)			
	Moderate				
	2 per 1000	**8 per 1000** (3 to 23)			
Supplemental oxygen therapy for RSV infection	**Study population**		**RR 1.49** (0.98 to 2.26)	7870 (2 studies)	⊕⊕⊕⊝ **moderate**[1]
	9 per 1000	**14 per 1000** (9 to 21)			
	Moderate				
	12 per 1000	**18 per 1000** (12 to 27)			
Number of children reporting any SAE	**Study population**		**RR 1.04** (0.96 to 1.13)	8238 (4 studies)	⊕⊕⊕⊕ **high**
	191 per 1000	**199 per 1000** (183 to 216)			
	Moderate				
	119 per 1000	**124 per 1000**			

		(114 to 134)		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval;**ICU:** intensive care unit; **RR:** risk ratio; **RSV :** respiratory syncytial virus; **SAE :** serious adverse event

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]No statistical significance in results and very wide 95% CI around pooled estimate of effect.
[2]The 95% CI includes no effect and confidence limits are very wide.
[3]Data on standard deviations missing in Carbonell-Estrany 2010.

BACKGROUND

Description of the condition

Respiratory syncytial virus (RSV) is one of the most important viral pathogens to cause acute respiratory infections (ARIs) in children (Nair 2010), with virtually all children having been infected with RSV at least once by their second birthday (Red Book 2012). In the United States (US), RSV infection is associated with substantial childhood morbidity, necessitating inpatient and outpatient care (Hall 2009a).

RSV infection carries a considerable disease burden, with an estimated 2.1 million children under five years of age requiring medical care in the US each year. Among children with RSV-related illnesses, approximately 3% are hospitalised, 25% are treated in emergency departments and 73% are treated by paediatricians. In the US each year, it is estimated that in children under five, RSV infection accounts for one out of every 334 hospitalisations, one out of 38 visits to an emergency department and one out of 13 visits to a primary care physician (Hall 2009a). Globally, it is estimated that RSV causes about 34 million episodes of acute lower respiratory tract infections in children under five, resulting in about 3.4 million hospitalisations each year (Nair 2010). RSV has also been shown to be the most important viral cause of death in children under five, especially in those younger than one year (Fleming 2005; Shay 2001; Thompson 2003). In data compiled by the Centers for Disease Control and Prevention (CDC), RSV pneumonia causes about 2700 adult and paediatric deaths each year in the US (Thompson 2003). Globally, it is estimated to result in up to 199,000 deaths per year (Nair 2010).

The exact timing of the RSV season varies by location and year (Mullins 2003). In temperate climates of the US, RSV outbreaks usually begin in November or December, peaking in January or February and end by March or April; whereas in tropical or subtropical climates, RSV activity correlates with rainy seasons and may be present throughout the year (AAP 2009; Hall 2009b; Simoes 2003). The most recent RSV season for which data are available in the US was July 2010 to June 2011, and this RSV season had a median duration of 19 weeks (CDC 2011). Knowledge of RSV seasonality can be used by clinicians and public health officials to determine when to consider RSV as a cause of ARIs and when to provide RSV immunoprophylaxis to children at high risk of serious disease (Red Book 2012).

The incubation period of infection frequently lasts four to six days. Inoculation of the virus happens through the upper respiratory tract (URT), followed by infection of the respiratory epithelium. The mechanism by which the virus spreads along the respiratory tract is not clear, but may occur through cell-to-cell transfer along intracytoplasmic bridges or through the aspiration of nasopharyngeal aspirations, and may involve the conducting airways at all levels (Domachowske 1999; Hall 2009b). Transmission of RSV is usually by direct or close contact with RSV-contaminated secretions. The virus can survive for several hours on surfaces, and for approximately half an hour on hands, reinforcing the need for stringent infection control policies within health facilities to reduce nosocomial infections. Transmission of the virus among household and child care contacts is common.

RSV initially manifests in infants as an upper respiratory tract infection, but progresses to a lower respiratory tract infection in approximately 20% to 30% of infants with varying degrees of severity, ranging from mild to life-threatening respiratory failure (Red Book 2012). Bronchiolitis usually develops one to three days following common cold symptoms such as nasal congestion and discharge, mild cough, fever and reduced appetite. As the infection progresses and the small airways are affected, other symptoms may develop, such as rapid breathing, wheezing, persistent cough and difficulty feeding, which can result in dehydration. Apnoea (a pause in breathing for more than 15 or 20 seconds) is the presenting symptom in up to 20% of infants admitted to hospital with RSV and may be the first symptom of bronchiolitis (Arms 2008; Hall 1979; Ralstone 2009). While most cases of RSV infection are not severe, in severe cases oxygenation may worsen and a child may develop acute respiratory or ventilatory failure, necessitating mechanical ventilation and admission to an intensive care unit (ICU). Approximately 1% to 3% of all children under 12 months of age will require hospitalization for the treatment of lower respiratory tract infection resulting from RSV (Red Book 2012).

Characteristics that are most frequently associated with RSV illness requiring hospitalization include male sex, chronic co-existing medical conditions, lower socio-economic status, smoke exposure, contact with other children and lack of breast-feeding (Hall 2009a). Characteristics that increase the risk of severe RSV illness are preterm birth, cyanotic or complicated congenital heart disease, especially conditions that cause pulmonary hypertension, chronic lung disease of prematurity (formerly called bronchopulmonary dysplasia) and immunodeficiency (Purcell 2004).

Description of the intervention

The observation that passively transferred maternal RSV-neutralising antibodies provided some protection from severe lower respiratory tract (LRT) disease has led to the development of passive immunity products to prevent and modify the severity of RSV infection. The first product available for this use was a respiratory syncytial virus immune globulin intravenous (RSV-IVIG, RespiGam), a polyclonal human RSV-neutralising antibody (a combination of different immunoglobulin molecules), administered intravenously during RSV-risk months. RSV-IVIG is no longer available.

In 1996, palivizumab (Synagis) entered into clinical trials. Palivizumab is an anti-RSV monoclonal antibody (a set of identical immunoglobulin molecules), administered intramuscularly at a dose of 15 mg/kg once every 30 days. The efficacy and safety of palivizumab has been evaluated in multicentre randomized controlled trials (RCTs), which in two trials demonstrated 45% and 55% decreases in RSV-related hospitalisations (Feltes 2003; IMpact-RSV 1998). In both trials, palivizumab prophylaxis was generally safe and well tolerated. In June 1998, palivizumab was licensed by the US Food and Drug Administration (FDA) for prevention of serious LRT disease caused by RSV in paediatric patients who are at an increased risk of severe disease (AAP 2009).

In 2008, MedImmune filed for FDA approval of motavizumab (Numax, Rezield), another RSV-neutralising monoclonal antibody intended for the same indication. The efficacy and safety of motavizumab and palivizumab were compared in a multinational non-inferiority RCT (Carbonell-Estrany 2010). However, the FDA did not approve motavizumab for RSV prophylaxis, due to concerns regarding ts safety and efficacy. Serious concerns were raised with regards to non-fatal hypersensitivity adverse events, which

were three times higher in the motavizumab group than in the palivizumab group. Additional questions were raised with regards to geographical stratification of study patients, since measures of motavizumab's non-inferiority relied heavily on data obtained from the 9% of participants enrolled in southern hemisphere countries. Removing this population led the FDA to determine that in the US population motavizumab did not meet the non-inferiority criterion relative to palivizumab. In December 2010, the company announced it had discontinued further development of motavizumab for the prophylaxis of serious RSV disease. Therefore, palivizumab is currently the only product approved for prevention of serious RSV disease in infants and children with chronic lung disease, with a history of preterm birth (35 weeks gestation or less), or with haemodynamically significant congenital heart disease (AAP 2009).

The cost of immunoprophylaxis with palivizumab is high and economic analyses have failed to demonstrate overall savings in healthcare dollars if all infants who are at risk receive prophylaxis (ElHassan 2006; Garcia-Altes 2010; Hampp 2011; Wang 2011). In the USA, it is considered that a total of five monthly doses for infants and young children with chronic lung disease, congenital heart disease or preterm birth born before 32 weeks gestation will provide an optimal balance of benefit and cost, even with variation in the season's onset and end (AAP 2009).

How the intervention might work

Respiratory syncytial virus is a ribonucleic acid (RNA) virus of the *Paramyxoviridae* family. The virus uses attachment (G) and fusion (F) surface glycoproteins to infect cells. Palivizumab is a humanised mouse monoclonal immunoglobulin G1, produced by recombinant DNA technology and directed to an epitope of the F glycoprotein of RSV. Palivizumab binds to this glycoprotein and prevents viral invasion of the host cells in the airway. This reduces viral activity and cell-to-cell transmission and blocks the fusion of infected cells (Johnson 1997). As a result, preventive use of palivizumab may be associated with reduced risk for developing LRT disease (Hall 2010).

Why it is important to do this review

In a previous Cochrane systematic review, the pooled effects of RSV-IVIG and palivizumab were assessed together, compared to placebo, with the last search performed in March 1999 (Wang 1999). That review included three studies with RSV-IVIG and one with palivizumab prophylaxis. The review was withdrawn from *The Cochrane Library* in 2003, as the authors could not commit time to update it. Since then, RSV-IVIG has been withdrawn from the market, methodologies of performing systematic reviews have changed and additional RCTs with palivizumab have been conducted. A new team of authors took over this review in 2007 and published a protocol which focused on effectiveness and safety of prophylaxis with palivizumab (Lozano 2007). The protocol was withdrawn from *The Cochrane Library* in 2010, as the authors could not commit time to writing a review.

Unlike the review by Wang 1999, ours focuses on palivizumab prophylaxis, in terms of effectiveness and safety, as well as its cost-effectiveness. We expect that our findings will provide comprehensive and up-to-date evidence on RSV immunoprophylaxis with palivizumab in infants and children at high risk of severe RSV disease.

OBJECTIVES

1. To assess the effectiveness and safety of palivizumab prophylaxis compared with placebo, or another type of prophylaxis, in reducing the risk of complications (hospitalization due to RSV infection) in high-risk infants and children.
2. To assess the cost-effectiveness (or cost-utility) of palivizumab prophylaxis compared with no prophylaxis in infants and children in different risk groups.

METHODS

Criteria for considering studies for this review

Types of studies

To study the effectiveness and safety of palivizumab, we included randomized controlled trials (RCTs) comparing palivizumab prophylaxis with a placebo, no prophylaxis or another type of prophylaxis in preventing serious LRT disease caused by RSV in paediatric patients at high risk of RSV disease.

To study cost-effectiveness (or cost-utility), we included full economic evaluation studies (cost-effectiveness analyses and cost-utility analyses) comparing palivizumab prophylaxis with no prophylaxis. We considered for inclusion health economics studies conducted alongside high-quality randomized trials, and economic modelling studies based on data from high-quality randomized trials or based on a comprehensive systematic review of the literature. We excluded partial economic evaluation studies that report cost analyses, or cost-outcome descriptions, due to the large number of available full economic evaluations. We also excluded economic evaluations of prophylaxis with RSV-IVIG, due to the fact that palivizumab is the only approved product for this purpose, and these analyses would be of no importance to health funds or patients.

Types of participants

We included infants and children at high risk of developing LRT disease caused by RSV, i.e. those with chronic lung disease (or bronchopulmonary dysplasia), congenital heart disease, immunodeficiency, chronic neuromuscular disease, congenital anomalies or those born preterm. We excluded children with cystic fibrosis as a related Cochrane Review has already been published on that topic (Robinson 2012).

Types of interventions

We compared passive immunisation of palivizumab (15 mg/kg dose, any setting and regimen) with placebo, no prophylaxis or another type of prophylaxis. In the critical assessment of health economics studies, we compared palivizumab prophylaxis with no prophylaxis.

Types of outcome measures

Primary outcomes

1. Hospitalisation for RSV infection.
2. All-cause mortality.

Secondary outcomes

Effectiveness outcomes

1. RSV-specific outpatient medically attended lower respiratory tract infection (MALRI).
2. Number of days in hospital attributable to RSV infection per 100 randomized children.
3. Admission to intensive care unit (ICU).
4. Number of days in the ICU per 100 randomized children.
5. Mechanical ventilation for RSV infection.
6. Number of days of mechanical ventilation per 100 randomized children.
7. Supplemental oxygen therapy for RSV infection.
8. Number of days of supplemental oxygen therapy per 100 randomized children.
9. Bronchodilator therapy for RSV infection.
10. Number of days of bronchodilator therapy per 100 randomized children.

Safety outcomes

1. Number of children reporting any adverse event (AE).
2. Number of children reporting related AE.
3. Number of children reporting any serious adverse event (SAE).
4. Number of children reporting related SAE.

Economic evaluation outcomes

1. Effectiveness outcome measures: hospitalization for RSV infection avoided (number of RSV hospitalisations avoided due to the use of prophylaxis), or any other effect measure reported by study authors such as quality-adjusted life-year (QALY), life-year gained (LYG) or life-year lost (LYL).
2. The direct medical costs associated with:
   - administration of palivizumab (palivizumab injections, administration by physicians, nurses or both);
   - length of hospital stay;
   - days of mechanical ventilation;
   - days in ICU;
   - need for supplemental oxygen;
   - incidence of complications such as air leak syndrome and aggregated bacterial infections;
   - treatment of adverse events;
   - number of outpatient visits;
   - number of outpatient emergency department visits.
3. The indirect medical costs associated with:
   - number of days off work (parents or caregivers);
   - patient out-of-pocket expenses;
   - future lost productivity of a child.
4. Incremental cost-effectiveness ratios (ICERs) expressed as incremental costs per hospitalization avoided, per quality-adjusted life-years (QALY) and per life-years gained (LYG).

Search methods for identification of studies

Electronic searches

To identify studies on effectiveness and safety, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012, Issue 7, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 8 August 2012), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, MEDLINE (1996 to July week 4, 2012), EMBASE (1996 to August 2012), CINAHL (1996 to August 2012) and LILACS (1996 to August 2012).

We searched MEDLINE and CENTRAL using the keywords and MeSH terms in Appendix 1. We used the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE; sensitivity- and precision-maximising version (2008 revision); Ovid format (Lefebvre 2011). We adapted this search strategy to search EMBASE (Appendix 2), CINAHL (Appendix 3) and LILACS (Appendix 4). In addition, we ran a search in MEDLINE and EMBASE for adverse effects based on the search strategy developed by Golder (Golder 2006) (Appendix 5). We did not use any language or publication restrictions.

To identify economic studies we based our search strategy on the search strategy in Appendix 1 and searched the NHS Economic Evaluations Database (NHS EED) 2012, Issue 4, part of *The Cochrane Library,* www.thecochranelibrary.com (accessed 9 August 2012), Health Economics Evaluations Database (HEED, searched 9 August 2012) and Paediatric Economic Database Evaluations (PEDE, 1980 to 2009, searched 29 July 2011). We also searched for economic evaluations in MEDLINE (1996 to July week 4, 2012) and EMBASE (1996 to August 2012) using a filter based on the work of Glanville 2009.

Searching other resources

We searched the reference lists of relevant studies and review articles to identify additional eligible studies and trial reports. We searched appropriate clinical trials databases utilising the World Health Organization's (WHO) International Clinical Trials Registry Platform (ICTRP), www.who.int/ictrp/ (accessed 9 August 2012, search terms: respiratory syncytial virus, palivizumab and synagis). We contacted the drug manufacturer (MedImmune LLC), trial authors and content experts to obtain information on ongoing or unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (TA, JWN) independently examined titles and abstracts for the selection of eligible studies. We removed records that did not report on RCTs and where palivizumab was used as a prophylaxis. We retrieved the full texts of potentially relevant reports and we linked multiple reports of the same study. Two review authors (TA, JWN) independently examined the full-text reports to determine which studies met the eligibility criteria. We resolved disagreements by discussion and consultation with a third review author (BB).

Two review authors (TA, JDR) independently examined titles and abstracts for the selection of health economics studies to be included in the critical review of economic data. We removed records that were not reporting on cost-effectiveness or cost-utility analysis of palivizumab prophylaxis. We retrieved full texts of potentially relevant reports (i.e. health economics studies conducted alongside randomized trials or economic modelling studies based on a meta-analysis of data from randomized trials or based on a comprehensive systematic review of literature). Two review authors (TA, JDR) independently examined full-text reports to determine which studies met the eligibility criteria. Any

disagreements were resolved by discussion and consultation with a third review author (MXRR). Only full economic evaluations with high methodological and reporting quality (see Assessment of risk of bias in included studies) were included.

Data extraction and management

Two review authors (TA, JWN) independently extracted data from eligible RCTs using customised data collection forms. The data collection forms were tested on a pilot sample of articles. Details on the source, eligibility and reasons for exclusion, methods, potential source of bias, participants, settings, interventions, outcomes and results were collected. Review authors were not blinded to the names of the authors, institutions, journals or results of a study. We attempted to contact trial authors for any of the missing data from studies. Any disagreements were resolved by discussion or consultation with a third review author (BB). We entered all collected data into the Review Manager (RevMan 2012) software for analysis.

Two review authors (TA, JDR) independently extracted data on the following aspects of each included economic evaluation study.

1. General information: population, intervention, comparator, results in clinical outcomes, costs of specific resources, study setting and sources of funding.
2. Methods: type of economic evaluation, study perspective, economic outcome measurements and time horizon.
3. Results: incremental costs, incremental effectiveness, discount rate, currency and price year of the reported values, and the final incremental cost-effectiveness ratios reported.

Assessment of risk of bias in included studies

Two review authors (TA, JWN) independently assessed risk of bias in the included RCTs using The Cochrane Collaboration's tool for assessing risk of bias, which addresses the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases, such as funding. We recorded each piece of information extracted for the 'Risk of bias' tool, together with the precise source of this information. We tabulated the risk of bias for each included RCT, along with a judgement of 'low', 'high' or 'unclear' risk of bias, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a).

Since none of the included economic evaluations (EEs) were conducted alongside a RCT, their quality could not be assessed using The Cochrane Collaboration's standard tool for assessing risk of bias in RCTs. Therefore, we critically appraised the quality of EEs using the Drummond checklist (Drummond 1996). We used an adapted Drummond checklist (Appendix 6) which addresses the following methodological and reporting aspects.

1. Was a well-defined question posed?
2. Was a comprehensive description of the competing alternatives given?
3. Does the paper provide evidence that the programme would be effective (i.e. would the programme do more harm than good)?
4. Were all important and relevant resource use (costs) and health outcome consequences for each alternative identified, measured accurately in appropriate units prior to evaluation, and valued credibly?
5. Were costs and health outcomes consequences adjusted for different times at which they occurred (i.e. was discounting applied)?
6. Was an incremental analysis of the consequences and costs of alternatives performed?
7. Was an adequate sensitivity analysis performed?

For each main efficacy and safety outcome in Summary of findings for the main comparison and Summary of findings 2, we assessed the overall quality of the evidence using the GRADE approach (Atkins 2004), as described in Appendix 7.

Measures of treatment effect

We calculated risk ratios (RRs) and their associated 95% confidence intervals (CIs) for dichotomous outcomes and for adverse events. We planned to report the mean post-intervention value, as well as the mean difference (MD) between treatment groups and their associated 95% CIs for continuous outcomes, but due to the lack of data on measures of dispersion for continuous outcomes (such as standard deviations), only a narrative summary is provided for those results. We analyzed count data in the following way.

1. Total days of RSV hospitalization per 100 randomized children as continuous data.
2. Total days in the ICU per 100 randomized children as continuous data.
3. Total days of mechanical ventilation per 100 randomized children as continuous data.
4. Total days of supplemental oxygen therapy per 100 randomized children as continuous data.

If it was not clearly stated in the study that total days were expressed as means per 100 randomized children, we contacted the study authors to attempt to clarify whether indexing was used, or not. Total days were expressed as means per 100 randomized children in all studies but one, where they were expressed as means and standard deviations per one child (Feltes 2011). In order to be consistent across studies, for Feltes 2011 the values per 100 randomized children were calculated and entered into RevMan for analysis.

We summarised the results reported in included economic evaluations, such as incremental cost, incremental effectiveness and incremental cost-effectiveness ratio, in Table 1, Table 2, Table 3 and Table 4, and we provided a commentary on tabulated results.

For readers to easily benchmark variations among different studies and settings, the final incremental cost-effectiveness ratios are also reported in 2011 Euros (EUR) as 'ICER present values'. Higher ICER values are indicative of less favorable results for the investigated intervention. The values of ICERs provided by study authors were adjusted for the time value of money, so that the cash flows inter projects over time are expressed on a common basis in terms of their present value. However, the use of these data for extrapolation of results among countries or throughout years is not anticipated, since the costs of the technologies and medical practices may have changed substantially throughout years and settings (the oldest included study Joffe 1999 uses the 1995 USD price year). Only the present values of ICERs from similar and closer

date studies that have evaluated the same effectiveness measure (e.g. hospitalization avoided, or QALY gained) should be taken into account while assessing the variation of ICER that could be expected if the technology would be adopted in similar settings.

We calculated the present values of ICERs at 2011 EUR in two steps. Firstly, we converted the values reported in the study in their original currency to Euros at the same price year, by multiplying the ICER reported value with the appropriate money exchange rate given in Appendix 8. Secondly, we multiplied those values with the appropriate gross domestic product (GDP) deflator given in Appendix 9, in order to get the final ICER present values at 2011 EUR.

We expressed all currencies as the currency abbreviation and amount (e.g. EUR 1376.50), using the ISO 4217 currency abbreviations available at http://www.xe.com/iso4217.php/. We chose Euros for present value calculations, as the majority of included studies were conducted in Europe. More details about present value calculations are given in Appendix 10.

Dealing with missing data

There are several types of missing data in a systematic review or meta-analysis as described in Table 16.1.a in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). The problem of missing studies and outcomes is addressed in the Assessment of reporting biases section of this review. A common problem is missing summary data, such as standard deviations (SDs) for continuous outcomes. The methods outlined in section 16.1.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b) for imputing missing values were considered. However, because the majority of studies in this review had missing SDs, we decided to not impute them. Studies were not excluded from the review because of missing summary data; rather, we contacted trial authors to attempt to obtain more information. Because authors have not provided the requested information, the results of available continuous data are summarised in a narrative way. The potential impact of missing data on the review's findings are addressed in the Discussion section.

Assessment of heterogeneity

We assessed heterogeneity between included studies using the Chi^2 test and I^2 statistic (Higgins 2003). We considered a Chi^2 P value of less than 0.10 to be indicative of statistical heterogeneity of intervention effects. However, if studies have a small sample size, or are few in number, the Chi^2 test has low power and should be interpreted with caution. In order to quantify inconsistency across studies, we calculated an I^2 statistic. We interpreted the I^2 statistic in the following way: heterogeneity might not be important (I^2 statistic value of 0% to 40%); heterogeneity may be moderate (I^2 statistic of 30% to 60%); heterogeneity may be substantial (I^2 statistic of 50% to 90%); and considerable heterogeneity (I^2 statistic of 75% to 100%).

Assessment of reporting biases

Possible reporting biases are assessed on two levels: within-study and between-studies.

We examined within-study selective outcome reporting as a part of the overall 'Risk of bias' assessment (see Assessment of risk of bias in included studies). We attempted to find protocols for included studies and compare the outcomes stated in the protocols with those reported in the publications. If protocols were not found, we compared the outcomes listed in the methods section of a publication with those whose results are reported.

We planned to create a funnel plot of effect estimates against their standard errors (SEs) to assess possible between-studies reporting bias, if there were at least 10 RCTs included in the review. However, this was not the case. We would consider possible explanations if we found asymmetry of the funnel plot, either by inspection or statistical tests, and we would have taken into account the interpretation of the overall estimate of treatment effects.

Data synthesis

We performed a fixed-effect meta-analysis for the estimation of pooled effects whenever there was no indication of heterogeneity between included studies (I^2 statistic < 40%). When some indication of heterogeneity between trials was identified (I^2 statistic > 40%), we used a random-effects model.

We did not perform pooled calculations of economic data. Rather, the characteristics and results of included economic studies are presented in a descriptive way in Table 1, Table 2, Table 3 and Table 4.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses for effectiveness and safety data, based on the presence of risk factors (preterm birth, chronic lung disease, congenital heart disease, immunodeficiency, chronic neuromuscular disease and congenital anomalies), in case there were at least three studies per subgroup in a specific comparison. However, that was not the case, and no subgroup analysis was performed.

The economic data (incremental cost, incremental effectiveness and incremental cost-effectiveness ratio) are reported separately for studies that evaluated the impact of passive immunisation given during the neonatal period or within the first six months of life (Table 2), and for studies that evaluated the impact of passive immunisation given to children aged six months and older (Table 3). In each of the two groups, data are presented separately for three subgroups, according to the baseline risk factors: preterm birth (≤ 35 weeks gestation), chronic lung disease of prematurity or bronchopulmonary dysplasia, and congenital heart disease. Additionally, the economic data are reported separately in Table 4 for studies that evaluated the impact of passive immunisation given at any time from birth to five years of age, to a high-risk population of infants and children born preterm, with or without bronchopulmonary dysplasia, or with congenital heart disease.

Sensitivity analysis

The sensitivity analysis takes into account those biases that could significantly impact on the outcomes of the included studies. As previously noted in the Assessment of risk of bias in included studies section, The Cochrane Collaboration's tool for assessing risk of bias in RCTs was used (categorised as 'low', 'high' and 'unclear'), focusing on domains such as random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other biases, such as the source of funding of the included studies.

We had planned to perform a sensitivity analysis to assess how the results of the meta-analysis would be affected by excluding studies determined to be at high risk of bias. However, all of the included efficacy and safety studies were of high overall methodological and reporting quality, and we meta-analysed all of these trials without performing a sensitivity analysis.

RESULTS

Description of studies

Results of the search

With duplicates removed, the electronic searches identified 630 records for effectiveness studies and 413 records for adverse effects studies. We screened titles and abstracts and 12 studies were identified as potentially eligible for inclusion. We retrieved the full-text articles. After reading the full texts, five studies were excluded and seven were found eligible for inclusion according to Criteria for considering studies for this review.

By searching the clinical trials registries, we identified three additional RCTs (NCT00233064; NCT00240929; NTR1023). According to available data, the three trials are not eligible for inclusion in this review. However, in an attempt to retrieve more information about them, they are listed under Studies awaiting classification.

The electronic searches for economic evaluations identified 703 records, with duplicates removed. We screened titles and abstracts and 58 studies were identified as potentially eligible for inclusion. After reading the full texts, 24 studies were excluded and 34 were found eligible for inclusion in this review according to Criteria for considering studies for this review. No other potentially eligible economic evaluations were found as a result of searching the reference lists of relevant studies and review articles.

Included studies

Of the seven included RCTs, three compared palivizumab with placebo (Feltes 2003; IMpact-RSV 1998; Subramanian 1998) and four compared motavizumab with palivizumab (Abarca 2009; Carbonell-Estrany 2010; Feltes 2011; Fernandez 2010). In all trials palivizumab was delivered intramuscularly, except in Subramanian 1998 where it was delivered intravenously. One study was a dose-escalation study (Subramanian 1998) and only data for the recommended approved dose of 15 mg/kg were included in our analyses. From all trials, data extracted for the analyses referred to five monthly injections of the study drug, except for Abarca 2009, where four or five doses were applied, and Fernandez 2010, where palivizumab and motavizumab were used sequentially, and only safety data after the first two doses were extracted for analysis. In Abarca 2009, only the second year of the study was a RCT eligible for inclusion. In all studies, children were followed up for 150 days after randomization (30 days after the final dose).

Of the 34 included economic evaluation studies, three were conducted in Italy (Chirico 2009; Chiroli 2005; Ravasio 2006), six in the US (ElHassan 2006; Hampp 2011; Joffe 1999; Lofland 2000; Weiner 2012; Yount 2004), four in the UK (Bentley 2011; Embleton 2007; Nuijten 2007; Wang 2011), five in Spain (Garcia-Altes 2010; Lazaro y de Mercado 2006; Lazaro y de Mercado 2007; Nuijten 2010; Raya Ortega 2006), four in Canada (Harris 2011; Lanctot 2008; Smart 2010; Tam 2009), one in France (Hascoet 2008), one in Korea (Kang 2009), two in Mexico (Mayen-Herrera 2011; Salinas-Escudero 2012), one in Sweden (Neovius 2011), two in the Netherlands (Nuijten 2009a; Rietveld 2010), two in Germany (Nuijten 2009b; Roeckl-Wiedmann 2003), two in Austria (Resch 2008; Resch 2012) and one in New Zealand (Vogel 2002).

Lazaro y de Mercado 2006 evaluated the economic impact of RSV immunoprophylaxis in children with bronchopulmonary dysplasia, children with congenital heart disease and in preterm infants born at 32 to 35 weeks' gestational age, presenting with two or more of the additional risk factors described by the Spanish Neonatology Society. The authors did not report data separately for any of the subgroups or categories of interest in this review. Kang 2009 is a study conducted in Korea, with only information from the abstract available. Similarly, for Bentley 2011 and Mayen-Herrera 2011 only the information from abstracts was available. The trial authors did not respond to e-mails asking for the full text. Characteristics of these four studies are presented in Table 1, but the economics results were not included in the related 'Additional tables' (Table 2; Table 3; Table 4).

Overall, 22 studies evaluated the economic impact of RSV immunoprophylaxis given during the neonatal period or within the first few months of life (Chirico 2009; ElHassan 2006; Embleton 2007; Hampp 2011; Hascoet 2008; Lanctot 2008; Lofland 2000; Neovius 2011; Nuijten 2007; Nuijten 2009a; Nuijten 2010; Ravasio 2006; Raya Ortega 2006; Resch 2008; Resch 2012; Rietveld 2010; Roeckl-Wiedmann 2003; Salinas-Escudero 2012; Smart 2010; Vogel 2002; Wang 2011; Weiner 2012); 10 studies evaluated the economic impact of RSV immunoprophylaxis given to children aged six months and older (Chiroli 2005; Hampp 2011; Harris 2011; Nuijten 2007; Nuijten 2009b; Resch 2008; Resch 2012; Tam 2009; Wang 2011; Yount 2004); and three studies evaluated the economic impact of RSV immunoprophylaxis given to a high-risk population of infants and children up to five years of age, either born preterm, with or without bronchopulmonary dysplasia, or with congenital heart disease (Garcia-Altes 2010; Joffe 1999; Lazaro y de Mercado 2007).

The study conducted by Wang 2011 reported a set of ICER values obtained when passive immunisation is given to infants and children at different birth ages (up to 24 months of life), with different gestational ages, and with or without other comorbidity (chronic lung disease or congenital heart disease). The results from Wang 2011 are presented as ranges of values for the following subgroups of interest in this review.

- Infants up to six months of age who were born at 35 weeks of gestation or less, without chronic lung disease or congenital heart disease.
- Infants up to six months of age who were born at 35 weeks of gestation or less, with chronic lung disease.
- Infants up to six months of age who were born at more than 35 weeks of gestation, with congenital heart disease.
- Children from 6 to 24 months of age who were born at 35 weeks of gestation or less, without chronic lung disease or congenital heart disease.
- Children from 6 to 24 months of age who were born at 35 weeks of gestation or less, with chronic lung disease.
- Children from 6 to 24 months of age who were born at more than 35 weeks of gestation, with congenital heart disease.

Excluded studies

Of the five excluded safety and effectiveness studies, four were not RCTs (Korbal 2003; Martinez 2002; Parmigiani 2001; Takeuchi 2002), and one did not assess effects of palivizumab prophylaxis (Meissner 1999).

Of the 24 excluded economic studies, most were partial economic evaluations that reported cost analyses or cost-outcome descriptions (Banerji 2009; Buckley 2010; Chan 2003; Clark 2000; Datar 2012; Farina 2002; Krilov 2010; Lapena Lopez 2003; Lee 2001; Marchetti 1999; Marques 2010; McCormick 2002; Meberg 2006; Rackham 2005; Reeve 2006; Rodriguez 2008; Vann 2007; Wegner 2004; Wendel 2010), two were neither a cost-effectiveness nor a cost-utility analysis (Numa 2000; Shireman 2002), one analyzed a combined effect of RSV-IVIG and palivizumab used together as prophylaxis (Stevens 2000), one was a systematic review of economic evaluations, and not a primary analysis (Strutton 2003), and one economic evaluation (Wang 2008) was later updated and reported by the same author in a more recent publication (Wang 2011).

Risk of bias in included studies

For efficacy and safety studies, see the 'Risk of bias' tables in Characteristics of included studies. We performed complete 'Risk of bias' assessment for all included RCTs. The methods used in some included studies were not clearly described; some data and explanations were missing and this could be a source of potential bias. Additionally, all of the included studies were sponsored by, and included authors from, the manufacturer of palivizumab, MedImmune. This does not, in of itself, imply any bias in the results and we have listed this as having an 'unclear' potential impact. Further explanation of these risks of bias is provided in the subsequent sections of this review.

The GRADE quality ratings of evidence for the main outcomes are summarised in Summary of findings for the main comparison and Summary of findings 2.

Results of the quality assessment of economic evaluation studies are summarised in Appendix 6.

Allocation

Randomisation was performed in all seven included studies. Methods of random sequence generation were clearly described in all trials except for Subramanian 1998 where insufficient information was given, with 'unclear' risk of bias. Study drugs were identical in appearance and their allocation was concealed in Carbonell-Estrany 2010; Feltes 2003; Feltes 2011; IMpact-RSV 1998 and Subramanian 1998; while methods of allocation concealment were 'unclear' in Abarca 2009 and Fernandez 2010.

Blinding

Adequate blinding of participants and study personnel was clearly stated in Carbonell-Estrany 2010; Feltes 2003; Feltes 2011; IMpact-RSV 1998 and Subramanian 1998. There were no details available in Abarca 2009 and Fernandez 2010, resulting in an 'unclear' risk of bias.

Incomplete outcome data

In six studies, comparable attrition rates were reported in both intervention groups, with reasons for attrition provided, making the risk of bias 'low' (Carbonell-Estrany 2010; Feltes 2003; Feltes 2011; Fernandez 2010; IMpact-RSV 1998; Subramanian 1998). In Abarca 2009, the risk of bias was 'high', because the reasons for attrition of patients between season one and season two were not given.

Selective reporting

For three of the seven included trials, protocols were registered in appropriate clinical trials databases, and for all of them the same outcomes were reported in protocols and in final published reports (Carbonell-Estrany 2010; Feltes 2011; Fernandez 2010). For all seven included trials, the outcomes listed in the methods were also reported in the results section of the final trial reports. RSV-specific outpatient medically attended lower respiratory tract infection was assessed in two studies (Carbonell-Estrany 2010; Feltes 2011), and in both of them in just a subset of patients, either in patients from selected study sites (Carbonell-Estrany 2010) or in patients in season two only (Feltes 2011). No explanations were provided, making the risk of reporting bias in these trials 'high'. In three trials, several outcomes of interest (total RSV-hospital days, days in the ICU, days of mechanical ventilation and days of supplemental oxygen therapy) were reported incompletely; data on standard deviations were missing and the risk of reporting bias in these trials was 'high' (Carbonell-Estrany 2010; Feltes 2003; IMpact-RSV 1998). None of the studies had prespecified nor reported the incidence and duration of bronchodilator therapy for RSV infection. Since this was not one of the key outcomes of this review, this does not present a risk of reporting bias.

Other potential sources of bias

All of the seven included randomized controlled trials were sponsored by the drug manufacturing company, and many of the study authors were its employees or consultants, or they received research grants and compensations from the company. This represented an 'unclear' risk of bias for all included RCTs.

Of the 34 economic evaluations eligible for inclusion, conflict of interest was clearly stated in 21 studies that were either funded by the drug manufacturing company, or included authors who were employees of the manufacturing company (Bentley 2011; Chirico 2009; Chiroli 2005; Hascoet 2008; Lanctot 2008; Lazaro y de Mercado 2006; Lofland 2000; Mayen-Herrera 2011; Neovius 2011; Nuijten 2007; Nuijten 2009a; Nuijten 2009b; Nuijten 2010; Ravasio 2006; Resch 2008; Resch 2012; Roeckl-Wiedmann 2003; Salinas-Escudero 2012; Tam 2009; Vogel 2002; Weiner 2012). For 10 studies no conflict of interest was declared (ElHassan 2006; Embleton 2007; Garcia-Altes 2010; Hampp 2011; Joffe 1999; Raya Ortega 2006; Rietveld 2010; Smart 2010; Wang 2011; Yount 2004); and for three studies it was not completely clear whether they were funded by the industry or not (Harris 2011; Kang 2009; Lazaro y de Mercado 2007).

Effects of interventions

See: **Summary of findings for the main comparison** Palivizumab compared to placebo for high risk of severe respiratory syncytial virus infection; **Summary of findings 2** Palivizumab compared to motavizumab for high risk of severe respiratory syncytial virus infection

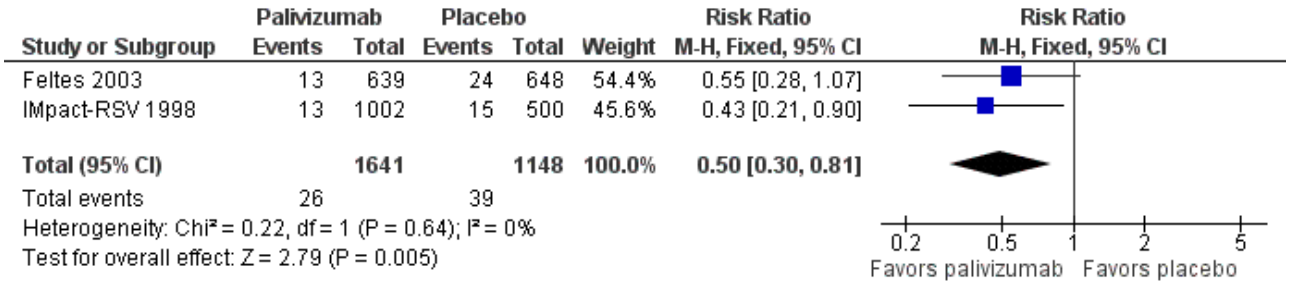
Palivizumab compared to placebo

Three randomized controlled trials (RCTs) compared palivizumab prophylaxis with a placebo in a total of 2831 patients, who were either born preterm and less than six months old, or less than two years old and with bronchopulmonary dysplasia (IMpact-RSV 1998; Subramanian 1998), or were less than two years old and with haemodynamically significant congenital heart disease (Feltes 2003). None of the included RCTs were performed in children with immunodeficiency, chronic neuromuscular disease or congenital anomalies. For all efficacy and safety outcomes, results were expressed as per intention-to-treat (ITT) population, which included all randomly assigned patients eligible for inclusion into the study. There was no indication of statistical heterogeneity across studies for most of the assessed outcomes, with the exceptions being the total days in the intensive care unit (ICU), and the incidence and total number of days of mechanical ventilation.

Palivizumab recipients had a statistically significant 51% relative risk reduction in respiratory syncytial virus (RSV) hospitalisations compared with placebo recipients (risk ratio (RR) was 0.49, 95% confidence interval (CI) 0.37 to 0.64) (Analysis 1.1; Figure 1), as well as a statistically significant 50% relative risk reduction in admissions to the ICU (RR 0.50, 95% CI 0.30 to 0.81) (Analysis 1.4; Figure 2), while the number of patients requiring mechanical ventilation for RSV infection seemed similar in the two groups (RR 1.10, 95% CI 0.20 to 6.09) (Analysis 1.6). However, in case of mechanical ventilation, statistical heterogeneity between the two trials may be substantial (I^2 statistic 60%; random-effects model applied) and results should be interpreted with caution.

Figure 1. Forest plot of comparison: 1 Palivizumab versus placebo, outcome: 1.1 Hospitalisation for RSV infection.

Figure 2. Forest plot of comparison: 1 Palivizumab versus placebo, outcome: 1.4 Admission to ICU.



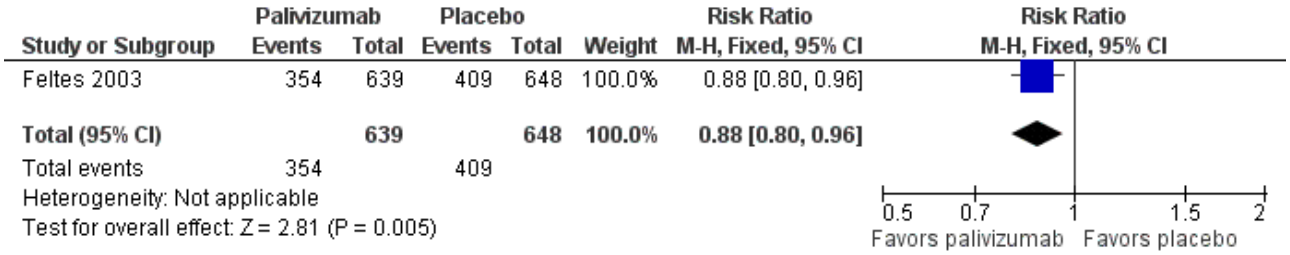
In both efficacy trials, total days were expressed as means per 100 randomized children (Feltes 2003; IMpact-RSV 1998). However, since data on days were reported incompletely, meta-analysis was not possible. Children randomly assigned to placebo had approximately twice as many days of hospitalization due to RSV infection (Analysis 1.3), and two to three times more days of supplemental oxygen therapy per 100 randomized children (Analysis 1.8), compared to palivizumab recipients. Results for total days in the ICU (Analysis 1.5) and total days of mechanical ventilation per 100 randomized children (Analysis 1.7) were quite heterogenous across the two trials. Feltes 2003, which included children with congenital heart disease, showed significantly fewer days in the ICU, and lower incidence and fewer days of mechanical ventilation in children treated with palivizumab compared with placebo. On the other hand, IMpact-RSV 1998, which included children born preterm with or without bronchopulmonary dysplasia, reported results with the opposite trend.

In all trials, mortality was reported as an all-cause mortality expressed per ITT population. Monthly prophylaxis with palivizumab, when compared to placebo, was associated with a statistically non-significant 31% relative risk reduction in all-cause mortality (RR 0.69, 95% CI 0.42 to 1.15) (Analysis 1.2).

Overall, rates of adverse events (AEs) and serious adverse events (SAEs) were consistent with the underlying medical conditions in this high-risk population. The proportion of children with any AE was similar between the two groups (RR 0.99, 95% CI 0.97 to 1.01) (Analysis 1.9), as well as the proportion of children with AE related to the study drug (RR 1.09, 95% CI 0.85 to 1.38) (Analysis 1.10). On the other hand, palivizumab recipients had a statistically significant 12% relative risk reduction in any SAE compared with placebo (RR 0.88, 95% CI 0.80 to 0.96) (Analysis 1.11; Figure 3), and a statistically non-significant 86% relative risk reduction in SAE related to study drug (RR 0.14, 95% CI 0.01 to 2.80) (Analysis 1.12).

However, only one study assessed these two outcomes (Feltes 2003). Common adverse events (when reported) included fever, injection site reactions and upper respiratory infections.

Figure 3. Forest plot of comparison: 1 Palivizumab versus placebo, outcome: 1.11 Number of children reporting any SAE.



Palivizumab compared to motavizumab

Four RCTs compared motavizumab prophylaxis with palivizumab prophylaxis in a total of 8265 patients, who were either born preterm and less than six months old, or less than two years old and with chronic lung disease of prematurity (Abarca 2009; Carbonell-Estrany 2010; Fernandez 2010), or were less than two years old and had haemodynamically significant congenital heart disease (Feltes 2011). None of the included RCTs were performed in children with immunodeficiency, chronic neuromuscular disease or congenital anomalies. Efficacy outcomes were assessed in two studies (Carbonell-Estrany 2010; Feltes 2011) and their results were expressed as per ITT population; while for safety outcomes (adverse events) results were expressed per safety population, which included all patients who received any study medication and had any safety follow-up. In order to be consistent with the objectives of this review, palivizumab was considered an intervention and motavizumab a control in all further analyses. There was no indication of statistical heterogeneity of intervention effects across studies.

Palivizumab recipients had a statistically non-significant 36% relative increase in the risk of hospitalization due to RSV infection, when compared with motavizumab recipients (RR 1.36, 95% CI 0.97 to 1.90) (Analysis 2.1; Figure 4). In a subset of patients, RSV-specific outpatient medically attended lower respiratory tract infections (MALRIs) were assessed. The risk of outpatient MALRI specific for RSV infection in the palivizumab group was twice that of the motavizumab group (RR 1.98, 95% CI 1.25 to 3.13) (Analysis 2.2; Figure 5). Palivizumab recipients had a statistically non-significant 68% relative risk increase in admission to the ICU compared with motavizumab recipients (RR 1.68, 95% CI 0.89 to 3.19) (Analysis 2.5), as well as a statistically non-significant 49% relative risk increase in incidence of supplemental oxygen therapy for RSV infection (RR 1.49, 95% CI 0.98 to 2.26) (Analysis 2.9), while the risk of mechanical ventilation in the palivizumab group was almost four times that of the motavizumab group (RR 3.79, 95% CI 1.26 to 11.42) (Analysis 2.7; Figure 6).

Figure 4. Forest plot of comparison: 2 Palivizumab versus motavizumab, outcome: 2.1 Hospitalisation for RSV infection.

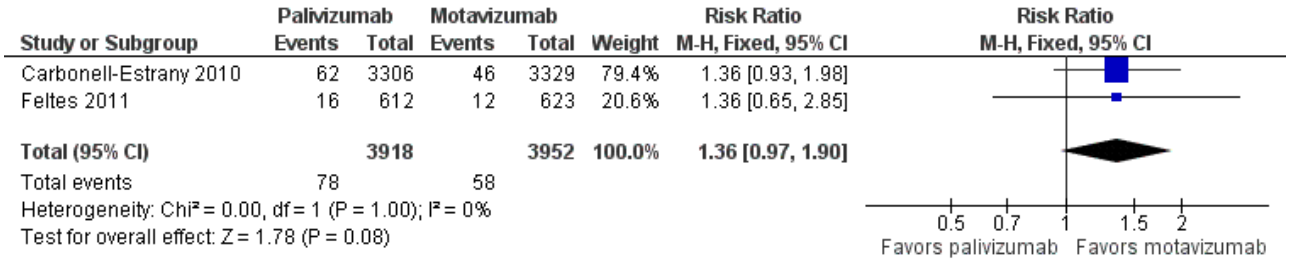


Figure 5. Forest plot of comparison: 2 Palivizumab versus motavizumab, outcome: 2.2 RSV-specific outpatient MALRI.

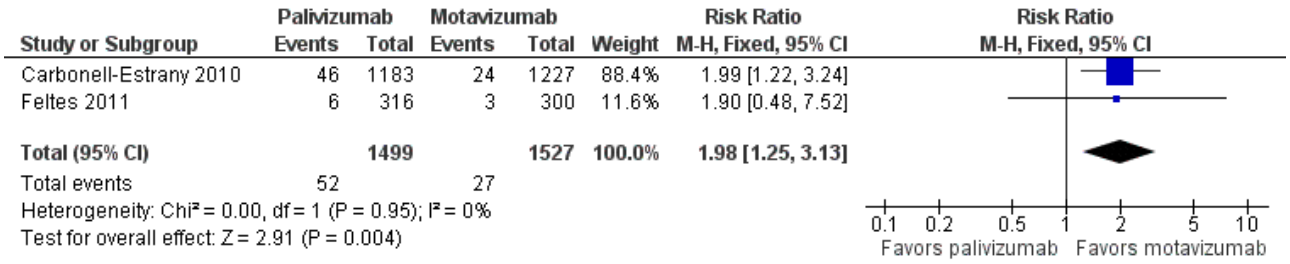
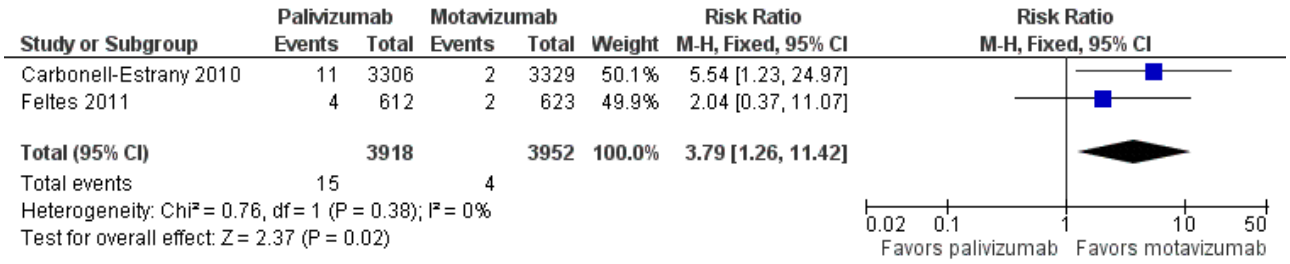


Figure 6. Forest plot of comparison: 2 Palivizumab versus motavizumab, outcome: 2.7 Mechanical ventilation for RSV infection.



In all trials but one (Abarca 2009), mortality was reported as all-cause mortality. In order to be consistent, for Abarca 2009 we reported the all-cause deaths, and for all four studies we expressed mortality per ITT population. Children randomly assigned to palivizumab had a statistically non-significant 26% relative risk reduction in all-cause mortality compared with motavizumab recipients (RR 0.74, 95% CI 0.38 to 1.43) (Analysis 2.3).

In Carbonell-Estrany 2010 total days were expressed as means per 100 randomized children, while for Feltes 2011 we calculated the means and standard deviations per 100 randomized children from the data originally reported per one child, and entered them in analyses. Since data on standard deviations are missing in Carbonell-Estrany 2010, only data from Feltes 2011 contributed to the meta-analysis, and results should be interpreted with caution. Children randomly assigned to palivizumab prophylaxis had approximately twice as many total RSV-hospital days, with a statistically non-significant mean difference (MD) of 24.95 days per 100 randomized children (MD 24.95, 95% CI -21.59 to 71.49) (Analysis 2.4), three to five times more days in the ICU, MD being 21.34 days per 100 randomized children (MD 21.34, 95% CI -13.69 to 56.37) (Analysis 2.6), seven to eight times more days of mechanical ventilation (MD 16.06, 95% CI -16.60 to 48.72) (Analysis 2.8), and two to three times more days of supplemental oxygen therapy per 100 randomized children (MD 28.42, 95% CI -13.64 to 70.48) (Analysis 2.10), compared to motavizumab recipients.

Again, rates of AEs and SAEs were consistent with the underlying medical conditions in this high-risk population. No significant differences were found in the proportion of children with any AE (RR 1.00, 95% CI 0.99 to 1.02) (Analysis 2.11), with AE related to study drug (RR 0.98, 95% CI 0.73 to 1.32) (Analysis 2.12), with any SAE (RR 1.04, 95% CI 0.96 to 1.13) (Analysis 2.13), or with SAE related to study drug (RR 0.88, 95% CI 0.32 to 2.43) (Analysis 2.14) between palivizumab and motavizumab recipients. Common adverse events (when reported) included fever, upper respiratory infections, cough and rhinitis.

Economic impact of immunoprophylaxis given at neonatal period or within the first six months of life

Out of the 22 studies that evaluated the economic impact of RSV immunoprophylaxis given during the neonatal period or within the first few months of life, 18 studies reported on preterm infants born at or before 35 weeks gestational age without other co-morbidities (Chirico 2009; ElHassan 2006; Embleton 2007; Hampp 2011; Lanctot 2008; Neovius 2011; Nuijten 2007; Nuijten 2010; Ravasio 2006; Raya Ortega 2006; Resch 2008; Resch 2012; Roeckl-Wiedmann 2003; Salinas-Escudero 2012; Smart 2010; Vogel 2002; Wang 2011; Weiner 2012); nine studies reported on preterm infants with bronchopulmonary dysplasia or chronic lung disease (Chirico 2009; Embleton 2007; Hascoet 2008; Lofland 2000; Nuijten 2009a; Ravasio 2006; Rietveld 2010; Roeckl-Wiedmann 2003; Wang 2011); and three studies reported on infants with congenital heart disease (Hascoet 2008; Nuijten 2009a; Wang 2011).

Of the studies evaluating immunoprophylaxis in preterm infants without other co-morbidities, 12 (Chirico 2009; Hampp 2011; Lanctot 2008; Nuijten 2007; Nuijten 2010; Resch 2008; Resch 2012; Ravasio 2006; Raya Ortega 2006; Salinas-Escudero 2012; Smart 2010; Wang 2011) reported costs from the payer's perspective, or from both the payer's and societal perspectives. Six studies (ElHassan 2006; Embleton 2007; Ravasio 2006; Raya Ortega 2006; Roeckl-Wiedmann 2003; Salinas-Escudero 2012) reported a time horizon different than the lifetime (e.g. one year, eight years, 14 years, 18 years). In studies where evaluation was conducted from the payer's perspective and with a lifetime horizon (Chirico 2009; Lanctot 2008; Nuijten 2007; Nuijten 2010; Resch 2008; Resch 2012; Smart 2010; Wang 2011), the incremental cost-effectiveness

ratio (ICER) present values at 2011 EUR expressed per quality-adjusted life-year (QALY) or life-year gained (LYG), vary widely across the studies (from EUR 7282 to EUR 27,068 per QALY, and from EUR 10,724 to EUR 36,098 per LYG). All of those studies considered different mortality rates for the intervention and non-intervention groups in the economic models, making the assumption that palivizumab prophylaxis has an effect on mortality, since there is evidence suggesting that palivizumab modifies the RSV hospitalization rates. Wang 2011 reported a range of ICERs in this population (from EUR 133,478 to EUR 1,651,357 per QALY); lower ICERs were obtained when passive immunisation is given during the neonatal period to preterm infants born at less than 24 weeks of gestational age, and higher ICERs (less favorable for the use of palivizumab) were obtained when prophylaxis was given to infants three to six months of age, born at 32 to 34 weeks of gestational age.

In studies evaluating preterm infants without other co-morbidities, with a one-year time horizon (Embleton 2007; Raya Ortega 2006; Roeckl-Wiedmann 2003; Vogel 2002), the effectiveness outcome measure was averted hospitalization. While Raya Ortega 2006 adopted the payer's perspective, Embleton 2007, Roeckl-Wiedmann 2003 and Vogel 2002 reported results from the societal perspective. The incremental costs per hospitalization averted for palivizumab prophylaxis were rather high in Embleton 2007 (EUR 72,780); while the ICERs reported by Roeckl-Wiedmann 2003 and Vogel 2002 were quite lower, and similar between them (EUR 29,199 and EUR 24,617 respectively). Roeckl-Wiedmann 2003 included the mortality benefits for the use of palivizumab prophylaxis and Vogel 2002 did not. However, Vogel 2002 considered a much lower total amount of the drug in the economic model.

Economic evaluations reporting incremental costs per LYG or QALY in preterm infants with bronchopulmonary dysplasia (or chronic lung disease), adopting the payer's perspective (Chirico 2009; Ravasio 2006; Wang 2011), showed rather favorable cost-effectiveness results for the use of palivizumab (from EUR 2968 to EUR 3317 per QALY, and from EUR 4707 to EUR 6253 per LYG). Wang 2011 reported a range of ICERs for this population (from EUR 17,113 to EUR 112,943 per QALY). All three studies allowed a mortality difference and difference in the risk of long-term sequelae in their models. ICER values reported in preterm infants with bronchopulmonary dysplasia (or chronic lung disease) were systematically lower than those reported in preterm infants without other comorbidity, indicating that palivizumab prophylaxis is more cost-effective in infants with bronchopulmonary dysplasia than in those born preterm without other comorbidity.

All three studies that evaluated the economic impact of RSV prophylaxis in infants with congenital heart disease (Hascoet 2008; Nuijten 2009a; Wang 2011) adopted a lifetime time horizon. However, analyses were conducted from different perspectives, and they included different mortality rates and different risks of sequelae (asthma or recurrent wheezing) in their models, which finally made them incomparable. The ICERs expressed per QALY or LYG showed big variations across studies. Wang 2011 reported on infants with acyanotic and cyanotic congenital heart disease, adopting the payer's perspective. The range of ICER values obtained in infants with acyanotic congenital heart disease was lower (more favorable) than the range of ICER values in infants with cyanotic congenital heart disease. In both cases, ICER values were dramatically higher than those reported by the other two studies in infants with congenital heart disease, which adopted the societal perspective. All three studies that reported results for infants with congenital heart disease also reported results for preterm infants with bronchopulmonary dysplasia (or chronic lung disease) and within-study comparisons were possible. In Hascoet 2008 and Nuijten 2009a, ICERs reported for infants with congenital heart disease showed to be systematically lower than the ICERs reported for infants with bronchopulmonary dysplasia (or chronic lung disease), while Wang 2011 showed the opposite trend in results.

Economic impact of immunoprophylaxis given to children aged six months and older

Out of 10 studies that evaluated the economic impact of RSV immunoprophylaxis given to children aged six months and older, two studies reported on children born at or before 35 weeks of gestational age without other co-morbidities (Tam 2009; Wang 2011); nine studies reported on children with congenital heart disease (Chiroli 2005; Hampp 2011; Harris 2011; Nuijten 2007; Nuijten 2009b; Resch 2008; Resch 2012; Wang 2011; Yount 2004); and five studies reported on children with bronchopulmonary dysplasia or chronic lung disease (Hampp 2011; Nuijten 2007; Resch 2008; Resch 2012; Wang 2011).

Tam 2009 and Wang 2011 performed evaluations from the payer's perspective in children born at or before 35 weeks of gestation without other co-morbidities, adopting a lifetime time horizon, and allowing the mortality benefits for the use of palivizumab prophylaxis. The ICER values expressed per QALYs varied across the studies substantially; Wang 2011 reported dramatically higher values than Tam 2009 (EUR 655,409 and EUR 29,663 respectively).

From the studies that analyzed the economic impact of passive immunisation given to children with congenital heart disease, six studies adopted a lifetime time horizon and a payer's perspective (Nuijten 2007; Nuijten 2009b; Resch 2008; Resch 2012; Wang 2011; Yount 2004). All six studies allowed a mortality difference and difference in the risk of long-term sequelae between the interventions. The ICER values expressed per QALYs reported in Wang 2011 and Yount 2004 were dramatically higher than those reported in other studies. Also, Wang 2011 and Nuijten 2007 reported on children with acyanotic and cyanotic congenital heart disease. The range of ICER values obtained in children with acyanotic congenital heart disease was lower than the range of ICER values in children with cyanotic congenital heart disease, indicating that palivizumab prophylaxis is more cost-effective among the first ones.

Hampp 2011 and Harris 2011 used the RSV hospitalization averted, and one day of RSV hospitalization averted as the effectiveness outcome measures, respectively. Hampp 2011 adopted a payer's perspective, and did not include the mortality benefits for the use of palivizumab into the model. Harris 2011 adopted a societal perspective, and included the mortality benefits into the model. Finally, the ICERs in the two studies differed substantially (EUR 689,645 per hospitalization averted and EUR 11,669 per one day of hospitalization averted, respectively).

All five studies that performed analyses in children with bronchopulmonary dysplasia or chronic lung disease adopted the payer's perspective. Hampp 2011 reported values of ICERs per hospitalization avoided, and did not allow a mortality difference

or a difference in the risk of long-term sequelae between the interventions. Nuijten 2007; Resch 2008; Resch 2012 and Wang 2011 reported ICERs per LYGs and/or QALYs, thereby adopting a lifetime time horizon, and allowing the mortality benefits for the use of palivizumab prophylaxis. The ICERs from these analyses are quite consistent across studies (from EUR 25,459 to EUR 36,794 per QALY, and from EUR 36,774 to EUR 50,557 per LYG). Again, the range of ICER values reported in Wang 2011 was very wide.

Resch 2012 reported on the same patient populations as Resch 2008, and conducted the analysis in the same country (Austria), by adopting a similar modelling approach. However, it incorporated changes in the total amount of the drug used, the medication costs and overall consumption of resources, and it included some new country-specific epidemiologic data. These changes led to obtaining more favorable ICERs as compared to ICERs reported in Resch 2008, both in children with congenital heart disease, and in children with bronchopulmonary dysplasia (or chronic lung disease).

Economic impact of immunoprophylaxis given to high-risk infants and children (born preterm, with or without bronchopulmonary dysplasia, or with congenital heart disease) up to five years of age

Three studies evaluated the economic impact of RSV immunoprophylaxis given to a mixed population of high-risk infants and children (preterm infants with or without bronchopulmonary dysplasia, infants with congenital heart disease, preterm children with or without bronchopulmonary dysplasia, and children with congenital heart disease) (Garcia-Altes 2010; Joffe 1999; Lazaro y de Mercado 2007). Garcia-Altes 2010 reported results from the payer's perspective, adopting a lifetime time horizon, and allowing for mortality difference between the treatments. Lazaro y de Mercado 2007 reported results from the societal perspective, adopting a lifetime time horizon, and allowing the mortality difference as well as the difference in the risk of long-term sequelae between the treatments. Both studies were conducted in Spain. The final results of ICERs expressed per LYGs differ immensely (EUR 174,642 and EUR 6256 respectively). We could not calculate the ICER present values at 2011 EUR for results reported in Joffe 1999, since exchange rates for Euros are not available for 1995.

Funding and results in economic evaluations

Overall, of the 34 included economic evaluations, 21 studies were funded by the drug manufacturing company, 10 studies had no conflict of interest declared and three studies were unclear as to whether they were industry funded or not (Characteristics of included studies).

All of the industry-sponsored economic evaluations supported the cost-effectiveness of palivizumab prophylaxis, except for Lofland 2000, which gave ranges of ICER values and left the conclusions at reader's discretion, Roeckl-Wiedmann 2003 which suggested a more restrictive policy, and Vogel 2002 that reported no cost savings with palivizumab prophylaxis.

All of the economic evaluations that were not industry-sponsored suggested within their final conclusions that palivizumab was not cost-effective in the analyzed settings, according to the established threshold values, and that a more restrictive passive immunisation policy should be used. The only exception was Smart 2010, which had the methodology based on Lanctot 2008 (industry-funded) and reported that palivizumab prophylaxis is cost-effective. Yount 2004 suggested that the routine use of palivizumab should be further evaluated.

Regarding the three studies where funding was questionable, Harris 2011 reported receiving a very small honorarium from the sponsoring company, and suggested that palivizumab was not cost-effective. For Kang 2009 only an abstract was available, suggesting that the use of palivizumab was cost-effective, with no details provided about the funding. In Lazaro y de Mercado 2007 no conflict of interest was declared, and cost-effectiveness of palivizumab was suggested, but should be noted that for the economic evaluation performed on the same topic by the same authors in 2006 (Lazaro y de Mercado 2006), the authors received a grant from the drug manufacturing company.

DISCUSSION

Summary of main results

Efficacy and safety evidence

The primary objective of this review was to assess the effects of palivizumab prophylaxis compared to placebo, or another type of prophylaxis (e.g. motavizumab), in reducing the risk of hospitalization due to respiratory syncytial virus (RSV) infection in high-risk infants and children.

Palivizumab prophylaxis was associated with a statistically significant reduction in RSV hospitalisations, when compared to placebo. The magnitude of this effect is considerable; palivizumab reduced the risk of RSV hospitalization by half. Children treated with palivizumab prophylaxis spent fewer days in hospital, were admitted to the intensive care unit (ICU) less often, and had fewer days of supplemental oxygen therapy for RSV infection than the placebo recipients. These results suggest a favorable effect of palivizumab prophylaxis on the incidence of serious lower respiratory tract RSV disease in children at high risk.

Results for the total days spent in the ICU and the incidence and total days of mechanical ventilation were inconsistent between the two trials, possibly due to different severity of underlying medical conditions in children included in the trials. Children with haemodynamically significant congenital heart disease experienced fewer days in the ICU, and lower incidence and fewer days of mechanical ventilation when treated with palivizumab prophylaxis compared with placebo, while children born preterm, with or without bronchopulmonary dysplasia, having less severe baseline risk factors for RSV disease, showed the opposite trend in results. It could be that a drug has a larger relative effect in sicker populations. But also, medical practices, guidelines and recommendations on when to discharge from an ICU, and when to initiate and wean mechanical ventilation, differ substantially in different settings.

When palivizumab was compared to motavizumab prophylaxis, there was an obvious trend of increase in the risk of acquiring severe lower respiratory tract RSV disease in patients receiving palivizumab. The risk of hospitalization due to RSV infection was increased by one-third in palivizumab patients. Children treated with palivizumab had more admissions to intensive care, a higher need for supplemental oxygen therapy and more

instances of mechanical ventilation than the children treated with motavizumab prophylaxis.

However, the results of trials comparing palivizumab and motavizumab should be interpreted with caution. The US Food and Drug Administration (FDA) cited methodological concerns (among others) in its review of a licensing application for motavizumab, specifically with regards to the laboratory testing of RSV, which may have biased the results toward motavizumab over palivizumab. The FDA also expressed concerns regarding both motavizumab's safety and efficacy. The non-fatal hypersensitivity adverse events were found to be three times higher in the motavizumab group than in the palivizumab group. Also, motavizumab's non-inferiority results are largely driven by data obtained from southern hemisphere countries, representing only about 9% of the total patient population. Removing this population led the FDA to determine that in the US population motavizumab did not meet the non-inferiority criterion relative to palivizumab (FDA 2010). These issues have implications for assessing the risk of bias in Carbonell-Estrany 2010, and the results should be interpreted with this in mind.

Total days in the hospital due to RSV infection, days spent in the ICU, receiving mechanical ventilation or with supplemental oxygen therapy were all much higher in palivizumab than in motavizumab-treated patients.

Data on days were summarised and presented as days per 100 randomized children in a study arm, and not as days per one child. That is why they are expected to be proportional to the number (or better, to the rate) of patients hospitalised from that study arm. For example, if two children out of 100 are hospitalised in one group, and one child out of 100 is hospitalised in the other group, and if each child from both groups stays in the hospital for five days, in the first group we would have 10 hospital days per 100 randomized children, and in the second five hospital days per 100 randomized children. The larger the incidence of RSV hospitalisations, the bigger are the numbers of days. This is a common problem in almost all RCTs in this review: results on total days presented in this way could be misleading. We cannot interpret them as a measure of severity of the disease, once a child has acquired an RSV infection. For both clinicians and patients it would be more beneficial for study authors to express the mean number of days per one child in future studies.

Another common problem of almost all studies reporting data on days is their incomplete reporting. Measures of dispersion were not provided and we cannot be confident about the precision of the results.

RSV-specific outpatient medically attended lower respiratory tract infections were assessed for motavizumab and palivizumab patients in two studies. Motavizumab was associated with statistically significant reduction in RSV-specific outpatient MALRIs when compared to palivizumab; the risk in the palivizumab group was twice that of the motavizumab group. However, this outcome was assessed in just a subset of patients, either in patients from selected study sites or in patients in season two only, making the risk of bias in these results high.

Palivizumab-treated children had lower mortality rates than children treated with placebo or motavizumab. However, it was hard to draw any conclusions since all studies expressed mortality as deaths due to any cause, regardless of their relation to study drug or to RSV infection. We were surprised to find that within-study mortality rates differed substantially between the studies (e.g. Carbonell-Estrany 2010 reports an all-cause mortality rate 30 times that of Feltes 2003). The difference could be attributed to different sample sizes and different underlying medical conditions in patient populations in the two studies.

For both comparisons we analyzed the proportion of children with adverse events in four categories, depending on the seriousness of the adverse event (AE) and its relatedness to the study drug. Unfortunately, we could not analyse a specific adverse event or adverse events grouped by organ systems, due to different reporting methodologies in studies.

As we expected, considering the underlying medical conditions in this high-risk population, rates of AEs and SAEs were high in all treated patients. Palivizumab was associated with a statistically significant reduction in the proportion of children reporting any SAE compared to placebo. After having confirmed the efficacy of palivizumab prophylaxis, these results are self explanatory. Palivizumab reduces the risk of severe RSV disease after the RSV infection has occurred, and thereby minimises hospitalisations, or possibly some life-threatening conditions or significant disabilities, which are all considered serious adverse events. It should also be noted that this result came from one study only. The proportion of children reporting any adverse event related to study drug, or any adverse event at all, was similar in palivizumab and placebo patients. Post-marketing surveillance data included in the Synagis (palivizumab) product leaflet provide additional insight into potential adverse events encountered, specifically: severe acute hypersensitivity reactions and anaphylaxis, which are described as rare and very rare (respectively) (FDA 2009).

We did not find any differences in the proportion of children reporting AE when palivizumab was compared to motavizumab in any of the four categories assessed. The proportion of children reporting any AE was similar between the two groups, and additional analyses of other groupings of AEs did not demonstrate any significant difference.

Economic evidence

In all included economic studies, a cost-effectiveness or a cost-utility analysis was conducted that compared the clinical and financial consequences of palivizumab prophylaxis and no prophylaxis in infants and children at high risk. In this section, the Drummond definitions of the types of economic evaluations were followed (Drummond 1996) and all studies were classified into a health sector (payer's) or a societal perspective.

In general, costs and outcomes can be combined in three different ways, resulting in three different types of analyses: cost–benefit analysis (where both inputs and outcomes are considered in monetary terms); cost–utility analysis (where inputs are considered in terms of costs, and outcomes are measured in utility measures, such as quality-adjusted life-years (QALYs)); and cost–effectiveness analysis (where inputs are measured in terms of costs, and outcomes are measured using measures specific to the disease). A QALY is estimated in terms of a year of life, adjusted by the amount of quality that the life is lived at. Therefore, one year lived at full quality is 1 QALY, but one year lived at half quality equates to 0.5 QALYs, and half a year at full quality is also 0.5 QALYs. Different diseases and conditions can be compared using the cost–utility

analysis and, therefore, these types of analyses are especially used by governmental approval groups, such as the UK National Institute for Health and Clinical Excellence, which often sets a threshold of utility gains per cost for all drugs and health technologies. A cost–effectiveness analysis usually compares the costs and outcomes of similar treatments for specific conditions. However, it would not provide data on the incremental cost–effectiveness ratio (ICER) per QALY, and if such data are required, would need to be modelled from the cost–effectiveness data.

Whether an intervention is cost-effective or not, and whether it should be provided or not, depends on the cost-effectiveness threshold established by the decision makers in a particular country. Following the recommendations of the Commission on Macroeconomics and Health, the World Health Organization (WHO) has derived three categories of cost-effectiveness using the nominal gross domestic product (GDP) per capita as a measure:

- highly cost-effective (ICER is less than one GDP per capita);
- cost-effective (ICER is between one and three times GDP per capita); and
- not cost-effective (ICER is more than three times GDP per capita).

The nominal GDP per capita for the European Union (EU) for year 2011, as calculated by the World Bank, was USD 34,848 (EUR 24,621.37) (available at http://data.worldbank.org/). Using this GDP to calculate the cost-effectiveness threshold, the immunoprophylaxis would be cost-effective for the EU countries if the ICER present value at 2011 EUR is lower than EUR 73,864.11 per QALY. However, this threshold is substantially higher than the thresholds established by particular EU countries, e.g. the United Kingdom's cost-effectiveness threshold has been in the range of GBP 20,000 to GBP 30,000 for over 10 years now (EUR 22,791.74 to EUR 34,187.61 respectively, using the 2011 exchange rates).

As Peter Jacobson (Jacobson 2001) stated: "Cost control is a primary objective of the managed care environment. It is no longer possible to provide health care without regard to cost or patient demand. The question is not whether there will be cost containment, but how to structure and oversee its implementation. The use of cost-effectiveness analysis (CEA) in making clinical and payment decisions has become a significant cost containment approach, however CEA should be treated as one piece of evidence to be considered by health care sector to define way of action rather than being used to determine the standard of care."

We presented and discussed economic data separately according to age and subgrouped data according to underlying medical conditions because, clinically, these patients are likely to have different baseline risks for serious complications due to RSV infection. We further classified the economic evaluations by whether they adopted the payer's or the societal perspective. We also debated about the main economic results obtained from the included studies and about variations in methodological approaches among studies that may justify the differences in cost-effectiveness results.

Data on cost–effectiveness of RSV immunoprophylaxis with palivizumab versus no prophylaxis are based on simulation modelling, rather than the direct collection of costs and outcomes. Data for the evaluations were drawn from a wide variety of sources, including the palivizumab clinical trials, published literature, hospital databases, country-specific price/tariff lists and national population statistics. Country-specific data sources were also used for economic measures and information on therapeutic choices. Clinical events and utilities in the majority of analyses are not country-specific and therefore were derived from international studies.

The main outcomes considered for cost-effectiveness analyses in the included economic studies were hospitalization due to RSV infection (ordinary ward or ICU) and life-years gained (LYGs). For cost-utility analysis, outcomes considered were QALYs. Challenges in the cost–utility approach for this specific problem lie in modelling of costs and QALY gains in the lifetime follow-up period to capture the impact of palivizumab on long-term morbidity and mortality, resulting from severe RSV infection beyond the RSV hospitalization period. Under the assumption that RSV hospitalisations are associated with clinical and economic consequences beyond the clinical trial period; a proportion of children may develop long-term sequelae (e.g. wheezing or asthma) leading to a reduction of QALYs and additional medical costs. It is known that the rates used to populate the economic models will drive the final results of the analyses towards higher or lower ICER values. The reduction in RSV hospitalization rate due to palivizumab prophylaxis corresponds to data available from the palivizumab clinical trials (e.g. IMpact-RSV 1998) that considered only one season period of follow-up, which is 150 days from the point of randomization (30 days after the last scheduled palivizumab injection). Therefore, for the economic models that adopted the lifetime time horizon it was necessary to extrapolate the efficacy data from the palivizumab clinical trials (reduction in the rate of RSV hospitalisations) to calculate the likely number of LYGs and QALYs gained from the use of palivizumab prophylaxis. Regardless of the time horizon considered in the analysis, if authors assumed that differences in RSV hospitalization rates allow for differences in mortality rates between the palivizumab prophylaxis and non-prophylaxis group, and thus populated the models from the beginning with differential mortality rates, the final results will favour palivizumab use, particularly if the societal perspective was adopted.

Modelling costs depend on the perspective of the analysis. The analyses performed from the societal perspective included not only the direct medical costs, but also costs for management of wheezing or asthma, and future lost productivity of a child resulting from mortality (a small proportion of children will die, which will lead to a lifetime loss of productivity benefits). The analyses that adopted the payer's perspective considered only direct medical costs. Generally, analyses that included direct medical costs associated with asthma (i.e. when asthma was included into the disease pathway modelled) showed moderately more favorable ICERs for palivizumab prophylaxis, while analyses that included the long-term indirect costs due to lost lifetime productivity following childhood mortality, showed a substantial improvement in the cost-effectiveness of prophylaxis with palivizumab. It means that palivizumab prophylaxis is more cost-effective if it has a long-term effect on the incidence of asthma and mortality.

A very important consideration that should be taken into account while interpreting the economic results presented in this review is that effectiveness data used to populate the models come from follow-up studies performed in hospitalised children, RSV-infected or not, with or without the underlying medical conditions (such as bronchopulmonary dysplasia or congenital heart disease); none

of the studies measured the long-term impact that palivizumab prophylaxis could have on asthma and mortality in these high-risk populations. So, data used by study authors to populate the economic models are based on unsupported assumptions. Whether or not these assumptions and modelling practices lead to underestimation or overestimation of the mortality rates in children born preterm or with underlying heart or lung disease, that have received immunoprophylaxis with palivizumab, is unclear.

Currently there are no longitudinal trials providing robust data on long-term effects of palivizumab prophylaxis on a child's morbidity and mortality beyond the standard follow-up period. The forthcoming results from one investigator-initiated RCT (NTR1023) that assessed the number of wheezing days in preterm children during the first year of life, and the quality of life and asthmatic symptoms up to six years of age, might be offering some answers to this question.

Owing to particular problems described above, and due to the fact that mortality rates could drive the final cost-effectiveness ratios, it is important to discuss the methodological approaches used by the authors to model this outcome in their economic analyses. Methods that were used for reporting, calculating and adjusting the probabilities of death that entered the models differed considerably across studies. In most cases, the absolute values of probabilities of death were not reported and the exact organisation of decision tree models was not presented. Some study authors directly modelled different mortality rates for patients receiving palivizumab prophylaxis and no prophylaxis. In some of the studies, models included difference in life-years gained between the two intervention groups, and this fact necessarily implies that a difference in mortality was also allowed. Some study authors assumed different mortality rates for hospitalised versus non-hospitalised patients. In other instances, different mortality rates were assumed for patients hospitalised with or without the RSV infection. Again, some other studies assumed the same mortality rates for the two intervention groups, but calculated the probabilities of death according to the related hospitalization rates in the two groups. The bottom line is that all these studies took into account that palivizumab prophylaxis reduces the rate of RSV-related hospitalisations, and this directly translates into reduced mortality risk in palivizumab group compared to no intervention group. Rare authors did not model a mortality benefit associated to the use of prophylaxis, but this was the case only in studies with a short time horizon (one year), and with final costs expressed per hospitalization avoided (the exception being the ElHassan 2006 study).

Other important differences in economic models included in this review are the different total amount of the drug, different resources and services consumed (depending on a healthcare system in a particular country), different overall costs (dependent on the costs that specific services/resources have in a specific country), different time horizons and different discount rates.

Each of the factors described could easily account for large differences in cost-effectiveness results across studies. An additional aspect that we have studied, while interpreting the economic results presented in this review, is whether the analysis was funded by the drug manufacturing company or not. Almost all included studies that were sponsored by the industry supported the cost-effectiveness of palivizumab prophylaxis, while practically all included studies that were not sponsored by the industry suggested that palivizumab was not cost-effective.

We made attempts to classify studies according to all these differing assumptions included in economic models, in an effort to identify premises that would be necessary for palivizumab prophylaxis to be regarded as acceptably cost-effective. However, by analysing the information available from the study reports, it became obvious that a huge problem lies in the lack of standardisation of the modelling approaches adopted in economic studies, and these differences can easily lead to big variations in cost-effectiveness results, making them almost incomparable. The use of palivizumab prophylaxis for reducing the risk of severe RSV infection might not be cost-effective enough to be considered a standard healthcare policy in the majority of low- and middle-income countries, because of the high costs of the drug. However, patient needs and individual risks should be considered in each case that physicians encounter in their everyday clinical practice.

Economic impact of immunoprophylaxis given at neonatal period or within the first six months of life

In an attempt to find systematic differences that could explain the variations in results of the studies reporting on preterm infants without other comorbidity, we analyzed patient populations, effectiveness outcomes, perspective taken and other methodological parameters. The doses of palivizumab varied across studies (from 3 to 6 doses at 15 mg/kg); gestational ages of preterm infants entered into the models differed between the studies; incremental effectiveness of palivizumab prophylaxis varied substantially across studies (i.e. RSV hospitalisations avoided, risk of asthma included, lower mortality rates due to palivizumab use). Finally, the included studies reported significant differences in economic results, coming primarily from the consumption of resources taken into account, and from the modelling approaches adopted. Many analyses considered a lifetime follow-up period to capture the impact of palivizumab on a long-term morbidity and mortality resulting from severe RSV infection. Since the available data from palivizumab clinical trials are all limited to a single RSV season, the way of modelling the evaluations presents an important source of variations leading to such differences in ICERs.

Economic impact of immunoprophylaxis given to children aged six months and older

Two studies evaluated the economic impact of RSV immunoprophylaxis in preterm children without other co-morbidities. The ICER values expressed per QALYs varied across these two studies substantially, making it difficult for decision-makers to identify the real magnitude of the economic impact that the palivizumab prophylaxis has in this population.

In the studies evaluating the economic impact of passive immunisation given to children with congenital heart disease, substantially higher ICER values expressed per QALYs and LYGs were reported by Wang 2011 and Yount 2004. These studies had comparable methodological characteristics to other studies, and they both included mortality benefits and lower risk of long-term sequelae for children receiving palivizumab prophylaxis. We did not find any clear explanations for this variation, other than that these two studies were the only ones not funded by the drug manufacturer.

Results from studies performed in children with bronchopulmonary dysplasia (or chronic lung disease) aged six months and older are quite consistent and rather high. Whether palivizumab prophylaxis is a cost-effective alternative, and whether it should be adopted as part of routine care in this population, depends on the threshold value set by the decision-makers in a particular country.

Economic impact of immunoprophylaxis given to high-risk infants and children (born preterm, with or without bronchopulmonary dysplasia, or with congenital heart disease) up to five years of age

From the evidence presented in the three included studies, it is very difficult to define the real economic impact that the RSV prophylaxis strategy has in a mixed population of high-risk infants and children.

Overall completeness and applicability of evidence

The review includes all relevant RCTs and economic evaluations identified by an up to date literature search, making this evidence report up to date and current. We had prespecified RSV hospitalization and mortality as the primary efficacy and safety outcomes, and they were reported by most of the RCTs included.

This report presents evidence about the effects of palivizumab prophylaxis in infants and children at high risk for the development of serious RSV disease, in terms of its efficacy, safety and cost-effectiveness.

Quality of the evidence

A total of seven RCTs and 34 economic evaluations were included in this review. The quality of evidence reflects the extent to which we are confident that an estimate of the effect is correct.

The quality of evidence was assessed and summarised for each main efficacy and safety outcome in this review by using the GRADE approach implemented in the GRADEpro software (GRADEpro 2008). The GRADE quality rating was high or moderate for all outcomes assessed, with minor exceptions. Data on several important outcomes were not reported in all included studies. Some measurements were missing standard deviations and meta-analysis was not possible.

When palivizumab was compared to placebo, the quality of the evidence was high for RSV hospitalization, admission to ICU and for number of children reporting any serious adverse events. We downgraded the quality for all-cause mortality to moderate, due to imprecision of results; for mechanical ventilation the quality rating was very low, due to very serious heterogeneity and imprecision of data; while for total RSV hospital days, standard deviations were missing and meta-analysis was not possible, and we downgraded the quality of evidence to moderate. When palivizumab was compared to motavizumab, the quality of evidence was high for mechanical ventilation and for the number of children reporting any serious adverse events. For RSV hospitalization, all-cause mortality, admission to ICU and supplemental oxygen therapy, the quality of evidence was moderate due to imprecision of results; while for total RSV hospital days a standard deviation was missing in one study and could not be provided by the authors, and data were imprecise in the other study; we downgraded the quality of evidence to low.

It should be noted that there are methodological and other concerns raised by the US Food and Drug Administration (FDA), with regards to some studies in which motavizumab was evaluated (Carbonell-Estrany 2010 among others), which resulted in rejecting a license application for motavizumab in 2010. A concern raised by the FDA was that the Carbonell-Estrany 2010 study may have utilised laboratory testing procedures which may have biased the study toward motavizumab over palivizumab. Another concern was related to hypersensitivity reactions which were more prevalent in children who received motavizumab compared to palivizumab. Further concerns were raised with regards to the geographic distribution of patients enrolled in Carbonell-Estrany 2010. Namely, motavizumab's efficacy results relative to palivizumab were largely driven by data from southern hemisphere countries, representing roughly 9% of the total data set. When compared with the northern hemisphere results, a substantial geographic heterogeneity of the treatment effect was observed (FDA 2010).

Results of the quality assessment of economic evaluation studies are summarised in Appendix 6. We assessed all included economic evaluations according to their full-text publications, except for Bentley 2011; Kang 2009 and Mayen-Herrera 2011, where only abstracts were available. In general, the included economic evaluations met the methodological and reporting aspects evaluated, and their results can be considered valid. In economic evaluations conducted by Chiroli 2005; Embleton 2007; Lofland 2000; Rietveld 2010 and Roeckl-Wiedmann 2003 the discounting was not applied to costs and consequences. However, it is considered to be methodologically correct since the time horizon used in these analyses was one year, making the discounting unnecessary. Studies conducted by Raya Ortega 2006 and Lofland 2000 were the only economic evaluations that did not meet three or more of methodological criteria assessed. The authors did not identify, measure accurately and value credibly relevant costs and consequences, and we cannot be confident in the final results presented in these studies.

Overall, the methodological and reporting quality of included economic evaluations was good, which is consistent with the criteria that we set for considering types of studies for inclusion. However, variations in the consumption of resources and in modelling approaches taken into account by a specific study appear to be a big drive for significant differences in the cost-effectiveness results.

Potential biases in the review process

Given our comprehensive search strategy and contact with the study authors and the drug manufacturer, it is unlikely that we missed any relevant studies. Two authors independently screened and selected studies, and extracted all data for RCTs and for economic evaluations. This we believe minimises errors in data extraction and biases. The quality of RCTs and economic evaluations was very good, although some studies did not report certain quality characteristics.

However, our review has several limitations, besides the fact that all included randomized controlled trials and two-thirds of the included economic evaluations were funded by the drug manufacturing company. We were limited in that palivizumab versus placebo, and palivizumab versus motavizumab comparisons only had three and four studies, respectively. Out of the total of seven RCTs, three were just safety studies (Abarca 2009;

Fernandez 2010; Subramanian 1998), without having evaluated the efficacy outcomes (except for one study where RSV hospitalisations were reported). That means that for most of the outcomes we assessed, we only had data from two studies that contributed to our analyses. Also, in one of the RCTs that we included (Subramanian 1998), the study drug was applied intravenously and not in the recommended approved dosing regimen, intramuscularly. In another study (Fernandez 2010), we presented safety information after two doses and not after the regular five doses of the study drug.

Two RCTs were conducted in children with haemodynamically significant congenital heart disease, and five RCTs in children born preterm, with or without chronic lung disease. We performed analyses in this review for all high-risk patient populations combined. In case we had three or more studies for each patient subpopulation, and for each comparison, we would have performed a subgroup analysis according to the presence of risk factors.

Agreements and disagreements with other studies or reviews

Our results agree with a previous Cochrane systematic review (Wang 1999) performed in children born preterm, with congenital heart disease or with bronchopulmonary dysplasia. However, in Wang 1999 the pooled effects of polyclonal (RSV-IVIG) and monoclonal (palivizumab) RSV-neutralising antibodies were assessed, in comparison to placebo. The review included four studies in a pooled analysis, three with RSV-IVIG and one (IMpact-RSV 1998) with palivizumab prophylaxis. Wang 1999 reports practically identical relative risk reduction in RSV hospitalisations (RR 0.48, 95% CI 0.37 to 0.64) and in admissions to ICU (RR 0.47, 95% CI 0.29 to 0.77); similar results in the incidence of mechanical ventilation (RR 0.99, 95% CI 0.48 to 2.07) and the opposite trend of a relative risk increase in mortality (RR 1.15, 95% CI 0.63 to 2.11), for RSV prophylaxis compared to placebo.

AUTHORS' CONCLUSIONS

Implications for practice

Palivizumab prophylaxis is effective in reducing the frequency of hospitalisations due to respiratory syncytial virus (RSV) infection, i.e. in reducing the incidence of serious lower respiratory tract RSV disease in children with chronic lung disease, congenital heart disease or those born preterm. Even though our search also included children with immunodeficiency, chronic neuromuscular disease or congenital anomalies, no studies were found for those patient populations, and no conclusions can be drawn for them. Also, it would be beneficial to have longitudinal studies that could demonstrate the long-term effects of RSV prophylaxis on a child's morbidity and mortality beyond the standard follow-up period of 30 days after completion of the prophylaxis regimen.

The results of incremental costs per hospitalization averted, life-year gained (LYG) or quality-adjusted life-year (QALY gained) showed substantial variations across the included economic evaluations, not only due to the differences in baseline risks of studied patient populations. Several sources of variation, including the source of funding, have led to incomparable cost-effectiveness results in evaluations performed in similar populations. How cost-effective palivizumab prophylaxis actually is in a high-risk population of infants and children is unclear. The use of palivizumab prophylaxis for reducing the risk of severe RSV infection might not be cost-effective enough to be considered a standard healthcare policy in the majority of low- and middle-income countries, because of the high costs of the drug. However, patient needs and individual risks should be considered individually by the attending physician.

Implications for research

A more precise definition of underlying medical conditions in the patient population at highest risk of severe RSV infection is necessary. Having a small number of efficacy studies for a specific subgroup of patients limited our ability to analyse data in that way. There are no published studies performed in children with immunodeficiency, chronic neuromuscular disease or congenital anomalies, all of whom may derive some benefit from RSV prophylaxis. Cohort studies are needed to determine the long-term effects of immunoprophylaxis on asthma, mortality and other important clinical outcomes. Conducting investigator-initiated studies would be beneficial, since all of the RCTs included in this review were sponsored by the manufacturer.

Evidence on the efficacy and safety of palivizumab prophylaxis in each subgroup of patients, together with the data about its cost-effectiveness in a specific population and setting, could be used for reconsidering current recommendations and developing national guidelines on when to provide RSV immunoprophylaxis. Also, the introduction of a low-cost vaccine against RSV would reduce the inequitable distribution and would make RSV prophylaxis available to the poorest countries where severe lower respiratory tract infections carry a substantial disease burden.

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REFERENCES

References to studies included in this review

Abarca 2009 *{published data only}*

Abarca K, Jung E, Fernandez P, Zhao L, Harris B, Connor EM, et al. Motavizumab Study Group. Safety, tolerability, pharmacokinetics, and immunogenicity of motavizumab, a humanized, enhanced-potency monoclonal antibody for the prevention of respiratory syncytial virus infection in at-risk children. *Pediatric Infectious Disease Journal* 2009;**28**(4):267-72.

Bentley 2011 *{published data only}*

Bentley A, Filipovic I, Gooch K, Buesch K. A cost-effectiveness analysis of respiratory syncytial virus (RSV) prophylaxis in infants in the UK. *Thorax* 2011;**66**(Suppl 4):A136-7.

Carbonell-Estrany 2010 *{published data only}*

Carbonell-Estrany X, Simões EA, Dagan R, Hall CB, Harris B, Hultquist M, et al. Motavizumab Study Group. Motavizumab for prophylaxis of respiratory syncytial virus in high-risk children: a non-inferiority trial. *Pediatrics* 2010;**125**(1):e35-51.

Chirico 2009 *{published data only}*

Chirico G, Ravasio R, Sbarigia U. Cost-utility analysis of palivizumab in Italy: results from a simulation model in the prophylaxis of respiratory syncytial virus infection (RSV) among high-risk preterm infants. *Italian Journal of Pediatrics* 2009;**35**:4. [DOI: 10.1186/1824-7288-35-4]

Chiroli 2005 *{published data only}*

Chiroli S, Macagno F, Lucioni C. Cost-efficacy analysis of palivizumab in the prevention of respiratory syncytial virus infections in young children with hemodynamically significant congenital heart disease. *Italian Journal of Pediatrics* 2005;**31**:188-94.

ElHassan 2006 *{published data only}*

ElHassan NO, Sorbero MES, Hall CB, Stevens TP, Dick AW. Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. *Archives of Pediatrics and Adolescent Medicine* 2006;**160**:1070-6.

Embleton 2007 *{published data only}*

Embleton ND, Dharmaraj ST, Deshpande S. Cost-effectiveness of palivizumab in infancy. *Expert Review of Pharmacoeconomics and Outcomes Research* 2007;**7**(5):445-58.

Feltes 2003 *{published data only}*

Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH Jr, et al. Cardiac Synagis Study Group. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *Journal of Pediatrics* 2003;**143**(4):532–40.

Feltes 2011 *{published data only}*

Feltes TF, Sondheimer HM, Tulloh RMR, Harris BS, Jensen KM, Losonsky GA, et al. Motavizumab Cardiac Study Group. A randomized controlled trial of motavizumab versus palivizumab for the prophylaxis of serious respiratory syncytial virus disease in children with hemodynamically significant congenital heart disease. *Pediatric Research* 2011;**70**(2):186-91.

Fernandez 2010 *{published data only}*

Fernandez P, Trenholme A, Abarca K, Griffin MP, Hultquist M, Harris B, et al. Motavizumab Study Group. A phase 2, randomized, double-blind safety and pharmacokinetic assessment of respiratory syncytial virus (RSV) prophylaxis with motavizumab and palivizumab administered in the same season. *BMC Pediatrics* 2010;**10**:38-50.

Garcia-Altes 2010 *{published data only}*

Garcia-Altes A, Paladio N, Tebe C, Pons JMV. Cost-effectiveness analysis of the administration of palivizumab as prophylaxis of severe bronchiolitis due to respiratory syncytial virus [Anàlisi cost-efectivitat de l'administració del palivizumab en la profilaxi de les bronquiolitis greus per virus respiratori sincicial]. *Pediatria Catalana* 2010;**70**:57-64.

Hampp 2011 *{published data only}*

Hampp C, Kauf TL, Saidi A, Winterstein AG. Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab from the perspective of a Southern US medicaid agency. *Value in Health* 2009;**12**(7):A301-2.

* Hampp C, Kauf TL, Saidi AS, Winterstein AG. Cost-effectiveness of respiratory syncytial virus prophylaxis in various indications. *Archives of Pediatrics and Adolescent Medicine* 2011;**165**(6):498-505.

Harris 2011 *{published data only}*

* Harris KC, Anis AH, Crosby MC, Cender LM, Potts JE, Human DG. Economic evaluation of palivizumab in children with congenital heart disease: a Canadian perspective. *Canadian Journal of Cardiology* 2011;**27**:523.e11-.e15.

Human DG, Harris KC, Anis AH, Crosby MC, Cender LM, Potts JE. Economic evaluation of palivizumab in children with congenital heart disease: a Canadian perspective. *Cardiology in the Young* 2010;**20**(Suppl 1):30.

Hascoet 2008 *{published data only}*

Hascoet JM, Fagnani F, Charlemagne A, Vieux R, Roze JC. Methodological aspects of economic evaluation in pediatrics: illustration by RSV infection prophylaxis in the French setting [Aspects methodologiques de l'evaluation economique du medicament en pediatrie: exemple de la prophylaxie de l'infection a VRS en France]. *Archives de Pediatrie* 2008;**15**:1739-48.

IMpact-RSV 1998 *{published data only}*

The IMpact-RSV Study Group. Palivizumab, a humanized respiratory syncytial virus monoclonal antibody, reduces hospitalization from respiratory syncytial virus infection in high-risk infants. *Pediatrics* 1998;**102**(3 Pt 1):531–7.

Joffe 1999 *{published data only}*

Joffe S, Ray GT, Escobar GJ, Black SB, Lieu TA. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics* 1999;**104**(3):419-27.

Kang 2009 *{published data only}*

Kang HY, Kim HS, Choi JY, Kim YH. Cost-effectiveness analysis of palivizumab in the prevention of respiratory syncytial virus infection in Korean children with congenital heart disease. *Value in Health* 2009;**12**(7):A424.

Lanctot 2008 *{published data only}*

Lanctot KL, Masoud ST, Paes BA, Tarride JE, Chiu A, Hui C, et al. The cost-effectiveness of palivizumab for respiratory syncytial virus prophylaxis in premature infants with a gestational age of 32-35 weeks: a Canadian-based analysis. *Current Medical Research and Opinion* 2008;**24**(11):3223-37.

Lazaro y de Mercado 2006 *{published data only}*

Carbonell-Estrany X, Lázaro y de Mercado P. Health economics and RSV. *Paediatric Respiratory Reviews* 2009;**10**(Suppl 1):12-3.

* Lazaro y de Mercado P, Figueras Aloy J, Domenech Martinez E, Echaniz Urcelay I, Closa Monasterolo R, Wood MA. The efficiency (cost-effectiveness) of palivizumab as prophylaxis against respiratory syncytial virus infection in premature infants with a gestational age of 32-35 weeks in Spain [La eficiencia (coste-efectividad) de palivizumab como profilaxis para la infección por virus respiratorio sincitial en prematuros de 32-35 semanas en España]. *Anales de Pediatria* 2006;**65**(4):316-24.

Lazaro y de Mercado 2007 *{published data only}*

Lazaro y de Mercado P, Figueras J, Domenech E, Closa R, Echaniz I, Wood MA, et al. Cost-effectiveness of palivizumab in preventing respiratory syncytial virus in premature infants and children with chronic lung disease in Spain [Coste-efectividad de palivizumab para prevenir el virus respiratorio sincitial en niños prematuros y niños con enfermedad pulmonar crónica en España]. *Pharmacoeconomics - Spanish Research Articles* 2007;**4**(2):57-68.

Lofland 2000 *{published data only}*

Lofland JH, Touch SM, O'Connor JP, Chatterton ML, Moxey ED, Paddock LE, et al. Palivizumab for respiratory syncytial virus prophylaxis in high-risk infants: a cost-effectiveness analysis. *Clinical Therapeutics* 2000;**22**(11):1357-69.

Mayen-Herrera 2011 *{published data only}*

Mayen-Herrera E, Buesch K, Cortina D. Economic evaluation of the use of palivizumab as prophylactic treatment for the reduction of complications associated with respiratory syncytial virus in pre-term patients. *Value in Health* 2011;**14**(7):A565-6.

Neovius 2011 *{published data only}*

Neovius K, Buesch K, Neovius M. Burden of respiratory syncytial virus (RSV) and potential impact of prophylaxis in infants in Sweden: a cost-effectiveness analysis. *Acta Paediatrica* 2010;**99**:96-7.

* Neovius K, Buesch K, Sandstrom K, Neovius M. Cost-effectiveness analysis of palivizumab as respiratory syncytial virus prophylaxis in preterm infants in Sweden. *Acta Paediatrica* 2011;**100**(10):1306-14. [DOI: 10.1111/j.1651-2227.2011.02309.x]

Nuijten 2007 *{published data only}*

Nuijten MJC, 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.

Nuijten 2009a *{published data only}*

Nuijten M, Lebmeier M, Wittenberg W. Cost effectiveness of palivizumab for RSV prevention in high-risk children in the Netherlands. *Journal of Medical Economics* 2009;**12**(4):291-300.

Nuijten 2009b *{published data only}*

Nuijten M, Lebmeier M, Wittenberg W. Cost effectiveness of palivizumab in children with congenital heart disease in Germany. *Journal of Medical Economics* 2009;**12**(4):301-8.

Nuijten 2010 *{published data only}*

Nuijten MJ, Wittenberg W. Cost effectiveness of palivizumab in Spain: an analysis using observational data. *European Journal of Health Economics* 2010;**11**:105-15.

Ravasio 2006 *{published data only}*

Ravasio R, Lucioni C, Chirico G. Cost-effectiveness analysis of palivizumab versus no prophylaxis in the prevention of respiratory syncytial virus infections among premature infants, with different gestational ages [Costo-efficacia di palivizumab versus non profilassi nella prevenzione delle infezioni da VRS nei bambini pretermine, a diversa età gestazionale]. *PharmacoEconomics - Italian Research Articles* 2006;**8**(2):105-17.

Raya Ortega 2006 *{published data only}*

Raya Ortega L, Marquez Calderon S, Navarro Caballero JA, Villegas Portero R. Cost-effectiveness of palivizumab in the prevention of hospital admissions for syncytial respiratory virus in pre-term babies born at 32 to 35 weeks. *Sevilla: Andalusian Agency for Health Technology Assessment (AETSA)* 2006;**Informe 14**:1-47.

Resch 2008 *{published data only}*

Resch B, Gusenleitner W, Nuijten MJC, Lebmeier M, Wittenberg W. Cost-effectiveness of palivizumab against respiratory syncytial viral infection in high-risk children in Austria. *Clinical Therapeutics* 2008;**30**(4):749-60.

Resch 2012 *{published data only}*

Resch B, Sommer C, Nuijten MJC, Seidinger S, Walter E, Schoellbauer V, et al. Cost-effectiveness of palivizumab for respiratory syncytial virus infection in high-risk children, based on long-term epidemiologic data from Austria. *Pediatric Infectious Disease Journal* 2012;**31**(1):e1-8.

Rietveld 2010 *{published data only}*

Rietveld E, Steyerberg EW, Polder JJ, Veeze HJ, Vergouwe Y, Huysman MWA, et al. Passive immunisation against respiratory syncytial virus: a cost-effectiveness analysis. *Archives of Disease in Childhood* 2010;**95**:493-8.

Roeckl-Wiedmann 2003 *{published data only}*

Roeckl-Wiedmann I, Liese JG, Grill E, Fischer B, Carr D, Belohradsky BH. Economic evaluation of possible prevention of

RSV-related hospitalisations in premature infants in Germany. *European Journal of Pediatrics* 2003;**162**:237-44.

Salinas-Escudero 2012 *{published data only}*

Salinas-Escudero G, Martinez-Valverde S, Reyes-Lopez A, Garduno-Espinosa J, Munoz-Hernandez O, Granados-Garcia V, et al. Cost-effectiveness analysis of the use of palivizumab in the prophylaxis of preterm patients in Mexico. *Salud Publica de Mexico* 2012;**54**(1):47-59.

Smart 2010 *{published data only}*

Smart KA, Paes BA, Lanctot KL. Changing costs and the impact on RSV prophylaxis. *Journal of Medical Economics* 2010;**13**(4):705-8.

Subramanian 1998 *{published data only}*

Subramanian SKN, Weisman LE, Rhodes T, Ariagno R, Sanchez PJ, Steichen J, et al. MEDI-493 Study Group. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. *Pediatric Infectious Disease Journal* 1998;**17**(2):110-5.

Tam 2009 *{published data only}*

Tam DY, Banerji A, Paes BA, Hui C, Tarride JE, Lanctot KL. The cost effectiveness of palivizumab in term Inuit infants in the Eastern Canadian Arctic. *Journal of Medical Economics* 2009;**12**(4):361-70.

Vogel 2002 *{published data only}*

Vogel AM, McKinlay MJ, Ashton T, Lennon DR, Harding JE, Pinnock R, et al. Cost-effectiveness of palivizumab in New Zealand. *Journal of Paediatrics and Child Health* 2002;**38**:352-7.

Wang 2011 *{published data only}*

Wang D, Bayliss S, Meads C. Palivizumab for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children: a systematic review and additional economic modelling of subgroup analyses. *Health Technology Assessment* 2011;**15**(5):1-124. [DOI: 10.3310/hta15050]

Weiner 2012 *{published data only}*

Weiner LB, Masaquel AS, Polak MJ, Mahadevia PJ. Cost-effectiveness analysis of palivizumab among pre-term infant populations covered by medicaid in the United States. *Journal of Medical Economics* 2012;**15**(5):997-1018.

Yount 2004 *{published data only}*

Yount LE, Mahle WT. Economic analysis of palivizumab in infants with congenital heart disease. *Pediatrics* 2004;**114**(6):1606-11.

References to studies excluded from this review

Banerji 2009 *{published data only}*

Banerji A, Lanctot KL, Paes BA, Masoud ST, Tam DY, Macdonald WA, et al. Comparison of the cost of hospitalization for respiratory syncytial virus disease versus palivizumab prophylaxis in Canadian Inuit infants. *Pediatric Infectious Disease Journal* 2009;**28**(8):702-6.

Buckley 2010 *{published data only}*

Buckley BC, Roylance D, Mitchell MP, Patel SM, Cannon HE, Dunn JD. Description of the outcomes of prior authorization of palivizumab for prevention of respiratory syncytial virus infection in a managed care organization. *Journal of Managed Care Pharmacy* 2010;**16**(1):15-22.

Chan 2003 *{published data only}*

Chan PWK, Abdel-Latif MEA. Cost of hospitalization for respiratory syncytial virus chest infection and implications for passive immunization strategies in a developing nation. *Acta Paediatrica* 2003;**92**(4):481-5.

Clark 2000 *{published data only}*

Clark SJ, Beresford MW, Subhedar NV, Shaw NJ. Respiratory syncytial virus infection in high risk infants and the potential impact of prophylaxis in a United Kingdom cohort. *Archives of Disease in Childhood* 2000;**83**(4):313-6.

Datar 2012 *{published data only}*

Datar M, Banahan BF. Palavizumab (Synagis) use and outcomes among medicaid beneficiaries. *Value in Health* 2012;**15**(4):A58-9.

Farina 2002 *{published data only}*

Farina D, Rodriguez SP, Bauer G, Novali L, Bouzas L, Gonzalez H, et al. Respiratory syncytial virus prophylaxis: cost-effective analysis in Argentina. *Pediatric Infectious Disease Journal* 2002;**21**(4):287-91.

Korbal 2003 *{published data only}*

Korbal P, Mikolajczak A, Szymanski W. Effectiveness of passive immunisation against respiratory syncytium virus in a group of premature infants with birth weight below 1000 grams [Ocena skutecznosci stosowania uodpornienia biernego przeciwko wirusom syncytium nablonka oddechowego (RSV) preparatem Synagis w grupie wczesniakow z masa urodzeniowa ciala ponizej 1000 gramow]. *Ginekologia Polska* 2003;**74**(10):1154-9.

Krilov 2010 *{published data only}*

Krilov LR, Palazzi DL, Fernandes AW, Klein RW, Mahadevia PJ. Prevalence of respiratory syncytial virus (RSV) risk factors and cost implications of immunoprophylaxis to infants 32 to 35 weeks gestation for health plans in the United States. *Value in Health* 2010;**13**(1):77-86.

Lapena Lopez 2003 *{published data only}*

Lapena Lopez de Armentia S, Robles Garcia MB, Martinez Badas JP, Castanon Fernandez L, Mallo Castano L, Herrero Mendoza B, et al. Potential impact and cost-efficacy of bronchiolitis prophylaxis with palivizumab in preterm infants with a gestational age of less than 33 weeks. *Anales de Pediatria* 2003;**59**(4):328-33.

Lee 2001 *{published data only}*

Lee SL, Etches P, Robinson JL. Net cost of palivizumab for respiratory syncytial virus prophylaxis during the 1998/99 season in northern Alberta. *Paediatrics and Child Health* 2001;**6**(8):525-32.

Marchetti 1999 *{published data only}*

Marchetti A, Lau H, Magar R, Wang L, Devercelli G. Impact of palivizumab on expected costs of respiratory syncytial virus infection in preterm infants: potential for savings. *Clinical Therapeutics* 1999;**21**(4):752-66.

Marques 2010 *{published data only}*

Marques T, Cardoso K. Palivizumab prophylaxis: comparative study between immunized and non immunized infants admitted with respiratory syncytial virus infection. *Early Human Development* 2010;**86**(Suppl):123-4.

Martinez 2002 *{published data only}*

Martinez JL. Palivizumab in preventing infection caused by respiratory syncitial virus (RSV) [Palivizumab en la prevención de infección por virus respiratorio sincicial]. *Revista Chilena de Pediatria* 2002;**73**(1):9-14.

McCormick 2002 *{published data only}*

McCormick J, Tubman R. Readmission with respiratory syncytial virus (RSV) infection among graduates from a neonatal intensive care unit. *Pediatric Pulmonology* 2002;**34**(4):262-6.

Meberg 2006 *{published data only}*

Meberg A, Bruu AL. Respiratory syncytial virus infections in congenital heart defects - hospitalisations and costs. *Acta Paediatrica* 2006;**95**(4):404-6.

Meissner 1999 *{published data only}*

Meissner HC, Groothuis JR, Rodriguez WJ, Welliver RC, Hogg G, Gray PH, et al. Safety and pharmacokinetics of an intramuscular monoclonal antibody (SB 209763) against respiratory syncytial virus (RSV) in infants and young children at risk for severe RSV disease. *Antimicrobial Agents and Chemotherapy* 1999;**43**(5):1183-8.

Numa 2000 *{published data only}*

Numa A. Outcome of respiratory syncytial virus infection and a cost-benefit analysis of prophylaxis. *Journal of Paediatrics and Child Health* 2000;**36**:422-7.

Parmigiani 2001 *{published data only}*

Parmigiani S, Ubaldi A, Capuano C, Magini GM, Bianchi ME. Palivizumab in infants with gestational age ≤ 28 weeks and bronchopulmonary dysplasia. *Acta Bio-Medica de l Ateneo Parmense* 2001;**72**(5-6):109-13.

Rackham 2005 *{published data only}*

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. *Cardiology in the Young* 2005;**15**(3):251-5.

Reeve 2006 *{published data only}*

Reeve CA, Whitehall JS, Buetnner PG, Norton R, Reeve DM, Francis F. Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab. *Journal of Paediatrics and Child Health* 2006;**42**(5):253-8.

Rodriguez 2008 *{published data only}*

Rodriguez SP, Farina D, Bauer G. Respiratory syncytial virus prophylaxis in a high-risk population in Argentina: a cost-effectiveness analysis. *Pediatric Infectious Disease Journal* 2008;**27**(7):660-1.

Shireman 2002 *{published data only}*

Shireman TI, Braman KS. Impact and cost-effectiveness of respiratory syncytial virus prophylaxis for Kansas medicaid's high-risk children. *Archives of Pediatrics and Adolescent Medicine* 2002;**156**(12):1251-5.

Stevens 2000 *{published data only}*

Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. *Archives of Pediatrics and Adolescent Medicine* 2000;**154**(1):55-61.

Strutton 2003 *{published data only}*

Strutton DR, Stang PE. Prophylaxis against respiratory syncytial virus (RSV), varicella, and pneumococcal infections: economic-based decision-making. *Journal of Pediatrics* 2003;**143**(Suppl 5):157-62.

Takeuchi 2002 *{published data only}*

Takeuchi Y, Cho H, Yamashita Y, Mishiku Y, Nakao A, Aso T, et al. Safety and pharmacokinetics of palivizumab, administered in infants with a history of prematurity or chronic lung disease. *Japanese Journal of Chemotherapy* 2002;**50**(4):215-22.

Vann 2007 *{published data only}*

Vann JJ, Feaganes J, Wegner S. Reliability of medicaid claims versus medical record data: in a cost analysis of palivizumab. *Pharmacoeconomics* 2007;**25**(9):793-800.

Wang 2008 *{published data only}*

Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation. *Clinical Governance: an International Journal* 2009;**14**(2):156-8.

* Wang D, Cummins C, Bayliss S, Sandercock J, Burls A. Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation. *Health Technology Assessment* 2008;**12**(36):1-86.

Wegner 2004 *{published data only}*

Wegner S, Vann JJ, Liu G, Byrns P, Cypra C, Campbell W, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid program. *Pediatrics* 2004;**114**(6):1612-9.

Wendel 2010 *{published data only}*

Wendel B, Jorden J. Financial impact of a clinically based palivizumab prior authorization program in a medicaid population. *Journal of the American Pharmacists Association* 2010;**50**(2):231.

References to studies awaiting assessment

NCT00233064 *{published data only}*

NCT00233064. A Phase IV, Randomized, Double-Blind Study to Assess the Immune Reactivity of the Liquid and Lyophilized Formulations of Palivizumab (MEDI-493, Synagis) in Children at High Risk for the Development of Serious RSV Disease. http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00233064 (accessed 27 July 2012).

NCT00240929 *{published data only}*

NCT00240929. A Phase II Randomized, Double-Blind, Two-Period Cross-Over Study to Evaluate the Pharmacokinetics, Safety and Tolerability of a Liquid Formulation of Palizvizumab (MEDI-493, Synagis), A Humanized Respiratory Syncytial Virus Monoclonal Antibody, in Children With a History of Prematurity. http://apps.who.int/trialsearch/Trial.aspx?TrialID=NCT00240929 (accessed 27 July 2012).

NTR1023 *{published data only}*

NTR1023. Effect of palivizumab on respiratory syncytial virus-associated burden of disease: a randomized controlled trial. http://apps.who.int/trialsearch/Trial.aspx?TrialID=NTR1023 (accessed 27 July 2012).

Additional references

AAP 2009

American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. Policy statement-modified recommendations for use of palivizumab for prevention of respiratory syncytial virus infections. *Pediatrics* 2009;**124**(6):1694-701.

Arms 2008

Arms JL, Ortega H, Reid S. Chronological and clinical characteristics of apnea associated with respiratory syncytial virus infection: a retrospective case series. *Clinical Pediatrics* 2008;**47**(9):953-8.

Atkins 2004

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. *BMJ* 2004;**328**(7454):1490.

CDC 2011

Centers for Disease Control and Prevention. Respiratory syncytial virus: United States, July 2007-June 2011. *Morbidity and Mortality Weekly Report* 2011;**60**(35):1203-6. [PUBMED: 21900874]

Domachowske 1999

Domachowske JB, Rosenberg HF. Respiratory syncytial virus infection: immune response, immunopathogenesis, and treatment. *Clinical Microbiology Reviews* 1999;**12**(2):298-309. [PUBMED: 0194461]

Drummond 1996

Drummond MF, Jefferson TO, The BMJ Economic Evaluation Working Party. Guidelines for authors and peer reviewers of economic submissions to the BMJ. *BMJ* 1996;**313**(7052):275-83.

FDA 2009

United States Food, Drug Administration. Safety Alerts for Human Medical Products > Synagis (palivizumab). http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm155089.htm 2009 (accessed 5 February 2013).

FDA 2010

United States Food, Drug Administration. Background Package for BLA 125283 motavizumab. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AntiviralDrugsAdvisoryCommittee/UCM213825.pdf 2010 (accessed 5 February 2013).

Fleming 2005

Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. *Journal of Epidemiology and Community Health* 2005;**59**(7):586-90.

Glanville 2009

Glanville J, Kaunelis D, Mensinkai S. How well do search filters perform in identifying economic evaluations in MEDLINE and EMBASE. *International Journal of Technology Assessment in Health Care* 2009;**25**(4):522-9.

Golder 2006

Golder S, McIntosh H, Duffy S, Glanville J, Centre for Reviews and Dissemination and UK Cochrane Centre Search Filters Design Group. Developing efficient search strategies to identify reports of adverse effects in MEDLINE and EMBASE. *Health Information and Libraries Journal* 2006;**23**(1):3-12.

GRADEpro 2008 [Computer program]

Brozek J, Oxman A, Schünemann H. GRADEpro. Version 3.2 for Windows. -, 2008.

Hall 1979

Hall CB, Hall WJ, Speers DM. Clinical and physiological manifestations of bronchiolitis and pneumonia. Outcome of respiratory syncytial virus. *American Journal of Diseases of Children* 1979;**133**(8):798-802.

Hall 2009a

Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. *New England Journal of Medicine* 2009;**360**(6):588-98.

Hall 2009b

Hall CB, Walsh EE. Respiratory syncytial virus. In: Feigin RD, et al. editor(s). Feigin and Cherry's Textbook of Pediatric Infectious Diseases. 6th Edition. Vol. **2**, Philadelphia: Saunders Elsevier, 2009:2462-87.

Hall 2010

Hall CB. Respiratory syncytial virus. In: Mendell GL, Bennett JE, Dolin R editor(s). Mendell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 7th Edition. Vol. **2**, Philadelphia: Churchill Livingstone Elsevier, 2010:2207-21.

Higgins 2003

Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistence in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011a

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Chichester, UK: Wiley-Blackwell, 2011.

Higgins 2011b

Higgins JPT, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Chichester, UK: Wiley-Blackwell, 2011.

Jacobson 2001

Jacobson PD, Kanna ML. Cost-effectiveness analysis in the courts: recent trends and future prospects. *Journal of Health Politics, Policy and Law* 2001;**26**(2):291-326.

Johnson 1997

Johnson S, Oliver C, Prince GA, Hemming VG, Pfarr DS, Wang SC. Development of a humanized monoclonal antibody (MEDI-493) with potent in vitro and in vivo activity against respiratory syncytial virus. *Journal of Infectious Diseases* 1997;**176**(5):1215–24.

Lefebvre 2011

Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JPT, Green S editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. Available from www.cochrane-handbook.org. Chichester, UK: Wiley-Blackwell, 2011.

Mullins 2003

Mullins JA, Lamonte AC, Bresee JS, Anderson LJ. Substantial variability in community RSV season timing. *Pediatric Infectious Disease Journal* 2003;**22**(10):857-62.

Nair 2010

Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. *Lancet* 2010;**375**(9725):1545-55.

Purcell 2004

Purcell K, Fergie J. Driscoll Children's Hospital respiratory syncytial virus database: risk factors, treatment and hospital course in 3308 infants and young children, 1991 to 2002. *Pediatric Infectious Disease Journal* 2004;**23**(5):418-23.

Ralstone 2009

Ralston S, Hill V. Incidence of apnea in infants hospitalized with respiratory syncytial virus bronchiolitis: a systematic review. *Journal of Pediatrics* 2009;**155**(5):728-33.

Red Book 2012

American Academy of Pediatrics. Respiratory syncytial virus. In: Pickering LK editor(s). Red Book: 2012 Report of the Committee on Infectious Diseases. 29th Edition. Elk Grove Village: Churchill Livingstone, 2012:609-18.

RevMan 2012 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Robinson 2012

Robinson KA, Odelola OA, Saldanha IJ, Mckoy NA. Palivizumab for prophylaxis against respiratory syncytial virus infection in children with cystic fibrosis. *Cochrane Database of Systematic Reviews* 2012, Issue 2. [DOI: 10.1002/14651858.CD007743.pub3]

Shay 2001

Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979-1997. *Journal of Infectious Diseases* 2001;**183**(1):16-22.

Simoes 2003

Simoes EA, Carbonell-Estrany X. Impact of severe disease caused by respiratory syncytial virus in children living in developed countries. *Pediatric Infectious Disease Journal* 2003;**22**(Suppl 2):13-8.

Thompson 2003

Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003;**289**(2):179–86.

References to other published versions of this review

Lozano 2007

Lozano JM, Escovar C, Vásquez V. Monoclonal antibodies for preventing respiratory syncytial virus infection. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD006602.pub2]

Wang 1999

Wang EEL, Tang NK. Immunoglobulin for preventing respiratory syncytial virus infection. *Cochrane Database of Systematic Reviews* 1999, Issue 3. [DOI: 10.1002/14651858.CD001725.pub2]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abarca 2009

Methods	Study design: 2-year study, using different methodologies. The first year of this study was a phase I/II, multicentre, open-label, dose-escalation study. The second year (consecutive RSV season) was a randomized (1:1), double-blind study Dates of study: late winter 2004 in the United States (year 1) and May to June 2005 (year 2). Dates for recruitment during year one in the Southern Hemisphere are not given Locations: year 1 - USA (9 sites), Chile (4 sites) and Brazil (3 sites). Year 2 - 6 sites in South America (4 in Chile and 2 in Brazil)
Participants	Season 1: 217 children with: 1) a gestational age between 32 and 35 weeks and were ≤ 6 months of chronological age; or 2) were ≤ 24 months of age and had CLD of prematurity requiring treatment with stable or decreasing doses of diuretics, steroids, or bronchodilators within the previous 6 months Children were excluded if they had any of the following: hospitalization at the time of entry (unless discharge was expected within 3 days of study entry); birth hospitalization of > 6 weeks' duration (for children without CLD) or birth hospitalization > 12 weeks' duration (for children with CLD); chronic oxygen therapy or mechanical ventilation at the time of study entry (including continuous positive airway pressure); congenital heart disease; evidence of infection with hepatitis A, B or C virus; known renal impairment; hepatic dysfunction; chronic seizure disorder; immunodeficiency or human immunodeficiency virus infection or mother with known infection; laboratory findings in blood obtained within 7 days before study entry for blood urea nitrogen or creatinine > 1.5 times the upper limit of normal for age; aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 1.5 times the upper limit of normal for age; haemoglobin < 9.5 G/dL, white blood cell count < 4000 cells/mm^3, or platelet count < 120,000 cells/mm^3; acute illness or progressive clinical disorder; active infection, including acute RSV infection; previous reaction to immunoglobulin intravenous (IVIG), blood products, or other foreign proteins; treatment with palivizumab; current or previous (within 120 days) treatment with immunoglobulin products (e.g. RSV-IVIG) or any investigational agents; current participation in any investigational study; or previous participation in any investigational study using RSV vaccines or monoclonal antibodies Season 2: 136 children (66 in motavizumab group and 70 in palivizumab group) who received ≥ 3 doses of motavizumab (3 or 15 mg/kg) in the previous RSV season and were ≤ 24 months of age at enrolment
Interventions	During season 1, children received between 2 and 5 doses of motavizumab (3 or 15 mg/kg) at 30-day intervals, depending on when during the RSV season a child was enrolled During season 2, children were randomized to receive intramuscular injections of motavizumab (15 mg/kg) or palivizumab (15 mg/kg) every 30 days for a total of 4 to 5 doses
Outcomes	Primary outcomes: adverse events and serious adverse events (assessed for severity and potential relationship to study drug) Children were followed for AEs and SAEs from the first study injection through 30 days after the final dose
Notes	The data extracted for our analysis includes only data from the second year, when the study was randomized and double-blind

Abarca 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Study has 2 phases: first phase was open-label, with motavizumab and no comparison group. In the second consecutive RSV season children were randomly assigned 1:1 to receive motavizumab or palivizumab. The randomization schedule was stratified by site with a block size of 4 (p. 268)
Allocation concealment (selection bias)	Unclear risk	During the second RSV season, treatment assignments were double-blind. Only the independent monitor and the study pharmacist had access to information that identified a patient's treatment allocation. Method of allocation concealment remains unclear (p. 268)
Incomplete outcome data (attrition bias) All outcomes	High risk	In season 1, 217 children were enrolled. Of these 217, 136 children participated in the next season. Of the 136 children, 131 (96.3%) completed the second season of the study. Reasons for attrition are given within season 2, though for attrition between season 1 and season 2 are not. Despite only 131/136 participants completing the study, data on all 136 participants are reported in Table 2
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods are also reported in the results section. Adverse events were described on an as-reported basis, with clear criteria for defining adverse events, severe adverse events, etc.
Other bias	Unclear risk	This study was sponsored by MedImmune. One of MedImmune employees assisted with data analysis and several study authors received research grants or were employees/consultants of MedImmune (p. 267, 272)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Treatment assignments were double-blind. Does not state how the treatments were delivered. Only the independent monitor and the study pharmacist had access to information that identified a patient's treatment allocation (p. 268)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This is an adverse events study, where the first phase was open-label. Details of monitoring regime are reported for season 1 and season 2, though it is unclear whether assessors had knowledge of which intervention participants received

Bentley 2011

Methods	Cost-utility analysis, payer's perspective, decision analytic model, lifetime follow-up, GBP, UK
Participants	Infants with CLD, and preterm infants born at less than 29, 29 to 32, and 33 to 35 weeks gestational age
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: QALYs, mortality benefits included, risk of sequelae included Summary measures: incremental cost per QALY
Notes	This is an abstract of a presentation at a conference. Authors IF, KG and KB are employed at Abbott. This study suggests that the use of palivizumab is cost-effective in the UK

Risk of bias

Bentley 2011 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Carbonell-Estrany 2010

Methods	Study design: randomized (1:1), double-blind, palivizumab-controlled, phase III, non-inferiority trial Dates of study: November 2004 and May 2006 during 2 RSV seasons in the northern hemisphere and 1 season in the southern hemisphere Locations: 347 sites in 24 countries
Participants	6635 preterm children (3329 to motavizumab group and 3306 to palivizumab group) with a gestational age ≤ 35 weeks who were either: 1) ≤ 24 months of age with chronic lung disease (CLD) that required medical management within 6 months before randomization, or 2) ≤ 6 months of age at enrolment Exclusion criteria were: hospitalization at randomization (unless discharge was anticipated within 10 days); mechanical ventilation or other mechanical support; life expectancy < 6 months; active RSV infection; known renal, hepatic, chronic seizure, unstable neurologic or haemodynamically significant congenital heart disorders; immunodeficiency; use of palivizumab or RSV intravenous immunoglobulin < 3 months before randomization or anticipated use during the study; receipt of RSV vaccine; and participation in any other investigational study
Interventions	Children received motavizumab (15 mg/kg) or palivizumab (15 mg/kg) applied as intramuscular injections at 30-day intervals for the total of 5 doses
Outcomes	Primary outcomes: hospitalization or death due to RSV Primary efficacy outcome was met when a child had a positive RSV test and was hospitalised for respiratory symptoms or had a new onset of RSV-positive lower respiratory illness with worsening respiratory status while already in the hospital or when a death caused by RSV occurred

Carbonell-Estrany 2010 *(Continued)*

	Secondary outcomes: all-cause and RSV-specific outpatient medically attended lower respiratory tract infection (MALRI), frequency and incidence of medically attended otitis media (OM), frequency of prescribed antibiotics for LRI and OM, adverse events and serious adverse events (graded for severity and causality), development of anti motavizumab antibodies, motavizumab serum concentrations Children were involved during only 1 season and were followed up for 150 days after randomization
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were randomly assigned 1:1 by using an interactive voice-response system to receive motavizumab or palivizumab. Randomisation was stratified by site and diagnosis of protocol-defined CLD (p. e36)
Allocation concealment (selection bias)	Low risk	All personnel at all sites were blind to study treatment. Motavizumab and palivizumab were provided in identical vials in coded kits (p. e36)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates in both groups were same (1.8%) and reasons for attrition were provided. The ITT population included all randomly assigned patients. The safety population included all patients who received any study medication and had any safety follow-up (p. e37)
Selective reporting (reporting bias)	High risk	6635 participants from 347 sites in 24 countries. RSV-specific outpatient MALRI was assessed only in children from 133 sites (p. e38). This likely represents the sample size calculation on page e37, though it is unclear how these sites were selected, possibly introducing bias toward sites with better outcomes data. Standard deviations for continuous data (days) are not reported (p. e46)
Other bias	High risk	This study was sponsored by MedImmune. All authors were compensated by or employees of MedImmune (p. e35). Differences in laboratory methods used to test for the presence of RSV in this study were cited by the FDA as a significant methodological concern which may have favoured motavizumab over palivizumab in this study. This was cited as one of the reasons for rejecting the licensing approval for motavizumab
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Injections were provided in identical vials in coded kits. All personnel at all sites were blind to study treatment (p. e36)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All personnel at all sites were blind to study treatment (p. e36)

Chirico 2009

Methods	Cost-utility and cost-effectiveness analysis, payer's perspective, decision analytic model, lifetime follow-up, 3% discount rate, 2007 EUR, Italy
Participants	Preterm infants of different gestational ages (GA) (less than 33 weeks, and 33 to 35 weeks), with or without bronchopulmonary dysplasia (BPD)

Chirico 2009 *(Continued)*

Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization due to RSV infection (ordinary ward or ICU), mortality benefits included, risk of recurrent wheezing included, LYGs and QALYs Summary measures: incremental cost per QALY, incremental cost per LYG
Notes	Author U.S. is employed at Abbott. This paper was supported by a non-binding contribution provided by Abbott. This study suggests that palivizumab prophylaxis is cost-effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Chiroli 2005

Methods	Cost-effectiveness analysis, payer's perspective, decision analytic model, 1-year follow-up, no discounting, 2004 EUR, Italy
Participants	Children with haemodynamically significant congenital heart disease (CHD)
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization due to RSV infection, ICU stay, mortality benefits included, risk of sequelae not included, LYGs Summary measures: incremental cost per LYG
Notes	Author SC is employed at Abbott. This study supports the cost-effectiveness of palivizumab prophylaxis

Risk of bias

Chiroli 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

ElHassan 2006

Methods	Cost-utility analysis, societal perspective, decision analytic model, 8 years follow-up, 3% discount rate, 2002 USD, USA
Participants	Preterm infants without chronic lung disease (CLD) born at 26 to 32 weeks' gestation
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization due to RSV infection, mortality benefits not included, risk of asthma included Summary measures: incremental cost per QALY
Notes	No conflict of interest declared. This study supports implementing more restrictive guidelines for palivizumab prophylaxis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

ElHassan 2006 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Embleton 2007

Methods	Cost-effectiveness analysis, societal perspective, 1-year follow-up, no discounting, 2005 GBP, UK
Participants	Preterm infants with less than 32 weeks gestational age without BPD, or preterm infants with BPD
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization, mortality benefits not included, risk of wheezing or asthma not included Summary measures: incremental cost per hospitalization averted
Notes	Not funded by the industry. This study does not support the cost-effectiveness of palivizumab prophylaxis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Embleton 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Feltes 2003

Methods	Study design: randomized (1:1), double-blind, placebo-controlled, multicentre trial Dates of study: 4 consecutive RSV seasons from 1998 through 2002 Locations: 76 – USA (47 sites), Canada (6 sites), Sweden (3 sites), Germany (4 sites), Poland (6 sites), France (4 sites) and UK (6 sites)
Participants	1287 children (639 to palivizumab group and 648 to placebo group) with congenital heart disease (CHD) who: 1) were ≤ 24 months old at the time of random assignment; 2) had documented haemodynamically significant CHD determined by the investigator; and 3) had unoperated or partially corrected CHD Children were not eligible if they had unstable cardiac or respiratory status, including cardiac defects so severe that survival was not expected or for which cardiac transplantation was planned or anticipated; were hospitalised, unless discharge was anticipated within 21 days; anticipated cardiac surgery within 2 weeks of random assignment; required mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, or other mechanical respiratory or cardiac support; had associated noncardiac anomalies or end-organ dysfunction resulting in anticipated survival of < 6 months or unstable abnormalities of end-organ function Additional exclusion criteria were known HIV infection; acute RSV or other acute infection or illness; previous receipt of palivizumab or other monoclonal antibody; receipt of investigational agents within the previous 3 months (other than investigational agents commonly used during cardiac surgery or the immediate postoperative period, i.e. nitric oxide); current participation in other investigational protocols of drugs or biological agents; or receipt of intravenous immune globulin (IVIG), including RSV-IVIG, within 3 months before random assignment or anticipated use of IVIG, RSV-IVIG, or open-label palivizumab during the study period. Children with uncomplicated small atrial or ventricular septal defects or patent ductus arteriosus were excluded Children with the following anatomic diagnoses were included in the cyanotic stratum: pulmonary atresia with ventricular septal defect, pulmonary atresia with intact septum, tetralogy of Fallot, single ventricle including hypoplastic left or right heart, tricuspid atresia, double-outlet right ventricle with transposed great arteries, Ebstein anomaly, or D-transposition of the great arteries with/without ventricular septal defect, with/without pulmonary stenosis. The remaining children were stratified to the "other" (acyanotic) stratum
Interventions	Children received palivizumab (15 mg/kg) or an equal volume of placebo by intramuscular injection every 30 days for a total of 5 doses
Outcomes	Primary outcome: incidence of RSV hospitalization, including primary RSV hospitalisations and nosocomial RSV hospitalisations A primary RSV hospitalization was defined as a hospitalization for an acute cardiorespiratory illness in which the RSV antigen test was positive within 48 hours before or after admission. Deaths occurring outside the hospital that could be demonstrated to be associated with RSV were also considered as primary RSV hospitalization end points. A nosocomial RSV hospitalization was one in which hospitalised patients had an objective measure of worsening cardiorespiratory status reported as a serious adverse event and the RSV antigen test was positive

Feltes 2003 *(Continued)*

	Secondary outcomes: total RSV hospital days, RSV hospital days with increased supplemental oxygen, incidence and total days of RSV-associated intensive care, incidence and total days of RSV-associated mechanical ventilation, serum palivizumab concentration, the palivizumab through concentrations before second and fifth doses, adverse events and serious adverse events (assessed for severity and potential relation to study drug) Children participated during only 1 season and were followed for 150 days after random assignment (30 days after the last scheduled study injection)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random assignment was based on a computer-generated sequence, and was stratified by site to reduce the effect of practice discrepancies and anatomic cardiac lesion. Randomisation was performed centrally with the use of an interactive voice response system (p. 533)
Allocation concealment (selection bias)	Low risk	Children were randomly assigned 1:1 to receive palivizumab or an equal volume of identically appearing placebo. Palivizumab and placebo were supplied in coded vials and dispensed in a syringe that did not identify the contents. Randomisation was performed centrally using an interactive voice response system (p. 533)
Incomplete outcome data (attrition bias) All outcomes	Low risk	95.6% of participants in the palivizumab group and 95.5% in the placebo group completed the study, and 93% of participants in the palivizumab group and 91.8% in the placebo group received all 5 injections. All randomly assigned patients were included in the safety and efficacy analyses, and patients who received at least 1 dose of study drug were included in the analyses of serum palivizumab concentrations (p. 534)
Selective reporting (reporting bias)	High risk	All primary and secondary outcomes and safety/adverse events data were included in report of results. Adverse events were categorised, and graded by a blinded investigator for potential relation to study drug (p. 534). Standard deviations for continuous data (days) are not reported (p. 536)
Other bias	Unclear risk	This study was supported by MedImmune, several MedImmune employees contributed to this study (p. 532, 538)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Palivizumab and placebo were identically appearing, supplied in coded vials and dispensed in a syringe that did not identify the contents (p. 533)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	This was a double-blind study with good randomization protocols. Adverse events were categorised, and graded by a blinded investigator for potential relation to study drug (p. 534)

Feltes 2011

Methods	Study design: randomized (1:1), multinational, double-blind, palivizumab-controlled, phase II trial Dates of study: 2 RSV seasons (2005 to 2006, and 2007 to 2008)

Feltes 2011 *(Continued)*

	Locations: 34 sites in season 1 (North America, 51; European Union, 56; and rest of the world, 27) and 100 sites in season 2 (North America, 37; European Union, 48; and rest of the world, 15)
Participants	1236 children (624 to motavizumab group and 612 to palivizumab group) aged ≤ 24 months who had: 1) Documented haemodynamically significant CHD defined as uncorrected or palliated cyanotic CHD or acyanotic CHD associated with documented pulmonary hypertension (systolic pulmonary arterial pressure ≥ 40 mm Hg) and/or a requirement for daily medication to manage congestive heart failure Patients not eligible for enrolment included those with unstable cardiac or respiratory status, including severe cardiac defects with unanticipated survival or with anticipated cardiac transplantation; hospitalization, unless discharge was anticipated within 21 days; cardiac surgery anticipated within 2 weeks of randomization; any requirement for mechanical ventilation, extracorporeal membrane oxygenation, continuous positive airway pressure, or other mechanical respiratory or cardiac support; any associated noncardiac anomalies or end organ dysfunction resulting in anticipated survival of < 6 months or unstable abnormalities of end organ function; acute respiratory illness, or other acute infection or illness (patients with respiratory symptoms were tested for RSV before randomization and were excluded if they were positive); chronic seizure or neurologic disorder; immunodeficiency; mother with human immunodeficiency virus (HIV) infection (unless the child was negative for HIV infection); known allergy to any immunoglobulin products; receipt of any polyclonal antibody or palivizumab within 3 months before randomization; use of any investigational agents other than those commonly used during cardiac surgery or the immediate postoperative period; or current participation in any other investigational protocols Children with cyanotic CHD included those with the most commonly encountered cyanotic cardiac lesions. Children who did not have one of the designated diagnoses to be included in the cyanotic stratum were classified as 'other' anticipating that this group would largely comprise children with acyanotic CHD lesions
Interventions	Children received motavizumab (15 mg/kg) or palivizumab (15 mg/kg) applied as intramuscular injections at 30-day intervals for a total of 5 doses
Outcomes	Primary outcomes: adverse events and serious adverse events (assessed for severity and relationship to study drug) Secondary outcomes: incidence of RSV hospitalization, RSV outpatient medically attended lower respiratory tract infection (for patients in season 2 only) RSV hospitalization was defined as hospitalization for cardiac/respiratory symptoms accompanied by a positive RSV test or a new onset of RSV-positive lower respiratory illness with worsening respiratory status while already in the hospital or death caused by RSV. RSV outpatient MALRI was an outpatient medically attended event diagnosed as a lower respiratory illness accompanied by a positive RSV test. Each patient participated during a single RSV season and was followed for 150 days after random assignment (30 days after the last dose of study drug)
Notes	Inclusion and exclusion criteria for patients in this study are consistent with criteria in Feltes 2003

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomly assigned 1:1 using an interactive voice-response system. Randomisation was stratified by site and the presence or absence of cyanotic CHD (p. 187)
Allocation concealment (selection bias)	Low risk	Motavizumab and palivizumab were provided in identical vials in coded kits. Randomisation was performed centrally. All study personnel were blinded to treatment assignments (p. 187)
Incomplete outcome data (attrition bias)	Low risk	Comparable attrition rates in both groups. Reasons for attrition given in supplemental material. The ITT population included all randomized patients. The

Feltes 2011 *(Continued)*

All outcomes		safety population included all patients who received any study medication and had any safety follow-up (p. 187)
Selective reporting (reporting bias)	High risk	Adverse events were determined on an as-encountered basis, and assessed for severity and relationship to study drug by the blinded site investigators (p. 187). Secondary outcomes reported in the methods are also reported in the results section. RSV outpatient MALRIs were assessed for patients in season 2 only, with no explanations provided, and without reporting the total number of randomized patients in the subset
Other bias	Unclear risk	This study was sponsored by MedImmune (p. 186). MedImmune was involved in study design; collection, analysis and interpretation of data; and writing of the manuscript. Several authors are employees/consultants/speakers of MedImmune
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Motavizumab and palivizumab were delivered in identical vials in coded kits. All study personnel were blinded to treatment assignments (p. 187)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Study was not powered as a stand-alone efficacy study, though it reports efficacy data (p. 189). The authors note that despite this, their results were consistent with previous studies, thus the actual impact of the study being underpowered may be minimal

Fernandez 2010

Methods	Study design: phase II, randomized (1:1:1), double-blind, cross-over study Dates of study: 1 RSV season (April 2006 through February 2007) Locations: 18 – Chile (7 sites), New Zealand (5 sites) and Australia (6 sites)
Participants	260 children (83 to M/P treatment group, 84 to P/M treatment group, and 93 to motavizumab only group) born preterm who: 1) had gestational age ≤ 35 weeks *and* the chronological age was ≤ 6 months at the time of entry into the study; or 2) if they were ≤ 24 months of age at the time of entry into the study and had a diagnosis of CLD of prematurity requiring medical management within 6 months before randomization Eligible children had to be in good health at the time of study entry. They could not be hospitalised (unless discharge was expected within 10 days); be receiving chronic oxygen therapy or any ventilatory support; have significant congenital heart disease; have evidence of infection with hepatitis A, B, or C virus or HIV; have any acute illness, including acute RSV infection; known renal impairment, hepatic dysfunction, chronic seizure disorder or immunodeficiency; have suspected serious allergic or immune-mediated events in association with prior receipt of immunoglobulins, blood products or other foreign proteins; have received within the past 120 days or currently be receiving immunoglobulin products, palivizumab or any investigational agent
Interventions	Children received motavizumab (15 mg/kg) or palivizumab (15 mg/kg) applied as intramuscular injections at 30-day intervals for a total of 5 doses in the following way: 1) 2 doses of motavizumab followed by 3 doses of palivizumab – M/P treatment group 2) 2 doses of palivizumab followed by 3 doses of motavizumab – P/M treatment group 3) 5 doses of motavizumab only – control

Fernandez 2010 *(Continued)*

Outcomes	Primary outcomes: adverse events, serious adverse events and laboratory evaluations AEs were assessed for severity, relationship to study treatment, and whether the event met criteria as an SAE Secondary outcomes: anti drug antibodies and serum trough concentrations of motavizumab and palivizumab Children were monitored for AEs and SAEs from the time of randomization through study day 150 (30 days after the final planned dose)
Notes	This is a cross-over study whereby participants received either motavizumab/palivizumab, palivizumab/motavizumab or motavizumab only, with cross-over occurring after dose 2, out of a total of 5 doses. The data extracted for our analysis include only data after the first 2 doses, before the cross-over occurred

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Children were randomly assigned 1:1:1 (stratified by site) using an automated randomization system (p. 2)
Allocation concealment (selection bias)	Unclear risk	This was a randomized, double-blind study (p. 2). Method of allocation concealment remains unclear; no information is provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	94.6% of subjects received all 5 doses of study drug and 92.7% subjects completed the study. Reasons for attrition are given (p. 5). The safety population included all randomized subjects who received study drug and had any safety follow-up (p. 4)
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods are also reported in the results section. Adverse events were determined on an as-encountered basis and assessed by the investigator for severity, relationship to study drug and whether it met criteria as an SAE (p. 3)
Other bias	Unclear risk	This study was sponsored by MedImmune (p. 12). All authors received research grants/funding or were employees of MedImmune. MedImmune was involved in study design, and analysis and interpretation of data
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Details on blinding of participants and personnel are not available
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Details on blinding of participants and personnel are not available

Garcia-Altes 2010

Methods	Cost-effectiveness analysis, payer's perspective, decision analytic model, 1-year and an alternative lifetime follow-up, 3% discount rate, 2008 EUR, Spain
Participants	Preterm children less than 2 years old with and without chronic lung disease, children less than 2 years old with chronic lung disease and children less than 5 years old with congenital heart disease

Garcia-Altes 2010 *(Continued)*

Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate, mortality benefits included, risk of sequelae not included, ICU stay Summary measures: incremental cost per hospitalization averted, incremental cost per LYG
Notes	Not funded by the industry. Administration of palivizumab is not cost-effective in these populations, neither for hospitalisations averted nor for LYGs. Paper is written in Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Hampp 2011

Methods	Cost-effectiveness analysis, payer's perspective, decision analytic model, no discounting, 2010 USD, Florida, USA
Participants	Children up to 2 years of age with: CLD only, CHD only, CLD and prematurity (≤ 32 weeks gestation), CHD and prematurity, CHD and CLD, any of these indications, none of these indications and premature infants up to 6 months of age
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: incidence rate of hospitalization due to RSV infection, absolute risk reduction, mortality benefits not included, risk of wheezing or asthma not included Summary measures: incremental cost per RSV hospitalization avoided

Hampp 2011 *(Continued)*

Notes	No conflict if interest reported. This study suggests that recommendations for the use of palivizumab should be reconsidered, because the cost of prophylaxis far exceeded the economic benefit of prevented hospitalisations in any risk group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Harris 2011

Methods	Cost-effectiveness analysis, societal perspective, decision analytic model, no discounting, 2007 CAD, Canada
Participants	Children less than 2 years old with haemodynamically significant CHD, born at 36 weeks gestation
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: risk of admission to hospital, days in hospital, mortality benefits included, risk of sequelae not included Summary measures: incremental cost to prevent one day of hospitalization
Notes	Author DGH received an honorarium of less than CAD 1000 from Abbott Laboratories. This study suggests that palivizumab is not cost-effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Harris 2011 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Hascoet 2008

Methods	Cost-effectiveness analysis, societal and payer's perspective, decision analytic model, lifetime follow-up, 3% discount rate, 2006 EUR, France
Participants	Preterm infants born at 32 weeks of gestational age or less, with BPD or CHD
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: mortality benefits included, risk of sequelae included, hospitalization due to RSV infection Summary measures: incremental cost per LYG, cost per hospitalization averted
Notes	Author HB is employed at Abbott. This study suggests that palivizumab prophylaxis is cost-effective. Paper is written in French

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Hascoet 2008 *(Continued)*

Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

IMpact-RSV 1998

Methods	Study design: multicentre, randomized, double-blind, placebo-controlled, phase III trial Dates of study: 1996 to 1997 RSV season Locations: 139 - USA (119 sites), UK (11 sites) and Canada (9 sites)
Participants	1502 children (1002 in palivizumab group and 500 in placebo group) who were either: 1) 35 weeks gestation or less and 6 months of age or younger; or 2) 24 months old or younger and had a clinical diagnosis of BPD requiring ongoing medical treatment (i.e. supplemental oxygen, steroids, bronchodilators or diuretics within the past 6 months) Children were excluded if they had any of the following: hospitalization at the time of entry that was anticipated to last more than 30 days; mechanical ventilation at the time of entry; life expectancy less than 6 months; active or recent RSV infection; known hepatic or renal dysfunction, seizure disorder, immunodeficiency, allergy to IgG products; receipt of RSV immune globulin within the past 3 months; or previous receipt of palivizumab, other monoclonal antibodies, RSV vaccines or other investigational agents. Children with congenital heart disease were excluded, except for those with a patent ductus arteriosus or a septal defect that was uncomplicated and haemodynamically insignificant Attrition: 16 participants due to death (n = 7), withdrawal of consent (n = 4) or loss to follow-up (n = 5)
Interventions	Children received palivizumab (15 mg/kg) or an equivalent volume of placebo applied as intramuscular injections every 30 days for a total of 5 doses
Outcomes	Primary outcome: hospitalization with confirmed RSV infection Children were considered to have reached the primary outcome if: 1) they were hospitalised for a respiratory illness and the RSV antigen test of respiratory secretions was positive; or 2) if children already hospitalised for reasons other than RSV illness had a positive RSV test, and had a minimum LRI score of 3 and at least 1 point higher compared with their last health visit Secondary outcomes: total RSV hospital days, RSV hospital days with increased supplemental oxygen, RSV hospital days with moderate/severe lower respiratory tract illness, incidence and total days of intensive care and mechanical ventilation, incidence of non-RSV hospitalization, incidence of otitis media, adverse events (assessed for severity and potential relationship to study drug) Children were followed for 150 days from randomization (30 days after the last scheduled injection)
Notes	

IMpact-RSV 1998 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation (2 treatment to 1 control) was performed centrally using an interactive voice randomization system (p. 532)
Allocation concealment (selection bias)	Low risk	Participants were centrally randomized to receive palivizumab or an equal volume of identically appearing placebo. Palivizumab and placebo were supplied as powder in coded vials and dispensed in a syringe that did not identify the contents (p. 532)
Incomplete outcome data (attrition bias) All outcomes	Low risk	99% of children completed the protocol follow-up, 94% of placebo group and 92% of palivizumab group received all 5 injections. All randomized patients were included in the safety and efficacy analyses (p. 532, 533)
Selective reporting (reporting bias)	High risk	Primary and secondary endpoints listed in the methods on page 532 are reported in results section on pages 533 to 534. Adverse events were defined as they happened, in both groups, and reported on page 534. Standard deviations for continuous data (days) are not reported (p. 533, 534)
Other bias	Unclear risk	Employees of MedImmune contributed to the study and assisted in preparation of the manuscript (p. 537)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were centrally randomized to receive palivizumab or an equal volume of identically appearing placebo (p. 532)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Adverse events were judged by the blinded investigator to be related or not to the study drug (p. 534) LRI score was completed on all patients, regardless and all patients were followed for 150 days (30 days after the last immunisation), regardless of the amount of study drug they received (p. 532)

Joffe 1999

Methods	Cost-effectiveness analysis, societal perspective, decision analytic model, 3% discount rate, 1995 USD, California, USA
Participants	Preterm infants discharged from the neonatal intensive care unit within 12 months prior to RSV season (8 risk groups)
Interventions	Palivizumab prophylaxis compared to RSV-IVIG prophylaxis and no prophylaxis
Outcomes	Effectiveness outcomes: number needed to treat to prevent 1 RSV hospitalization, mortality benefits included, risk of sequelae not included Summary measures: incremental cost per hospitalization averted, incremental cost per LYG
Notes	No conflict of interest declared. This study suggests more restrictive recommendations for the use of palivizumab

Risk of bias

Joffe 1999 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Kang 2009

Methods	Cost-effectiveness analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 5% discount rate, KW, Korea
Participants	Children with congenital heart disease
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: number of RSV hospitalisations and deaths avoided Summary measures: incremental cost per LYG
Notes	This is an abstract of a presentation at a conference. This study suggests that the use of palivizumab is cost-effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Kang 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Lanctot 2008

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 5% discount rate, 2007 CAD, Canada
Participants	Preterm infants born at 32 to 35 weeks of gestational age without chronic lung disease
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization due to RSV infection (general ward or ICU), risk of asthma and recurrent wheezing included, mortality benefits included, LYGs, QALYs Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Abbott provided financial support for this analysis. This study suggests that palivizumab prophylaxis is cost-effective from both perspectives, in patients with 2 or more risk factors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Lanctot 2008 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Lazaro y de Mercado 2006

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 3% discount rate, 2006 EUR, Spain
Participants	Preterm infants born at 32 to 35 weeks' gestational age with 2 or more risk factors described by the Spanish Neonatology Society
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: life expectancy, mortality benefits included, hospitalization rate, risk of recurrent wheezing included, number needed to treat Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Funded by the industry. This study suggests that palivizumab is a cost-effective alternative for the prophylaxis of RSV in preterm children with 2 or more risk factors. Paper is written in Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Lazaro y de Mercado 2007

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 3.5% discount rate, 2006 EUR, Spain
Participants	Preterm infants born at 35 weeks of gestational age or less and 6 months of age or younger, or 24 months old or younger and with a clinical diagnosis of BPD requiring ongoing medical treatment
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: life expectancy, mortality benefits included, hospitalization rate, risk of recurrent wheezing included, number needed to treat Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	No conflict of interest declared. However, for the economic evaluation performed on the same topic by the same authors in 2006, the authors received a grant from Abbott. This study suggests that palivizumab is a cost-effective alternative for the prophylaxis of RSV in preterm children with 2 or more risk factors. Paper is written in Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Lofland 2000

Methods	Cost-effectiveness analysis, payer's perspective, decision analytic model, 1-year follow-up, no discounting, 1999 USD, USA
Participants	Preterm infants (≤ 35 weeks of gestational age) and children with BPD
Interventions	Palivizumab prophylaxis compared to no prophylaxis

Lofland 2000 *(Continued)*

Outcomes	Effectiveness outcomes: hospitalization due to RSV infection, mortality benefits not included, risk of sequelae not included Summary measures: incremental cost per RSV hospitalization avoided
Notes	Paper was supported by a grant from MedImmune, Inc., Gaithersburg. This study gives ICER ranges for different palivizumab prophylaxis costs, and leaves the conclusions about the cost-effectiveness up to the readers

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Mayen-Herrera 2011

Methods	Cost-utility analysis, payer's perspective, decision analytic model, 3% discount rate, MXN, Mexico
Participants	Preterm infants born at less than 29 weeks of gestational age
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: QALYs Summary measures: incremental cost per QALY
Notes	This is an abstract of a presentation at a conference. Author EMH is employed at Abbott. This study suggests that palivizumab prophylaxis is cost-effective

Risk of bias

Bias	Authors' judgement	Support for judgement

Mayen-Herrera 2011 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Neovius 2011

Methods	Cost-utility and cost-effectiveness analysis, societal perspective, decision analytic Markov model, lifetime follow-up, 3% discount rate, 2009 SEK, Sweden
Participants	Preterm infants born at less than 29 weeks of gestation
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization due to RSV infection, risk of asthma included, mortality benefits included Summary measures: incremental cost per QALY, incremental cost per LYG
Notes	Authors KB and KS are employed at Abbott. Study was funded by Abbott Scandinavia. Palivizumab was found to be cost-effective, based on a willingness-to-pay of SEK 500,000 per QALY

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Neovius 2011 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Nuijten 2007

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 3.5% discount rate, 2003 GBP, UK
Participants	Preterm infants born at 35 weeks of gestation or less, children with BPD (≤ 2 years) and children with CHD (≤ 2 years)
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: mortality benefits included, risk of sequelae included, hospitalization rate, life expectancy, utilities Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Funded by the industry. This study suggests that palivizumab prophylaxis may be a cost-effective option against severe RSV infections in the UK versus no prophylaxis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Nuijten 2007 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Nuijten 2009a

Methods	Cost-utility and cost-effectiveness analysis, societal perspective, decision analytic model, lifetime follow-up, no discounting, 2006 EUR, Netherlands
Participants	Preterm infants and infants with BPD (as one subgroup) and children with CHD (as another subgroup)
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization due to RSV infection, risk of asthma and recurrent wheezing included, mortality benefits included, life expectancy, utilities Summary measures: incremental cost per QALY, incremental cost per LYG
Notes	Author WW is employed at Abbott. Author MN was paid by Abbott to conduct this analysis. This study suggests that palivizumab prophylaxis is cost-effective

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Nuijten 2009b

Methods	Cost-utility and cost-effectiveness analysis, societal and payer's perspective, decision analytic model, lifetime follow-up, 5% discount rate, 2006 EUR, Germany

Nuijten 2009b *(Continued)*

Participants	Infants with haemodynamically significant congenital heart disease
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization due to RSV infection, risk of asthma and recurrent wheezing included, mortality benefits included, utilities Summary measures: incremental cost per QALY, incremental cost per LYG
Notes	Author WW is employed at Abbott. Author MN was paid by Abbott to conduct this analysis. This study suggests that palivizumab prophylaxis is cost-effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Nuijten 2010

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 3% discount rate, 2006 EUR, Spain
Participants	Preterm children born at or before 32 weeks of gestational age who were less than 6 months old at the onset of RSV season
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: mortality benefits included, risk of sequelae included, hospitalization rate, life expectancy, utilities Summary measures: incremental cost per LYG, incremental cost per QALY

Nuijten 2010 *(Continued)*

Notes	Funded by the industry. This study suggests that palivizumab may be a cost-effective prophylactic option against severe RSV infections in Spain compared to no prophylaxis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Ravasio 2006

Methods	Cost-effectiveness and cost-utility analysis, payer's perspective, decision analytic model, 14 years follow-up, 3% discount rate, EUR, Italy
Participants	Preterm infants of less than 33 weeks, or 33 to 35 weeks of gestation, with and without BPD
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: mortality benefits included, hospitalization rate, risk of asthma included Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Funded by the industry. This study suggests that palivizumab is cost-effective in prevention of RSV infection in preterm infants. Paper is written in Italian

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Ravasio 2006 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Raya Ortega 2006

Methods	Cost-effectiveness analysis, payer's perspective, decision analytic model, 1-year follow-up, no discounting, 2006 EUR, Spain
Participants	Preterm infants born at 32 to 35 weeks of gestation
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate Summary measures: incremental cost per hospitalization avoided
Notes	Not funded by the industry. This study suggests that palivizumab prophylaxis is not cost-effective. Paper is written in Spanish

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Raya Ortega 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Resch 2008

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 5% discount rate, 2006 EUR, Austria
Participants	Preterm infants born at 35 weeks of gestation or less, children with BPD and children with CHD
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization, mortality benefits included, life expectancy, risk of asthma included Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Author WW is employed at Abbott. Palivizumab was cost-effective compared to no prophylaxis in high-risk infants in Austria

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Resch 2012

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 5% discount rate, 2010 EUR, Austria
Participants	Preterm infants born at 36 weeks of gestation or less, children with BPD and children with CHD
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: LYG, QALY, mortality benefits included, risk of sequelae included Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Conflicts of interest are not clearly stated. Author SS is employed at Abbott. Study suggests that palivizumab is cost-effective in prevention of RSV disease in high-risk infants. This study incorporated changes in medication costs and new country-specific epidemiologic data, as compared to Resch 2008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Rietveld 2010

Methods	Cost-effectiveness analysis, societal perspective, decision analytic model, 1-year follow-up, no discounting, 2000 EUR, Netherlands
Participants	Preterm infants born at 28 weeks of gestation or less, with birth weight ≤ 2500 g, having BPD and aged 0 months at the beginning of the season (October)
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate, mortality benefits not included, risk of sequelae not included

Rietveld 2010 *(Continued)*

	Summary measures: cost per hospitalization averted
Notes	Not funded by the industry. This study recommends a restrictive immunisation policy, immunizing only the children with BPD in high-risk months

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Roeckl-Wiedmann 2003

Methods	Cost-effectiveness analysis, societal perspective, decision analytic model, 1-year follow-up, no discounting, EUR, Germany
Participants	Preterm infants of male gender born at ≤ 35 weeks of gestational age, with siblings in daycare, discharge between October and December, and with or without CLD. Economic evaluation is nested in the Munich RSV study.
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate, mortality benefits included, risk of sequelae not included Summary measures: cost per hospitalization averted
Notes	Funded by the industry. This study suggests restrictive use of palivizumab prophylaxis in preterm infants with CLD in their risk combination

Risk of bias

Bias	Authors' judgement	Support for judgement

Roeckl-Wiedmann 2003 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Salinas-Escudero 2012

Methods	Cost-effectiveness and cost-utility analysis, payer's perspective, decision analytic model, 18 years follow-up, 3% discount rate, 2009 USD, Mexico
Participants	Preterm infants without CLD or CHD, born at less than 29, or at 29 to 32 weeks of gestational age, and up to 6 months old at the start of the RSV season, or born during the season
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: LYG, QALY, risk of asthma included, mortality benefits included Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	The authors received support of Abbott Laboratories in Mexico. This study suggests that palivizumab is a cost-effective alternative for preterm infants ≤ 32 weeks of gestational age (wGA) in Mexico

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Salinas-Escudero 2012 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Smart 2010

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 5% discount rate, 2010 CAD, Canada
Participants	Preterm infants born at 32 to 35 weeks' gestational age
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate, mortality benefits included, with and without risk of sequelae included, life expectancy Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Not funded by the industry. Palivizumab was cost-effective compared to no prophylaxis in high-risk infants in Canada. Methodology was based on Lanctot 2008 study

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Smart 2010 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Subramanian 1998

Methods	Study design: randomized (2:1), double-blind, placebo-controlled, phase I/II, multicentre, dose-escalation trial Dates of study: 1995 to 1996 RSV season Locations: 10 sites (locations not specified)
Participants	62 patients (42 to palivizumab group and 20 to placebo group) who: 1) were born at ≤ 35 weeks of gestation and were ≤ 6 months of age; or 2) had bronchopulmonary dysplasia and were ≤ 24 months of age Infants were excluded if they had any of the following: mechanical ventilation at the time of enrolment; life expectancy < 1 year; known renal impairment, hepatic dysfunction, persistent seizure disorder or immunodeficiency; blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase or bilirubin > 1.5 times the upper limit of normal for age; haemoglobin < 9.0 g/dl; white blood cell count < 2000 cells/mm^3; platelet count < 110,000 cells/mm^3; abnormal serum IgG, IgM and IgA values, positive hepatitis B surface antigen, hepatitis C antibody or HIV antibody (unless provided to be not infected with HIV); supplemental oxygen requirement of > 30% FiO_2 or > 1.5 litres/min; any acute illness or progressive clinical disorder, including acute RSV infection; previous reaction to intravenous immunoglobulin, blood products or other foreign proteins; treatment with intravenous immunoglobulin or other immunoglobulin products within the past 2 months; treatment with other investigational agents or participation in any investigational study of RSV agents; or expectation that the patient would not be able to be followed for the duration of the study
Interventions	Children received 3, 10 or 15 mg/kg of palivizumab intravenously, or an equal volume of placebo applied as intravenous infusion every 30 days (- 3 to + 7 days) for up to 5 doses
Outcomes	Primary outcomes: adverse events (assessed for severity, seriousness and relationship to study drug) Secondary outcomes: frequency and severity of RSV infection Infants who were assessed by the family or the patient's physician as having a respiratory infection or who had 2 or more of the following new respiratory symptoms (coryza, fever, cough, wheezing, intercostal retractions or nasal flaring) or who had exacerbation of existing respiratory conditions were evaluated for evidence of RSV infection (RSV antigen). When a child was hospitalised for RSV illness, the child was evaluated daily until discharge Patients were followed for 150 days (30 days after the last infusion)
Notes	The data extracted for our analysis includes only data for 15 mg/kg dosing regimen

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation (1 placebo: 2 MEDI-493 within each dosage) was done centrally. Insufficient information about sequence generation process is given (p. 111)

Subramanian 1998 *(Continued)*

Allocation concealment (selection bias)	Low risk	The study drug (palivizumab or placebo) was dispensed from the pharmacy in a syringe enclosed in a plastic bag that did not contain the drug assignment on the label (p. 111, 112)
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized patients who received study drug were included in analyses. Overall 91.9% patients completed the study. Reasons for attrition are given (p. 112)
Selective reporting (reporting bias)	Low risk	All outcomes reported in the methods are also reported in the results section. LRI score was used; adverse events were reported on as-encountered basis and assessed by the blinded investigator for relationship to study drug (p. 111)
Other bias	Unclear risk	Several authors of this study are MedImmune employees (p. 110)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drug assignment and the investigators were blinded. Study drugs were dispensed from the pharmacy in a syringe enclosed in a plastic bag that did not contain the drug assignment on the label. The safety monitoring committee had the power to unblind the study group assignment if needed, but didn't do it during their review (p. 111, 112)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were assessed by the blinded investigator. The treatment assignment was unblinded by the medical monitor for 1 child who died who was assigned to the placebo group (p. 111, 112)

Tam 2009

Methods	Cost-effectiveness and cost-utility analysis, payer's and societal perspective, decision analytic model, lifetime follow-up, 5% discount rate, 2007 CAD, Canada
Participants	Infants less than 1 year of age on Baffin Island
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate, mortality benefits included, risk of sequelae not included, life expectancy, utilities Summary measures: incremental cost per LYG, incremental cost per QALY
Notes	Funded by the industry. Palivizumab was cost-effective in infants less than 1 year of age residing in the Eastern Canadian Arctic. However, palivizumab was not cost-effective for infants of all ages residing in Iqaluit

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Tam 2009 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Vogel 2002

Methods	Cost-effectiveness analysis, societal perspective, decision analytic model, no discounting, 2000 NZD, New Zealand
Participants	Preterm infants < 32 weeks' gestational age
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate, mortality benefits not included, risk of sequelae not included, number needed to treat Summary measures: cost per hospitalization averted
Notes	Funded by the industry. This study does not indicate cost savings associated with the use of palivizumab for any subgroup

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Vogel 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Wang 2011

Methods	Cost-utility analysis, payer's perspective, decision analytic model, lifetime follow-up, 3.5% discount rate, 2006 GBP, UK
Participants	Preterm infants ≤ 35 weeks gestational age. Subgroup analyses in four categories: CLD, CLD/CHD, acyanotic CHD and cyanotic CHD
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: odds ratios for age, gestational age, gender, CHD, CLD, sibling at school, multiple births, smoking exposure, overcrowding, parental education of high school or less, mortality benefits included, with and without risk of sequelae included Summary measures: incremental cost per QALY
Notes	Not funded by the industry. This study suggests that palivizumab is not cost-effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Weiner 2012

Methods	Cost-utility analysis, societal perspective, decision analytic model, lifetime follow-up, 3% discount rate, 2010 USD, USA
Participants	Preterm infants without CLD or CHD divided in 4 subgroups; data presented for infants born at less than 32 weeks of gestation and with 6 months of chronological age or less
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: QALYs, utilities, mortality benefits included, risk of sequelae not included Summary measures: incremental cost per QALY
Notes	Funded by the industry. This study suggests that palivizumab prophylaxis is highly cost-effective

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

Yount 2004

Methods	Cost-effectiveness and cost-utility analysis, payer's perspective, decision analytic model, lifetime follow-up, 3% discount rate, 2002 USD, USA
Participants	Children with congenital hearth disease ≤ 2 years old
Interventions	Palivizumab prophylaxis compared to no prophylaxis
Outcomes	Effectiveness outcomes: hospitalization rate, life expectancy, mortality benefits included, risk of sequelae included Summary measures: incremental cost per LYG, incremental cost per QALY

Yount 2004 *(Continued)*

Notes	Not funded by the industry. Routine use of palivizumab in young children with haemodynamically significant CHD needs to be evaluated further

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Allocation concealment (selection bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Selective reporting (reporting bias)	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Other bias	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	See Appendix 6 for assessment of risk of bias in economic evaluations

AEs = adverse events
BPD = bronchopulmonary dysplasia
CAD = Canadian dollar
CHD = congenital heart disease
CLD = chronic lung disease
EUR = Euro
GA = gestational age
GBP = Great British pound
HIV = human immunodeficiency virus
ICER = incremental cost-effectiveness ratio
ICU = intensive care unit
IVIG = intravenous immunoglobulin
ITT = intention-to-treat
KW = Korean won
LRI = lower respiratory tract infection
LYGs = life-years gained
MALRI = medically attended lower respiratory tract infection
MXN = Mexican peso
NZD = New Zealand dollar
RSV = respiratory syncytial virus
QALYs = quality-adjusted life-years
SAEs = serious adverse events
SEK = Swedish krona
UK = United Kingdom
USA = United States of America
USD = United States dollar
wGA = weeks of gestational age

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Banerji 2009	This is a partial economic evaluation study
Buckley 2010	This is a partial economic evaluation study
Chan 2003	This is a partial economic evaluation study
Clark 2000	This is a partial economic evaluation study
Datar 2012	This is a partial economic evaluation study
Farina 2002	This is a partial economic evaluation study
Korbal 2003	This is a retrospective analysis, not a randomized controlled trial
Krilov 2010	This is a partial economic evaluation study
Lapena Lopez 2003	This is a partial economic evaluation study
Lee 2001	This is a partial economic evaluation study
Marchetti 1999	This is a partial economic evaluation study
Marques 2010	This is a partial economic evaluation study
Martinez 2002	This is a trial with a historical control, not a randomized controlled trial
McCormick 2002	This is a partial economic evaluation study
Meberg 2006	This is a partial economic evaluation study
Meissner 1999	Product SB 209763 is not palivizumab. It is another kind of intramuscular monoclonal antibody against respiratory syncytial virus (RSV) that failed to prove efficacy in preventing severe RSV disease
Numa 2000	This is neither a cost-effectiveness nor a cost-utility analysis
Parmigiani 2001	This is not a randomized controlled trial
Rackham 2005	This is a partial economic evaluation study
Reeve 2006	This is a partial economic evaluation study
Rodriguez 2008	This is a partial economic evaluation study
Shireman 2002	This is neither a cost-effectiveness nor a cost-utility analysis
Stevens 2000	This economic evaluation analyses RSV-IVIG and palivizumab together. Results of these analyses represent combined effect of both prophylaxis. There is no comparison of palivizumab prophylaxis alone with placebo, no prophylaxis or other prophylaxis
Strutton 2003	This is a systematic review of economic evaluations and not a primary analysis

Study	Reason for exclusion
Takeuchi 2002	This is not a randomized controlled trial
Vann 2007	This is a partial economic evaluation study
Wang 2008	The technology assessment performed in Wang 2008 was later updated and reported in Wang 2011
Wegner 2004	This is a partial economic evaluation study
Wendel 2010	This is a partial economic evaluation study

Characteristics of studies awaiting assessment *[ordered by study ID]*

NCT00233064

Methods	Study design: phase IV, randomized, double-blind, dose comparison trial Date of first enrolment: October 2005 Target sample size: 417 Recruitment status: completed in November 2007 Locations: sites in USA Sponsor: MedImmune LLC
Participants	Inclusion criteria: 1. Medically stable child with chronic lung disease of prematurity who is ≤ 24 months of age at randomization or child with premature birth (gestational age ≤ 35 weeks or less) and who is 6 months of age or younger at randomization 2. Written informed consent obtained from the patient's parent(s) or legal guardian(s) 3. The child must be able to complete the follow-up visit 4 to 6 months after the last dose of study drug Exclusion criteria: 1. Hospitalisation at the time of randomization (unless discharge is anticipated within 3 weeks) 2. Be receiving mechanical ventilation at the time of study entry (including CPAP) 3. Congenital heart disease (children with uncomplicated CHD (e.g. PDA, small septal defect) and children with complicated CHD who are currently anatomically and haemodynamically normal can be enrolled) 4. Mother with HIV infection (unless the child has been proven to be not infected) 5. Life expectancy < 6 months 6. Known allergy to Ig products 7. Acute respiratory or other acute infection or illness 8. Previous reaction to IVIG, blood products, or other foreign proteins 9. Receipt of lyophilised palivizumab, RSV-IVIG, or other RSV-specific monoclonal antibody, or any other polyclonal antibody (for example, hepatitis B IG, IVIG, VZIG) within 3 months prior to randomization 10. Any previous receipt of MEDI-524 11. Participation in other investigational drug product studies
Interventions	Children received 15 mg/kg of liquid palivizumab, or 15 mg/kg of lyophilised palivizumab administered intramuscularly every 30 days for a total of 5 injections

NCT00233064 *(Continued)*

Outcomes	Primary outcome: number and percentage of participants with immune reactivity Children were followed for 240 to 300 days
Notes	

NCT00240929

Methods	Study design: phase II, randomized, double-blind, dose comparison, cross-over trial Date of first enrolment: September 2002 Target sample size: 150 Recruitment status: completed in April 2003 Locations: 20 sites in the USA Sponsor: MedImmune LLC
Participants	Inclusion criteria: 1. The child must have been born at less than or equal to 35 weeks gestation and be less than or equal to 6 months of age at the time of randomization (child must be randomized on or before their 6-month birthday) 2. The child's parent or legal guardian must provide written informed consent 3. The child must be able to complete the follow-up visits on study days 30 and 60 within the protocol specified windows (± 2 days) 4. Parent/legal guardian of patient has available telephone access Exclusion criteria: 1. Hospitalised 2. Birth hospitalization > 6 weeks duration 3. Receiving mechanical ventilation at the time of study entry (including CPAP) 4. Bronchopulmonary dysplasia (BPD), defined as history of prematurity and associated chronic lung disease with oxygen requirement for > 28 days 5. Congenital heart disease (CHD) (children with medically or surgically corrected (closed) patent ductus arteriosus and no other CHD may be enrolled) 6. Known renal impairment, hepatic dysfunction, chronic seizure disorder or immunodeficiency 7. Any of the following laboratory findings in blood obtained within 7 days prior to study entry: BUN or creatinine > 1.5 the upper limit of normal for age, AST (SGOT) or ALT (SGPT) > 1.5 the upper limit of normal for age, haemoglobin < 9.0 gm/dL, white blood cell count < 4000 cells/mm3, platelet count < 110,000 cells/mm3 8. Acute illness or progressive clinical disorder 9. History of recent difficult venous access 10. Active infection, including acute RSV infection 11. Previous reaction to IVIG, blood products or other foreign proteins 12. Received within the past 120 days or currently receiving IVIG, other immunoglobulin products or any investigational agents 13. Have ever received palivizumab 14. Currently participating in any investigational study 15. Previously participated in any investigational study of RSV vaccines or monoclonal antibodies

NCT00240929 *(Continued)*

Interventions	Children received sequence A (single dose of the liquid formulation on study day 0 and a single dose of the lyophilised formulation on study day 30), or sequence B (single dose of the lyophilised formulation on study day 0 and single dose of the liquid formulation on study day 30)
Outcomes	Primary outcomes: adverse events and palivizumab concentrations in serum Secondary outcomes: adverse events and serious adverse events Children were followed for 30 days after each injection
Notes	

NTR1023

Methods	Study design: randomized, double-blind, placebo-controlled trial Date of first enrolment: 1 October 2007 Target sample size: 452 Recruitment status: completed Locations: sites in Netherlands
Participants	Inclusion criteria: 1. Gestational age 32 to 35 weeks Exclusion criteria: 1. Severe congenital anomaly 2. Congenital heart disease 3. Down syndrome
Interventions	Children received monthly injection of placebo or palivizumab 15 mg/kg during the winter season
Outcomes	Primary outcome: number of wheezing days during the first year of life Secondary outcomes: health-related quality of life at age 1, 3 and 6 years, and asthmatic symptoms at age 3 and 6 years measured by questionnaires
Notes	

ALT = alanine aminotransferase
AST = aspartate aminotransferase
BPD = bronchopulmonary dysplasia
BUN = blood urea nitrogen
CHD = congenital heart disease
CPAP = continuous positive airway pressure
HIV = human immunodeficiency virus
IG = immunoglobulin
IVIG = intravenous immunoglobulin
PDA = persistent ductus arteriosus
RSV = respiratory syncytial virus
SGOT = serum glutamic oxaloacetic transaminase
SGPT = serum glutamic pyruvic transaminase
USA = United States of America
VZIG = varicella zoster immunoglobulin

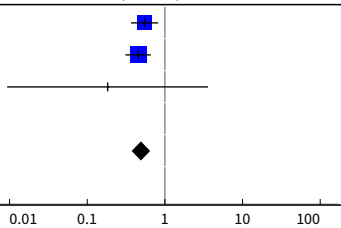
DATA AND ANALYSES

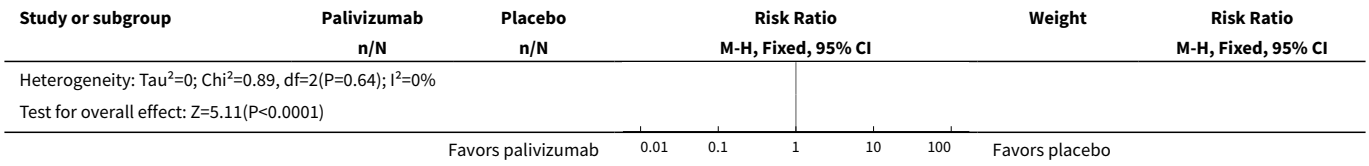
Comparison 1. Palivizumab versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospitalisation for RSV infection	3	2831	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.37, 0.64]
2 All-cause mortality	3	2831	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.42, 1.15]
3 Total RSV hospital days per 100 children	2	2789	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Admission to ICU	2	2789	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.30, 0.81]
5 Days in the ICU per 100 children	2	2789	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Mechanical ventilation for RSV infection	2	2789	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.20, 6.09]
7 Days of mechanical ventilation per 100 children	2	2789	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Days of supplemental oxygen therapy per 100 children	2	2789	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Number of children reporting any AE	1	1287	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.97, 1.01]
10 Number of children reporting related AE	3	2831	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.38]
11 Number of children reporting any SAE	1	1287	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.96]
12 Number of children reporting related SAE	1	1287	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.80]

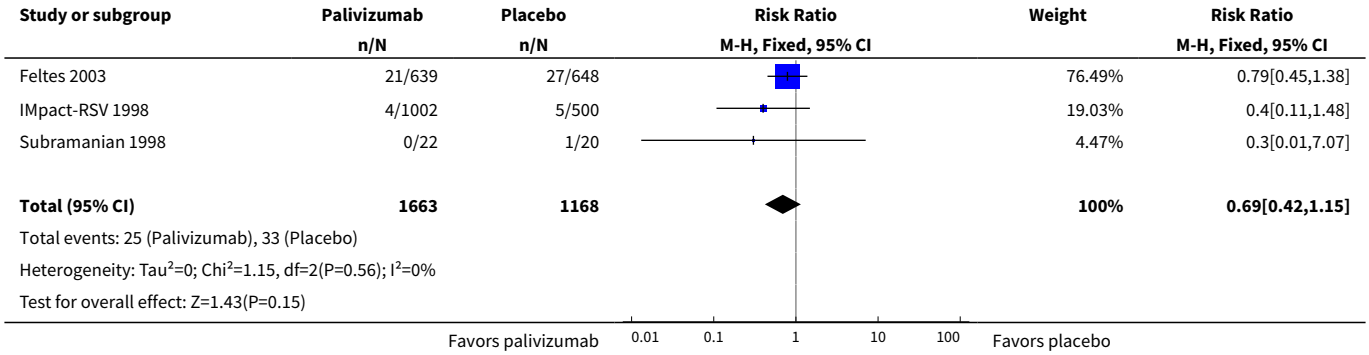
Analysis 1.1. Comparison 1 Palivizumab versus placebo, Outcome 1 Hospitalisation for RSV infection.

Study or subgroup	Palivizumab n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Feltes 2003	34/639	63/648		46.04%	0.55[0.37,0.82]
IMpact-RSV 1998	48/1002	53/500		52.04%	0.45[0.31,0.66]
Subramanian 1998	0/22	2/20		1.92%	0.18[0.01,3.59]
Total (95% CI)	**1663**	**1168**		**100%**	**0.49[0.37,0.64]**
Total events: 82 (Palivizumab), 118 (Placebo)					

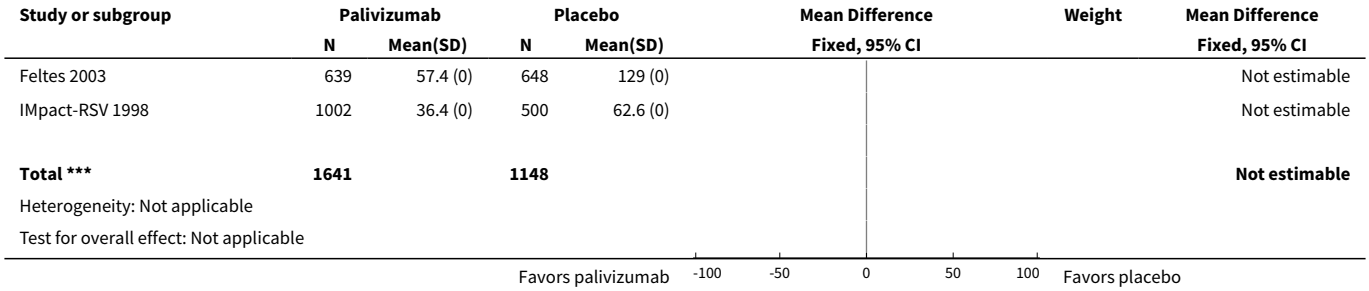




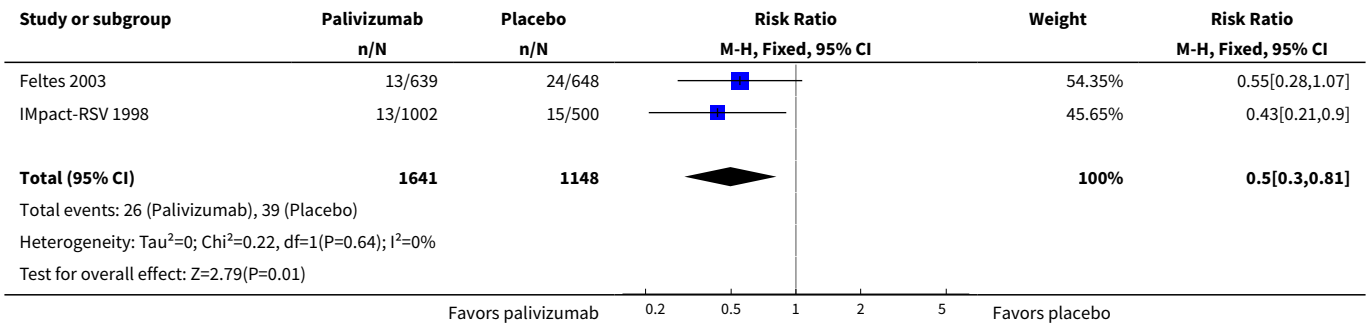
Analysis 1.2. Comparison 1 Palivizumab versus placebo, Outcome 2 All-cause mortality.



Analysis 1.3. Comparison 1 Palivizumab versus placebo, Outcome 3 Total RSV hospital days per 100 children.



Analysis 1.4. Comparison 1 Palivizumab versus placebo, Outcome 4 Admission to ICU.



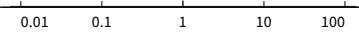
Analysis 1.5. Comparison 1 Palivizumab versus placebo, Outcome 5 Days in the ICU per 100 children.

Study or subgroup	Palivizumab N	Palivizumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Feltes 2003	639	15.9 (0)	648	71.2 (0)			Not estimable
IMpact-RSV 1998	1002	13.3 (0)	500	12.7 (0)			Not estimable
Total ***	**1641**		**1148**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favors palivizumab — Favors placebo

Analysis 1.6. Comparison 1 Palivizumab versus placebo, Outcome 6 Mechanical ventilation for RSV infection.

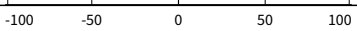
Study or subgroup	Palivizumab n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Feltes 2003	8/639	14/648		64.28%	0.58[0.24,1.37]
IMpact-RSV 1998	7/1002	1/500		35.72%	3.49[0.43,28.31]
Total (95% CI)	**1641**	**1148**		**100%**	**1.1[0.2,6.09]**
Total events: 15 (Palivizumab), 15 (Placebo)					
Heterogeneity: Tau^2=0.99; Chi^2=2.49, df=1(P=0.11); I^2=59.78%					
Test for overall effect: Z=0.11(P=0.91)					



Favors palivizumab — Favors placebo

Analysis 1.7. Comparison 1 Palivizumab versus placebo, Outcome 7 Days of mechanical ventilation per 100 children.

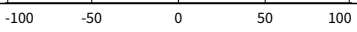
Study or subgroup	Palivizumab N	Palivizumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Feltes 2003	639	6.5 (0)	648	54.7 (0)			Not estimable
IMpact-RSV 1998	1002	8.4 (0)	500	1.7 (0)			Not estimable
Total ***	**1641**		**1148**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							



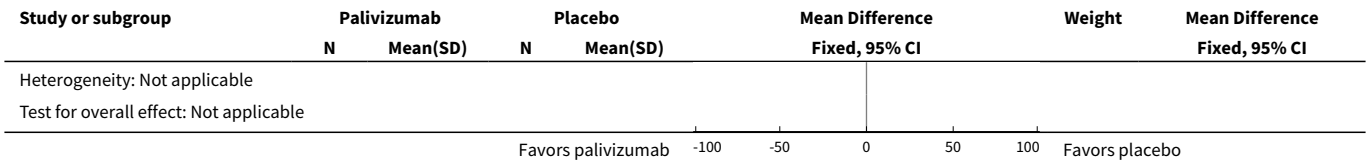
Favors palivizumab — Favors placebo

Analysis 1.8. Comparison 1 Palivizumab versus placebo, Outcome 8 Days of supplemental oxygen therapy per 100 children.

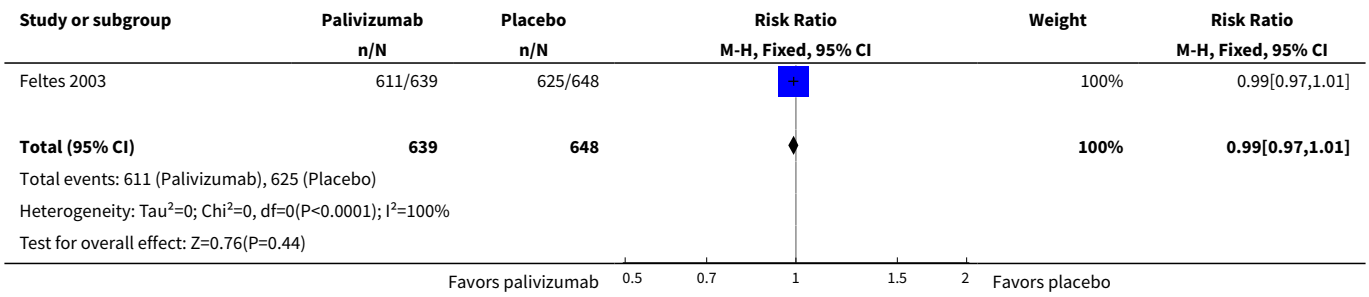
Study or subgroup	Palivizumab N	Palivizumab Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Feltes 2003	639	27.9 (0)	648	101.5 (0)			Not estimable
IMpact-RSV 1998	1002	30.3 (0)	500	50.6 (0)			Not estimable
Total ***	**1641**		**1148**				**Not estimable**



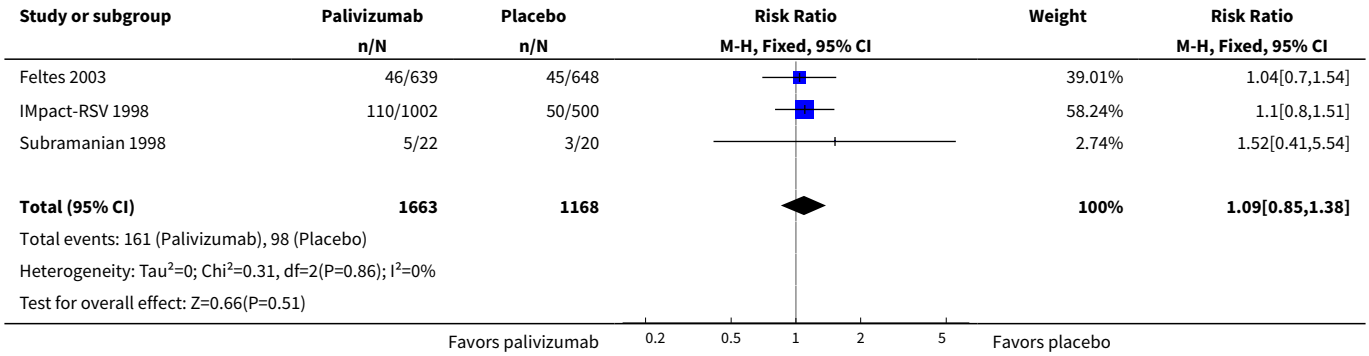
Favors palivizumab — Favors placebo



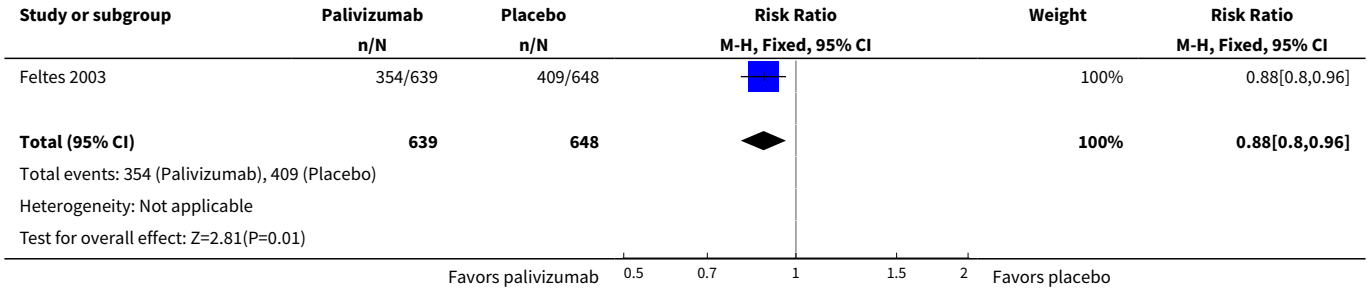
Analysis 1.9. Comparison 1 Palivizumab versus placebo, Outcome 9 Number of children reporting any AE.



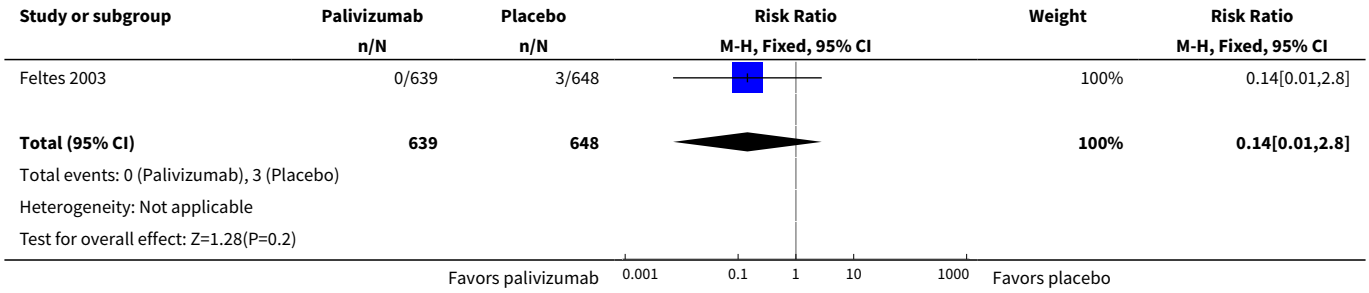
Analysis 1.10. Comparison 1 Palivizumab versus placebo, Outcome 10 Number of children reporting related AE.



Analysis 1.11. Comparison 1 Palivizumab versus placebo, Outcome 11 Number of children reporting any SAE.



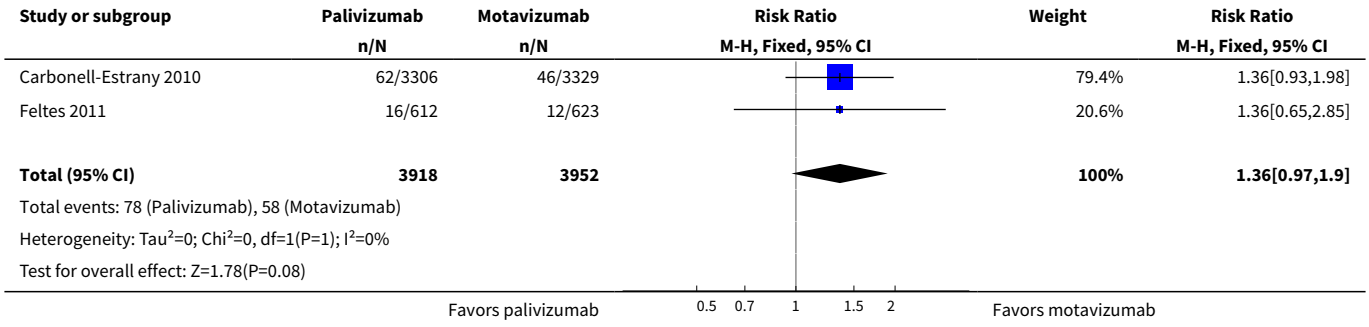
Analysis 1.12. Comparison 1 Palivizumab versus placebo, Outcome 12 Number of children reporting related SAE.



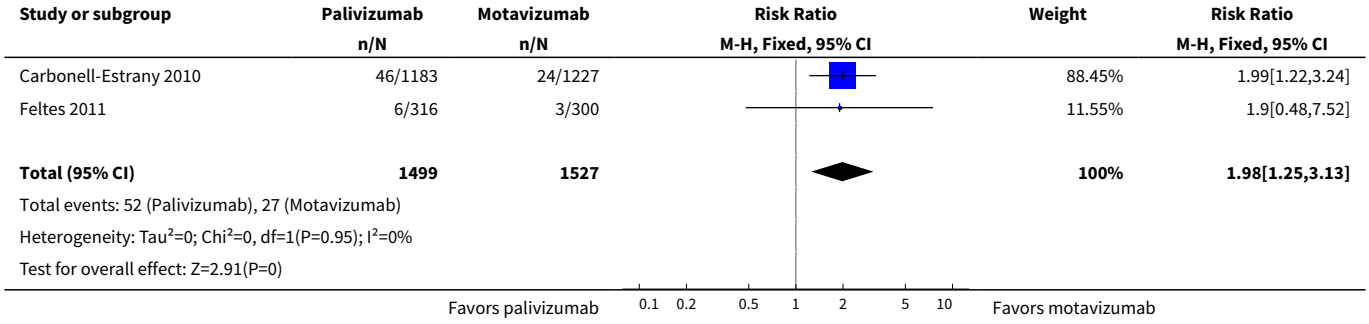
Comparison 2. Palivizumab versus motavizumab

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospitalisation for RSV infection	2	7870	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.97, 1.90]
2 RSV-specific outpatient MALRI	2	3026	Risk Ratio (M-H, Fixed, 95% CI)	1.98 [1.25, 3.13]
3 All-cause mortality	4	8265	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.38, 1.43]
4 Total RSV hospital days per 100 children	2	7870	Mean Difference (IV, Fixed, 95% CI)	24.95 [-21.59, 71.49]
5 Admission to ICU	2	7870	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.89, 3.19]
6 Days in the ICU per 100 children	2	7870	Mean Difference (IV, Fixed, 95% CI)	21.34 [-13.69, 56.37]
7 Mechanical ventilation for RSV infection	2	7870	Risk Ratio (M-H, Fixed, 95% CI)	3.79 [1.26, 11.42]
8 Days of mechanical ventilation per 100 children	2	7870	Mean Difference (IV, Fixed, 95% CI)	16.06 [-16.60, 48.72]
9 Supplemental oxygen therapy for RSV infection	2	7870	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.98, 2.26]
10 Days of supplemental oxygen therapy per 100 children	2	7870	Mean Difference (IV, Fixed, 95% CI)	28.42 [-13.64, 70.48]
11 Number of children reporting any AE	4	8238	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.99, 1.02]
12 Number of children reporting related AE	3	1625	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.73, 1.32]
13 Number of children reporting any SAE	4	8238	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.96, 1.13]
14 Number of children reporting related SAE	3	1625	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.32, 2.43]

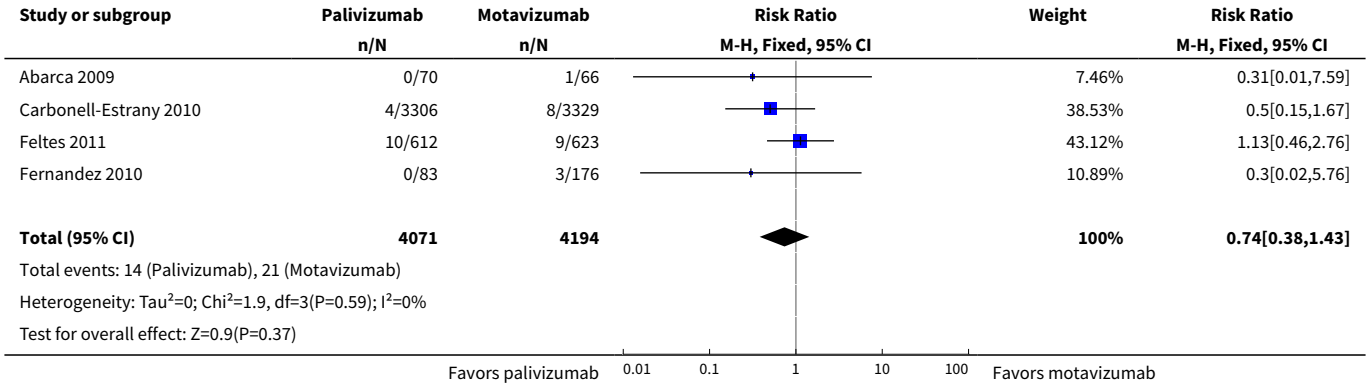
Analysis 2.1. Comparison 2 Palivizumab versus motavizumab, Outcome 1 Hospitalisation for RSV infection.



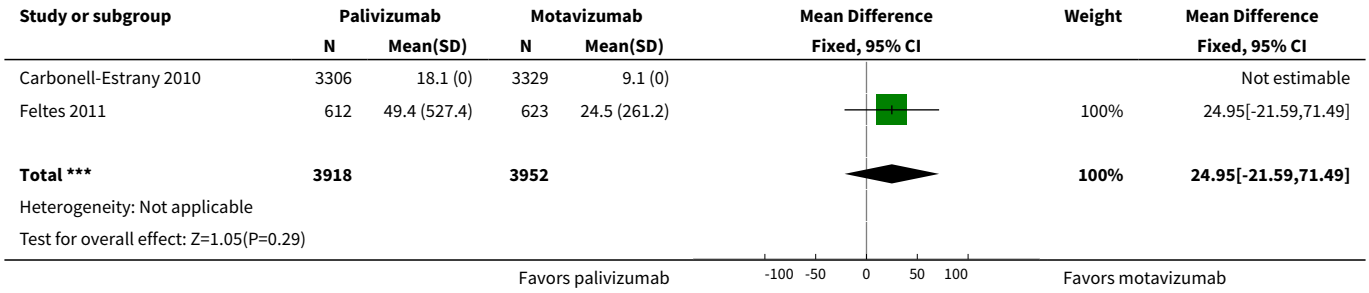
Analysis 2.2. Comparison 2 Palivizumab versus motavizumab, Outcome 2 RSV-specific outpatient MALRI.



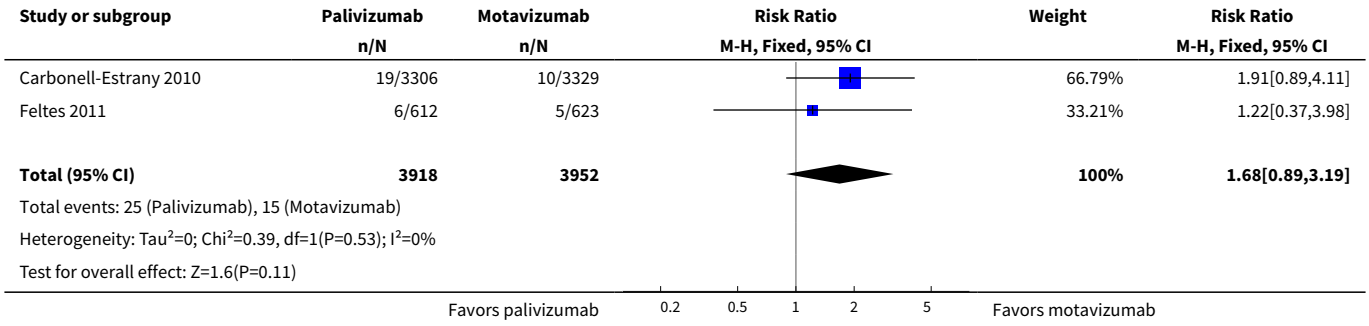
Analysis 2.3. Comparison 2 Palivizumab versus motavizumab, Outcome 3 All-cause mortality.



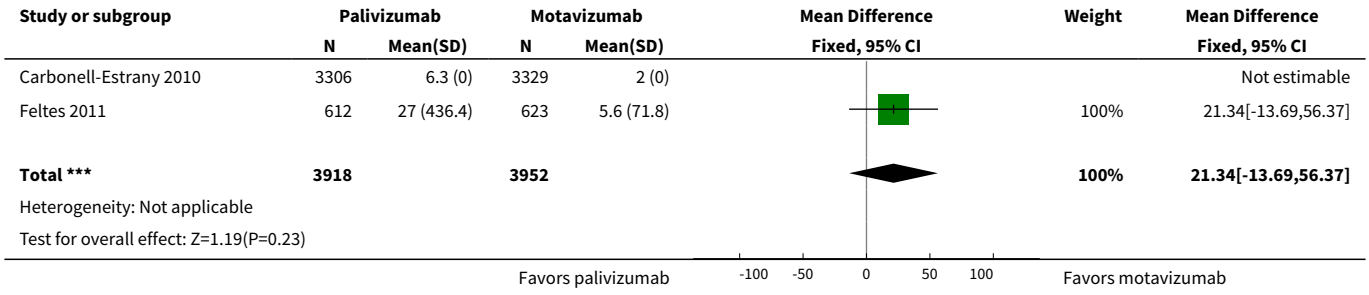
Analysis 2.4. Comparison 2 Palivizumab versus motavizumab, Outcome 4 Total RSV hospital days per 100 children.



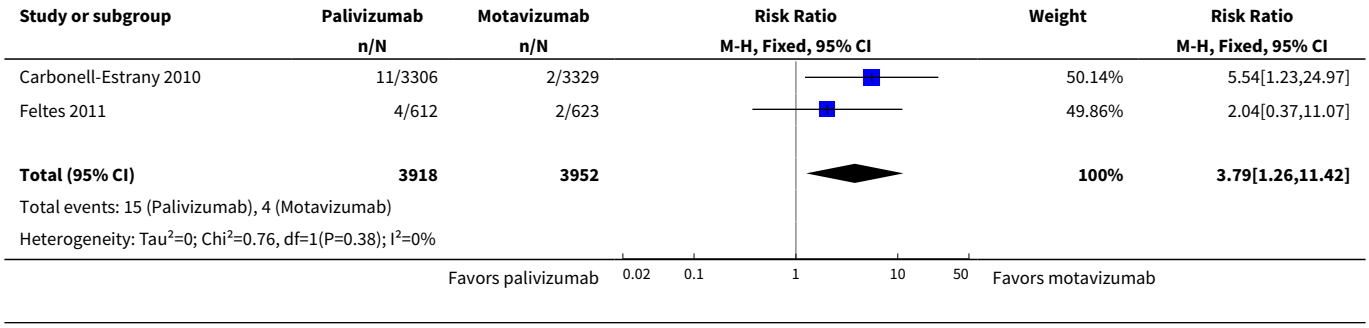
Analysis 2.5. Comparison 2 Palivizumab versus motavizumab, Outcome 5 Admission to ICU.

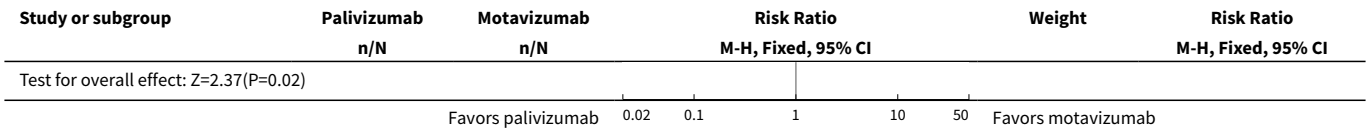


Analysis 2.6. Comparison 2 Palivizumab versus motavizumab, Outcome 6 Days in the ICU per 100 children.

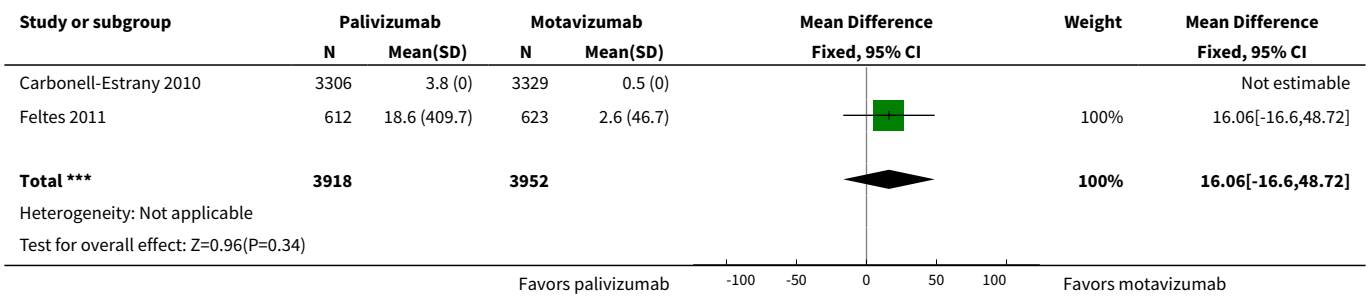


Analysis 2.7. Comparison 2 Palivizumab versus motavizumab, Outcome 7 Mechanical ventilation for RSV infection.

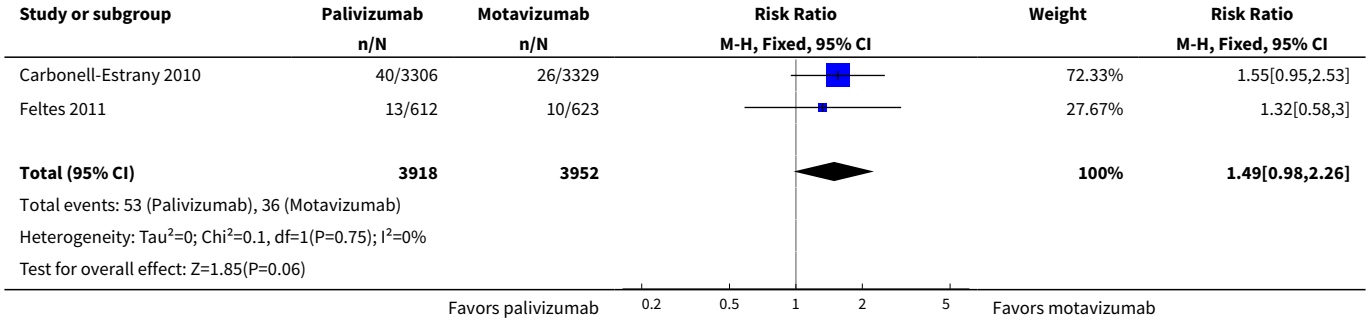




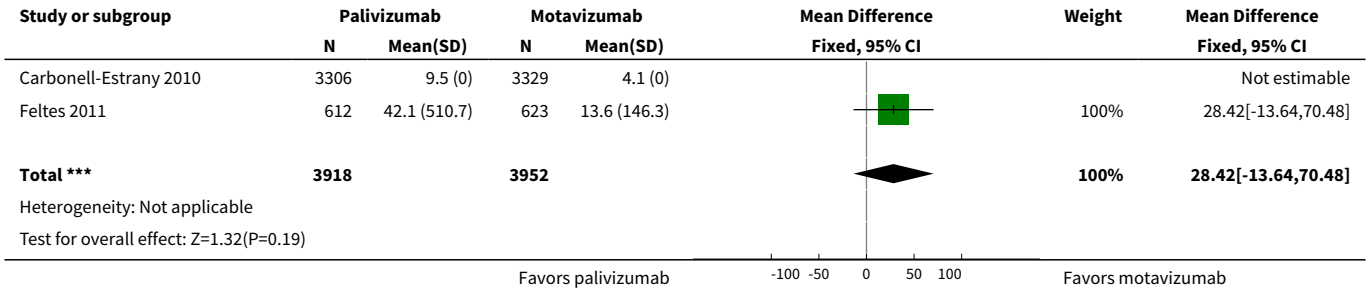
Analysis 2.8. Comparison 2 Palivizumab versus motavizumab, Outcome 8 Days of mechanical ventilation per 100 children.



Analysis 2.9. Comparison 2 Palivizumab versus motavizumab, Outcome 9 Supplemental oxygen therapy for RSV infection.



Analysis 2.10. Comparison 2 Palivizumab versus motavizumab, Outcome 10 Days of supplemental oxygen therapy per 100 children.



Analysis 2.11. Comparison 2 Palivizumab versus motavizumab, Outcome 11 Number of children reporting any AE.

Study or subgroup	Palivizumab n/N	Motavizumab n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abarca 2009	62/70	56/66		1.62%	1.04[0.91,1.19]
Carbonell-Estrany 2010	2837/3298	2839/3315		79.81%	1[0.98,1.02]
Feltes 2011	566/612	575/618		16.13%	0.99[0.96,1.03]
Fernandez 2010	64/83	135/176		2.44%	1.01[0.87,1.16]
Total (95% CI)	**4063**	**4175**		**100%**	**1[0.99,1.02]**
Total events: 3529 (Palivizumab), 3605 (Motavizumab)					
Heterogeneity: Tau^2=0; Chi^2=0.71, df=3(P=0.87); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					

Analysis 2.12. Comparison 2 Palivizumab versus motavizumab, Outcome 12 Number of children reporting related AE.

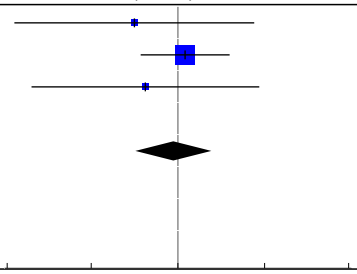
Study or subgroup	Palivizumab n/N	Motavizumab n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abarca 2009	12/70	12/66		15.49%	0.94[0.46,1.95]
Feltes 2011	54/612	51/618		63.62%	1.07[0.74,1.54]
Fernandez 2010	9/83	26/176		20.89%	0.73[0.36,1.5]
Total (95% CI)	**765**	**860**		**100%**	**0.98[0.73,1.32]**
Total events: 75 (Palivizumab), 89 (Motavizumab)					
Heterogeneity: Tau^2=0; Chi^2=0.86, df=2(P=0.65); I^2=0%					
Test for overall effect: Z=0.14(P=0.89)					

Analysis 2.13. Comparison 2 Palivizumab versus motavizumab, Outcome 13 Number of children reporting any SAE.

Study or subgroup	Palivizumab n/N	Motavizumab n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abarca 2009	1/70	4/66		0.52%	0.24[0.03,2.05]
Carbonell-Estrany 2010	506/3298	485/3315		61.34%	1.05[0.93,1.18]
Feltes 2011	304/612	292/618		36.84%	1.05[0.94,1.18]
Fernandez 2010	4/83	16/176		1.3%	0.53[0.18,1.54]
Total (95% CI)	**4063**	**4175**		**100%**	**1.04[0.96,1.13]**
Total events: 815 (Palivizumab), 797 (Motavizumab)					
Heterogeneity: Tau^2=0; Chi^2=3.41, df=3(P=0.33); I^2=11.91%					
Test for overall effect: Z=0.89(P=0.37)					

Analysis 2.14. Comparison 2 Palivizumab versus motavizumab, Outcome 14 Number of children reporting related SAE.

Study or subgroup	Palivizumab n/N	Motavizumab n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abarca 2009	0/70	1/66		18.99%	0.31[0.01,7.59]
Feltes 2011	6/612	5/618		61.21%	1.21[0.37,3.95]
Fernandez 2010	0/83	2/176		19.8%	0.42[0.02,8.68]
Total (95% CI)	**765**	**860**		**100%**	**0.88[0.32,2.43]**
Total events: 6 (Palivizumab), 8 (Motavizumab)					
Heterogeneity: Tau^2=0; Chi^2=0.91, df=2(P=0.63); I^2=0%					
Test for overall effect: Z=0.24(P=0.81)					



Favors palivizumab

Favors motavizumab

ADDITIONAL TABLES

Table 1. Characteristics of included economic evaluations

Study ID	Country	Study design	Population	Economic outcomes	Intervention[1] (doses)	Perspective	Price year	Time horizon
Bentley 2011	UK	CUA	Infants with CLD, preterm infants < 29 wGA, 29 to 32 wGA, and 33 to 35 wGA	ICER (per QALY)	Palivizumab	Payer's	GBP	Lifetime
Chirico 2009	Italy	CUA CEA	Preterm infants born at < 33 wGA, and 33 to 35 wGA, with and without BPD	ICER (per QALY and LYG)	Palivizumab (5 doses at 15 mg/kg)	Payer's	2007 EUR	Lifetime
Chiroli 2005	Italy	CEA	Children with haemodynamically significant CHD	ICER (per LYG)	Palivizumab (5 doses at 15 mg/kg)	Payer's	2004 EUR	1 year
ElHassan 2006	USA	CUA	Preterm infants born at 26 to 32 wGA without CLD	ICER (per QALY)	Palivizumab (5 doses at 15 mg/kg)	Societal	2002 USD	8 years
Embleton 2007	UK	CEA	Preterm infants born at < 32 wGA without BPD and with BPD	ICER (per hospitalization averted)	Palivizumab (5 doses at 15 mg/kg)	Societal	2005 GBP	1 year
Garcia-Altes 2010	Spain	CEA	Preterm children < 2 years old with and without CLD, children < 2 years old with CLD, and children < 5 years old with CHD	ICER (per hospitalization avoided and LYG)	Palivizumab (3 doses at 15 mg/kg)	Payer's	2008 EUR	1 year Lifetime
Hampp 2011	USA	CEA	Children < 2 years old with different combinations of risk factors (8 subgroups)	ICER (per hospitalization avoided)	Palivizumab (6 doses, 50 to 200 mg vials used)	Payer's	2010 USD	Not stated
Harris 2011	Canada	CEA	Children < 2 years old, born at 36 wGA, with haemodynamically significant CHD	ICER (per 1 day of hospitalization prevented)	Palivizumab (4.5 doses at 15 mg/kg)	Societal	2007 CAD	Not stated
Hascoet 2008	France	CEA	Preterm infants born at ≤ 32 wGA with BPD or CHD (2 subgroups)	ICER (per LYG and hospitalization averted)	Palivizumab (4.87 and 4.93 doses at 15 mg/kg)	Societal Payer's	2006 EUR	Lifetime

Table 1. Characteristics of included economic evaluations *(Continued)*

Joffe 1999	USA	CEA	Preterm infants discharged within 12 months prior to RSV season (8 risk groups)	ICER (per hospitalization averted and LYG)	Palivizumab (4 doses at 15 mg/kg)	Societal	1995 USD	Not stated
Kang 2009	Korea	CEA	Children with CHD	ICER (per LYG)	Palivizumab (5 doses)	Payer's Societal	KW	Lifetime
Lanctot 2008	Canada	CUA	Preterm infants born at 32 to 35 wGA without CLD	ICER (per LYG and QALY)	Palivizumab (5.39 doses at 15 mg/kg)	Payer's Societal	2007 CAD	Lifetime
Lazaro y de Mercado 2006	Spain	CEA CUA	Preterm infants born at 32 to 35 wGA with 2 or more risk factors	ICER (per LYG and QALY)	Palivizumab (3.88 doses at 15 mg/kg)	Societal Payer's	2006 EUR	Lifetime
Lazaro y de Mercado 2007	Spain	CEA CUA	Preterm infants born at ≤ 35 wGA and 6 months of age or younger, or ≤ 24 months old and with BPD requiring treatment	ICER (per LYG and QALY)	Palivizumab (4.1 doses at 15 mg/kg)	Societal Payer's	2006 EUR	Lifetime
Lofland 2000	USA	CEA	Preterm infants born at ≤ 35 wGA and children with BPD	ICER (per hospitalization avoided)	Palivizumab (5 doses at 15 mg/kg)	Payer's	1999 USD	1 year
Mayen-Herrera 2011	Mexico	CUA	Preterm infants < 29 wGA	ICER (per QALY)	Palivizumab (5 doses at 15 mg/kg)	Payer's	MXN	Not stated
Neovius 2011	Sweden	CUA CEA	Preterm infants born at < 29 wGA	ICER (per QALY and LYG)	Palivizumab (5 doses at 15 mg/kg)	Societal	2009 SEK	Lifetime
Nuijten 2007	UK	CEA CUA	Preterm infants born at ≤ 35 wGA, children with BPD (≤ 2 years) and children with CHD (≤ 2 years)	ICER (per LYG and QALY)	Palivizumab (4.87 doses at 15 mg/kg)	Societal Payer's	2003 GBP	Lifetime
Nuijten 2009a	Netherlands	CUA CEA	Preterm infants, preterm children, children with BPD and children with CHD	ICER (per QALY and LYG)	Palivizumab (4.87 and 4.93 doses at 15 mg/kg)	Societal	2006 EUR	Lifetime

Table 1. Characteristics of included economic evaluations *(Continued)*

Nuijten 2009b	Germany	CUA CEA	Children with haemodynamically significant CHD	ICER (per QALY and LYG)	Palivizumab (4.93 doses at 15 mg/kg)	Societal Payer's	2006 EUR	Lifetime
Nuijten 2010	Spain	CEA CUA	Children born at ≤ 32 wGA who were < 6 months old at the onset of RSV season	ICER (per LYG and QALY)	Palivizumab (4.1 doses at 15 mg/kg)	Societal Payer's	2006 EUR	Lifetime
Ravasio 2006	Italy	CEA CUA	Preterm infants < 33 wGA, and 33 to 35 wGA, with and without BPD	ICER (per LYG and QALY)	Palivizumab (5 doses at 15 mg/kg)	Payer's	2005 EUR	14 years
Raya Ortega 2006	Spain	CEA	Preterm infants born at 32 to 35 wGA	ICER (per hospitalization avoided)	Palivizumab (3.8 doses at 15 mg/kg)	Payer's	2006 EUR	1 year
Resch 2008	Austria	CEA CUA	Preterm infants born at ≤ 35 wGA, children with BPD and children with CHD	ICER (per LYG and QALY)	Palivizumab (4.87 doses at 15 mg/kg)	Societal Payer's	2006 EUR	Lifetime
Resch 2012	Austria	CEA CUA	Preterm infants ≤ 36 wGA, children with BPD and children with CHD	ICER (per LYG and QALY)	Palivizumab (3.98 doses at 15 mg/kg)	Payer's Societal	2010 EUR	Lifetime
Rietveld 2010	Netherlands	CEA	Preterm infants ≤ 28 wGA, birth weight ≤ 2500 g, having BPD, aged 0 months at the beginning of season (October)	Cost per hospitalization averted	Palivizumab	Societal	2000 EUR	1 year
Roeckl-Wiedmann 2003	Germany	CEA	Preterm infants of male gender born at ≤ 35 wGA, with siblings in day care, discharge between October and December, and with or without CLD	Cost per hospitalization averted	Palivizumab (4 to 5 doses at 15 mg/kg)	Societal	EUR	1 year
Salinas-Escudero 2012	Mexico	CEA CUA	Preterm infants < 29 wGA or 29 to 32 wGA	ICER (per LYG and QALY)	Palivizumab (4.1 doses at 15 mg/kg)	Payer's	2009 USD	18 years

Table 1. Characteristics of included economic evaluations *(Continued)*

Smart 2010	Canada	CEA CUA	Preterm infants born at 32 to 35 wGA	ICER (per LYG and QALY)	Palivizumab (5.39 doses at 15 mg/kg)	Societal Payer's	2010 CAD	Lifetime
Tam 2009	Canada	CEA CUA	Infants < 1 year of age from Baffin Island	ICER (per LYG and QALY)	Palivizumab (5 doses at 15 mg/kg)	Societal Payer's	2007 CAD	Lifetime
Vogel 2002	New Zealand	CEA	Preterm infants born at < 32 wGA	Cost per hospitalization averted	Palivizumab (3 doses at 15 mg/kg)	Societal	2000 NZD	Not stated
Wang 2011	UK	CUA	Preterm infants born at ≤ 35 wGA or children with CLD and CHD; 4 subgroup analyses: CLD, CLD/CHD, acyanotic CHD, and cyanotic CHD	ICER (per QALY)	Palivizumab (5 doses at 15 mg/kg)	Payer's	2006 GBP	Lifetime
Weiner 2012	USA	CUA	Preterm infants < 32 wGA and ≤ 6 months of age, without CLD or CHD	ICER (per QALY)	Palivizumab (≤ 5 doses at 15 mg/kg, depending on month of birth)	Societal	2010 USD	Lifetime
Yount 2004	USA	CUA CEA	Children with CHD ≤ 2 years old	ICER (per LYG and QALY)	Palivizumab (5 doses at 15 mg/kg)	Societal Payer's	2002 USD	Lifetime

BPD = bronchopulmonary dysplasia
CAD = Canadian dollar
CEA = cost-effectiveness analysis
CHD = congenital heart disease
CLD = chronic lung disease
CUA = cost-utility analysis
EUR = Euro
GBP = Great British pound
ICER = incremental cost-effectiveness ratio
KW = Korean won
LYG = life-year gained
MXN = Mexican peso
NZD = New Zealand dollar
QALY = quality-adjusted life-year
RSV = respiratory syncytial virus
SEK = Swedish krona
UK = United Kingdom
USA = United States of America
USD = United States dollar

wGA = weeks of gestational age
1Palivizumab prophylaxis was compared to no prophylaxis in all included economic evaluations.

Table 2. Economic impact of immunoprophylaxis given at neonatal period or within the first 6 months of life

Study ID	Funded by industry	Incremental effectiveness	Incremental cost	Discount rate (%) Price year	ICER reported	ICER present value at 2011 EUR
Infants born at ≤ 35 weeks of gestation without other comorbidity						
Payer's perspective						
Chirico 2009	Yes	0.088 LYG 0.159 QALY	EUR 1376.50	3% 2007 EUR	Preterms < 33 wGA: EUR 17,885.86/LYG EUR 9380.00/QALY Preterms 33 to 35 wGA: EUR 28,417.08/LYG EUR 14,937.32/QALY	Preterms < 33 wGA: EUR 19,433.61/LYG EUR 10,191.70/QALY Preterms 33 to 35 wGA: EUR 30,876.15/LYG EUR 16,229.92/QALY
Hampp 2011	No	3.29% absolute risk reduction	Any studied indication: USD 4805	NA 2010 USD	USD 302,103/hosp. averted	EUR 252,885.00/hosp. averted
Lanctot 2008	Yes	0.137 LYG 0.198 QALY	Direct costs including asthma: CAD 4140	5% 2007 CAD	Direct costs including asthma: CAD 30,230/LYG CAD 20,924/QALY	Direct costs including asthma: EUR 22,738.62/LYG EUR 15,738.76/QALY
Nuijten 2007	Yes	0.14 LYG 0.19 QALY	GBP 2858	3.5% 2003 GBP	GBP 20,344/LYG GBP 14,883/QALY	EUR 35,724.66/LYG EUR 26,134.98/QALY
Nuijten 2010	Yes	-0.33 LYL 0.49 QALY	Direct costs: EUR 6321 Direct costs with sequelae:	3% 2006 EUR	Direct costs: EUR 18,872/LYL EUR 12,814/QALY	Direct costs: EUR 21,147.66/LYL

Table 2. Economic impact of immunoprophylaxis given at neonatal period or within the first 6 months of life *(Continued)*

			EUR 3205		Direct costs with sequelae: EUR 9570/LYL EUR 6498/QALY	EUR 14,359.16/ QALY Direct costs with sequelae: EUR 10,723.99/LYL EUR 7281.55/ QALY
Ravasio 2006	Yes	Preterms < 33 wGA: 0.080 LYG 0.150 QALY Preterms 33 to 35 wGA: 0.080 LYG 0.151 QALY	Preterms < 33 wGA: EUR 1873.80 Preterms 33 to 35 wGA: EUR 2834.99	3% 2005 EUR	Preterms < 33 wGA: EUR 23,413.52/LYG EUR 12,452.72/QALY Preterms 33 to 35 wGA: EUR 35,255.90/LYG EUR 18,790.96/QALY	Preterms < 33 wGA: EUR 26,439.11/LYG EUR 14,061.91/ QALY Preterms 33 to 35 wGA: EUR 39,811.81/LYG EUR 21,219.20/ QALY
Raya Ortega 2006	No	Hospitalisation avoided: 42 cases	EUR 2,860,367	NA 2006 EUR	EUR 68,104/hosp. avoided	EUR 76,316.25/ hosp. avoided
Resch 2008	Yes	0.10 LYG 0.14 QALY	Direct costs without asthma: EUR 2955	5% 2006 EUR	Direct costs without asthma: EUR 29,558/LYG EUR 20,704/QALY	Direct costs without asthma: EUR 32,938.16/LYG EUR 23,071.65/ QALY
Resch 2012	Yes	Preterms ≤ 36 wGA: 0.09 LYG 0.13 QALY	Direct costs without wheezing: EUR 3146	5% 2010 EUR	Direct costs without wheezing: EUR 34,956/LYG EUR 26,212/QALY	Direct costs without wheezing: EUR 36,097.98/LYG EUR 27,068.32/ QALY
Salinas-Es-	Yes	Preterms < 29 wGA and 29 to 32 wGA:	Preterms < 29 wGA:	3% 2009 USD	Preterms < 29 wGA: USD 25,029/LYG	Preterms < 29 wGA:

Table 2. Economic impact of immunoprophylaxis given at neonatal period or within the first 6 months of life *(Continued)*

Leader 2012		0.12 LYG 0.16 QALY	USD 2871 Preterms 29 to 32 wGA: USD 3400		USD 17,532/QALY Preterms 29 to 32 wGA: USD 29,637/LYG USD 20,760/QALY	EUR 19,425.36/LYG EUR 13,606.84/QALY Preterms 29 to 32 wGA: EUR 23,001.70/LYG EUR 16,112.13/QALY
Smart 2010	No	0.137 LYG 0.198 QALY (from Lanctot 2008)	Not stated	5% 2010 CAD	Direct costs including asthma: CAD 20,814/QALY Direct costs without asthma: CAD 31,360/QALY	Direct costs including asthma: EUR 16,981.12/QALY Direct costs without asthma: EUR 25,585.08/QALY
Wang 2011	No	0.0072 QALY	GBP 3315	3.5% 2006 GBP	Range: GBP 78,000/QALY to GBP 965,000/QALY	Range: EUR 133,477.60/QALY to EUR 1,651,357.46/QALY
Societal perspective						
ElHassan 2006	No	Range (min to max): 0.0018 QALY (32 wGA) to 0.0060 QALY (26 wGA)	Preterms 29 to 30 wGA: USD 2449 Preterms 32 wGA: USD 6330	3% 2002 USD	Preterms 29 to 30 wGA: USD 675,780/QALY Preterms 32 wGA: USD 1,855,000/QALY	Preterms 29 to 30 wGA: EUR 894,362.54/QALY Preterms 32 wGA: EUR 2,455,003.86/QALY
Embleton 2007	No	Not stated	Preterms < 32 wGA: GBP 2550	NA 2005 GBP	Preterms < 32 wGA: GBP 40,400/hosp. averted	Preterms < 32 wGA:

Table 2. Economic impact of immunoprophylaxis given at neonatal period or within the first 6 months of life *(Continued)*

						EUR 72,780.17/ hosp. averted
Lanctot 2008	Yes	0.137 LYG 0.198 QALY	Direct and indirect including asthma: CAD 2578	5% 2007 CAD	Direct and indirect including asthma: CAD 18,825/LYG CAD 13,029/QALY	Direct and indirect including asthma: EUR 14,159.92/ LYG EUR 9800.25/ QALY
Neovius 2011	Yes	0.102 QALY 0.073 LYG	SEK 20,020	3% 2009 SEK	SEK 275,907/LYG SEK 195,420/QALY	EUR 26,448.33/LYG EUR 18,732.88/ QALY
Nuijten 2010	Yes	-0.33 LYL 0.49 QALY	Indirect costs: - EUR 3601 Total costs: - EUR 396	3% 2006 EUR	Total costs: Dominant	Total (direct and indirect) costs: Dominant
Roeckl-Wiedmann 2003	Yes	Hospitalisation averted: 125 cases	EUR 3,161,000	NA 2002 EUR	EUR 25,288/hosp. averted	EUR 29,199.27/ hosp. averted
Vogel 2002	Yes	Hospitalisation averted: 29 infants	NZD 1,090,000	NA 2000 NZD	NZD 37,000/hosp. averted	EUR 24,617.27/ hosp. averted
Weiner 2012	Yes	Preterms < 32 wGA: 0.046 QALY	Total costs: - USD 2339	3% 2010 USD	Dominant	Dominant
Infants with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD)						
Payer's perspective						
Chirico 2009	Yes	0.088 LYG 0.159 QALY	EUR 1376.50	3% 2007 EUR	EUR 4332.29/LYG EUR 2731.81/QALY	EUR 4707.18/ LYG EUR 2968.21/ QALY
Lofland 2000	Yes	5% lower incidence of hospitalization	Not stated	NA 1999 USD	USD 79,706/hosp. averted	EUR 104,456.40/ hosp. averted
Ravasio 2006	Yes	0.122 LYG	EUR 677.36	3%	EUR 5537.03/LYG	EUR 6252.55/ LYG

Table 2. Economic impact of immunoprophylaxis given at neonatal period or within the first 6 months of life *(Continued)*

		0.231 QALY		2005 EUR	EUR 2937.84/QALY	EUR 3317.48/QALY
Wang 2011	No	0.052 QALY	GBP 3315	3.5% 2006 GBP	Range: GBP 10,000/QALY to GBP 66,000/QALY	Range: EUR 17,112.51/QALY to EUR 112,942.58/QALY
Societal perspective						
Embleton 2007	No	Not stated	GBP 2663	NA 2005 GBP	GBP 54,800/hosp. averted	EUR 98,721.62/hosp. averted
Hascoet 2008	Yes	0.18 LYG Hospitalisations: not clear	EUR 4905	3% 2006 EUR	EUR 27,255/LYG	EUR 29,511.31/LYG
Nuijten 2009a	Yes	0.42 QALY 0.37 LYG	Direct costs including asthma: EUR 5369 Direct and indirect including asthma: EUR 3007	NA 2006 EUR	Direct costs including asthma: EUR 12,728/QALY EUR 14,701/LYG Direct and indirect including asthma: EUR 7130/QALY	Direct costs including asthma: EUR 13,901.85/QALY EUR 16,056.81/LYG Direct and indirect including asthma: EUR 7787.57/QALY
Rietveld 2010	No	Hospitalisation risk difference: 0.1 to 4.2	Range: EUR 550 to EUR 955	NA 2000 EUR	Range: EUR 13,190/hosp. averted to EUR 833,695/hosp. averted	Range: EUR 16,481.18/hosp. averted to EUR 1,041,719.41/hosp. averted
Roeckl-Wiedmann 2003	Yes	Hospitalisation averted: 296 cases	EUR 1,965,000	NA 2002 EUR	EUR 6639/hosp. averted	EUR 7665.85/hosp. averted
Infants with congenital heart disease (CHD)						
Payer's perspective						

Table 2. Economic impact of immunoprophylaxis given at neonatal period or within the first 6 months of life *(Continued)*

Wang 2011	No	Acyanotic CHD: 0.0670 QALY Cyanotic CHD: 0.0226 QALY	Acyanotic CHD: GBP 3285 Cyanotic CHD: 3609	3.5% 2006 GBP	Acyanotic CHD (range): GBP 100,000/QALY to GBP 266,000/QALY Cyanotic CHD (range): GBP 230,000/QALY to GBP 596,000/QALY	Acyanotic CHD (range): EUR 171,125.13/QALY to EUR 455,192.83/QALY Cyanotic CHD (range): EUR 393,587.79/QALY to EUR 1,019,905.75/QALY
Societal perspective						
Hascoet 2008	Yes	0.26 LYG Hospitalisations: not clear	EUR 5405	3% 2006 EUR	EUR 20,788/LYG Hospitalisations: not clear	EUR 22,508.93/LYG
Nuijten 2009a	Yes	1.39 QALY 1.36 LYG	Direct costs including asthma: EUR 5926 Direct and indirect including asthma: EUR 2670	NA 2006 EUR	Direct costs including asthma: EUR 4256/QALY EUR 4353/LYG Direct and indirect including asthma: Dominant	Direct costs including asthma: EUR 4648.51/QALY EUR 4754.46/LYG Direct and indirect including asthma: Dominant

CAD = Canadian dollar
EUR = Euro
ICER = incremental cost-effectiveness ratio
GBP = Great British pound
hosp. = hospitalization
LYL = life-year lost
LYG = life-year gained
NA = not applied
NZD = New Zealand dollar
QALY = quality-adjusted life-year
SEK = Swedish krona
wGA = weeks of gestational age
USD = United States dollar

Table 3. Economic impact of immunoprophylaxis given to children aged 6 months and older

Study ID	Funded by industry	Incremental effectiveness	Incremental cost	Discount rate (%) Price year	ICER reported	ICER present value at 2011 EUR
Children born at ≤ 35 weeks of gestation without other comorbidity						
Payer's perspective						
Tam 2009	Yes	Children living in rural and urban areas (all areas): 0.13 QALY Children living in high-risk areas: 0.36 QALY	Direct costs: All areas: CAD 5057 High-risk areas: CAD 119	5% 2007 CAD	Direct costs: All areas: CAD 39,435/QALY High-risk areas: CAD 334/QALY	Direct costs: All areas: EUR 29,662.50/QALY High-risk areas: EUR 251.23/QALY
Wang 2011	No	0.0072 QALY	GBP 3263	3.5% 2006 GBP	Range: GBP 383,000/QALY to GBP 54,436,000/QALY	Range: EUR 655,409.23/QALY to EUR 93,153,673.29/QALY
Societal perspective						
Tam 2009	Yes	Children living in rural and urban areas (all areas): 0.13 QALY Children living in high-risk areas: 0.36 QALY	Direct and indirect costs: All areas: CAD 4753 High-risk areas: -CAD 730	5% 2007 CAD	Direct and indirect costs: All areas: CAD 37,070/QALY High-risk areas: Dominant	Direct and indirect costs: All areas: EUR 27,883.58/QALY High-risk areas: Dominant
Children with congenital heart disease (CHD)						
Payer's perspective						
Chiroli 2005	Yes	0.5 LYG	EUR 3394.16	NA 2004 EUR	EUR 7186/LYG	EUR 8276.82/LYG
Hampp 2011	No	1.65% absolute risk reduction	Any studied indication:	NA 2010 USD	USD 823,868/hosp. averted	EUR 689,645.11/

Table 3. Economic impact of immunoprophylaxis given to children aged 6 months and older *(Continued)*

			USD 4805			hosp. averted
Nuijten 2007	Yes	Cyanotic CHD: 0.25 LYG 0.26 QALY Acyanotic CHD: 0.74 LYG 0.78 QALY	Cyanotic CHD: GBP 3904 Acyanotic CHD: GBP 2733	3.5% 2003 GBP	Cyanotic CHD: GBP 15,575/LYG GBP 14,816/QALY Acyanotic CHD: GBP 3688/LYG GBP 3512/QALY	Cyanotic CHD: EUR 27,350.15/LYG EUR 26,017.33/QALY Acyanotic CHD: EUR 6476.24/LYG EUR 6167.17/QALY
Nuijten 2009b	Yes	0.38 QALY 0.36 LYG	Payer's perspective: EUR 6364	5% 2006 EUR	Payer's perspective: EUR 16,673/QALY EUR 17,700/LYG	Payer's perspective: EUR 18,166.72/QALY EUR 19,285.73/LYG
Resch 2008	Yes	0.36 LYG 0.38 QALY	Direct costs without asthma: EUR 4349 Direct costs including asthma: EUR 3724	5% 2006 EUR	Direct costs without asthma: EUR 12,091/LYG EUR 11,390/QALY Direct costs including asthma: EUR 10,355/LYG EUR 9754/QALY	Direct costs without asthma: EUR 13,473.69/LYG EUR 12,692.53/QALY Direct costs including asthma: EUR 11,539.17/LYG EUR 10,869.44/QALY
Resch 2012	Yes	0.36 LYG 0.38 QALY	Direct costs without wheezing: EUR 3224	5% 2010 EUR	Direct costs without wheezing: EUR 8956/LYG EUR 8484/QALY	Direct costs without wheezing:

Table 3. Economic impact of immunoprophylaxis given to children aged 6 months and older *(Continued)*

						EUR 9248.58/ LYG EUR 8761.16/ QALY
Wang 2011	No	Acyanotic CHD: 0.0670 QALY Cyanotic CHD: 0.0226 QALY	Acyanotic CHD: GBP 3285 Cyanotic CHD: GBP 3609	3.5% 2006 GBP	Acyanotic CHD (range): GBP 523,000/QALY to GBP 14,545,000/QALY Cyanotic CHD (range): GBP 1,127,000/QALY to GBP 30,203,000/QALY	Acyanotic CHD (range): EUR 894,984.41/ QALY to EUR 24,890,149.50/ QALY Cyanotic CHD (range): EUR 1,928,580.16/ QALY to EUR 51,684,921.64/ QALY
Yount 2004	No	203.33 LYG QALY: not stated	USD 20,415,753	3% 2002 USD	USD 100,338/LYG USD 114,337/QALY	EUR 132,792.55/ LYG EUR 151,319.56/ QALY
Societal perspective						
Harris 2011	No	1 day of hospitalization averted	CAD 8292	NA 2007 CAD	CAD 15,514/day of hosp. averted	EUR 11,669.43/ day of hosp. averted
Nuijten 2009b	Yes	0.38 QALY 0.36 LYG	Societal perspective: EUR 3637	5% 2006 EUR	Societal perspective: EUR 9529/QALY EUR 10,116/LYG	Societal perspective: EUR 10,382.69/ QALY EUR 11,022.28/ LYG
Children with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD)						
Payer's perspective						
Hampp 2011	No	1.03% absolute risk reduction	Any studied indication: USD 4805	NA 2010 USD	USD 1,322,422/hosp. averted	EUR 1,106,975.71/

Table 3. Economic impact of immunoprophylaxis given to children aged 6 months and older *(Continued)*

						hosp. averted
Nuijten 2007	Yes	0.11 LYG 0.15 QALY	GBP 3122	3.5% 2003 GBP	GBP 28,569/LYG GBP 20,953/QALY	EUR 50,168.00/LYG EUR 36,794.08/QALY
Resch 2008	Yes	0.08 LYG 0.11 QALY	Direct costs without asthma: EUR 3527	5% 2006 EUR	Direct costs without asthma: EUR 45,369/LYG EUR 31,867/QALY	Direct costs without asthma: EUR 50,557.26/LYG EUR 35,511.21/QALY
Resch 2012	Yes	0.09 LYG 0.13 QALY	Direct costs without wheezing: EUR 3205	5% 2010 EUR	Direct costs without wheezing: EUR 35,611/LYG EUR 24,654/QALY	Direct costs without wheezing: EUR 36,774.38/LYG EUR 25,459.42/QALY
Wang 2011	No	0.052 QALY	GBP 3315	3.5% 2006 GBP	Range: GBP 29,000/QALY to GBP 3,456,000/QALY	Range: EUR 49,626.29/QALY to EUR 5,914,084.34/QALY

CAD = Canadian dollar
CHD = congenital heart disease
EUR = Euro
GBP = Great British pound
hosp. = hospitalization
ICER = incremental cost-effectiveness ratio
hosp. = hospitalization
LYG = life-year gained
NA = not applied
QALY = quality-adjusted life-year
USD = United States dollar

Table 4. Economic impact of immunoprophylaxis given to high-risk infants and children up to five years of age (born preterm, with or without bronchopulmonary dysplasia, or with congenital heart disease)

Study ID	Funded by industry	Incremental effectiveness	Incremental cost	Discount rate (%) Price year	ICER reported	ICER present value at 2011 EUR
Payer's perspective						
Garcia-Altes 2010	No	Hospitalisation averted: 0.058 LYG: not stated	Not stated	3% 2008 EUR	Range: EUR 17,337/hosp. averted to EUR 68,380/hosp. averted EUR 166,721/LYG to EUR 147,656,881/LYG	Range: EUR 18,160.68/hosp. averted to EUR 71,628.73/hosp. averted EUR 174,641.91/LYG to EUR 154,672,059.42/LYG
Societal perspective						
Joffe 1999	No	Number needed to treat: 7.4 to 152	USD 1618.14	NA for hosp. averted 3% for LYG 1995 USD	Range: USD 12,000/hosp. averted to USD 420,000/hosp. averted USD 33,000/LYG to USD 1,200,000/LYG	*Exchange rate to Euros not available for 1995*
Lazaro y de Mercado 2007	Not clear	0.13 LYG 0.18 QALY	Direct and indirect costs: EUR 726	3.5% 2006 EUR	EUR 5583/LYG EUR 4095/QALY	EUR 6256.22/LYG EUR 4588.79/QALY

EUR = Euro
hosp. = hospitalization
ICER = incremental cost-effectiveness ratio
LYG = life-year gained
NA = not applied
QALY = quality-adjusted life-year
USD = United States dollar

APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

1 Respiratory Syncytial Virus Infections/
2 respiratory syncytial viruses/ or respiratory syncytial virus, human/
3 (respiratory syncytial vir* or rsv).tw.
4 Respiratory Tract Infections/
5 (acute respiratory infection* or acute respiratory tract infection*).tw.
6 (lower respiratory tract infection* or lrti).tw.
7 exp Bronchiolitis/

8 bronchiolit*.tw.
9 pneumonia/ or pneumonia, viral/
10 pneumon*.tw.
11 or/1-10
12 palivizumab.tw,nm.
13 synagis.tw,nm.
14 exp Antibodies, Monoclonal/
15 (monoclonal antibod* or mab or mabs).tw.
16 Antiviral Agents/
17 Antibodies, Viral/
18 or/12-17
19 11 and 18

Appendix 2. Embase.com search strategy

#21. #16 AND #20 524 29 Jul 2011
#20. #17 OR #18 OR #19 858,638 29 Jul 2011
#19. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR allocat*;ti,ab OR
assign*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti AND [embase]/lim 818,196 29 Jul 2011
#18. 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp AND [embase]/lim 110,071 28 Jul 2011
#17. 'randomised controlled trial'/exp AND [embase]/lim 214,265 28 Jul 2011
#16. #10 AND #15 6,262 28 Jul 2011
#15. #11 OR #12 OR #13 OR #14 238,285 28 Jul 2011
#14. 'monoclonal antibody':ab,ti OR 'monoclonal antibodies':ab,ti OR mabs:ab,ti OR mab:ab,ti AND [embase]/lim 149,633 28 Jul 2011
#13. 'monoclonal antibody'/de OR 'virus antibody'/de OR 'antivirus agent'/de AND [embase]/lim 176,627 28 Jul 2011
#12. palivizumab:ab,ti OR synagis:ab,ti AND [embase]/lim 495 28 Jul 2011
#11. 'palivizumab'/de AND [embase]/lim 1,410 28 Jul 2011
#10. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 174,739 28 Jul 2011
#9. pneumon*:ab,ti AND [embase]/lim 104,459 28 Jul 2011
#8. 'pneumonia'/de OR 'virus pneumonia'/de AND [embase]/lim 67,722 28 Jul 2011
#7. bronchiolit*:ab,ti AND [embase]/lim 6,906 28 Jul 2011
#6. 'bronchiolitis'/exp AND [embase]/lim 9,404 28 Jul 2011
#5. 'acute respiratory infection':ab,ti OR 'acute respiratory infections':ab,ti OR 'lower respiratory tract infection':ab,ti OR 'lower respiratory tract infections':ab,ti OR lrti:ab,ti AND [embase]/lim 5,440 28 Jul 2011
#4. 'respiratory tract infection'/de AND [embase]/lim 27,544 28 Jul 2011
#3. 'respiratory syncytial virus':ab,ti OR 'respiratory syncytial viruses':ab,ti OR rsv:ab,ti AND [embase]/lim 9,483 28 Jul 2011
#2. 'respiratory syncytial pneumovirus'/de AND [embase]/lim 8,983 28 Jul 2011
#1. 'respiratory syncytial virus infection'/de AND [embase]/lim 440 28 Jul 2011

Appendix 3. CINAHL (Ebsco) search strategy

S29 S19 and S28 72
S28 S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 157323
S27 (MH "Quantitative Studies") 6708
S26 TI placebo* OR AB placebo* 17633
S25 (MH "Placebos") 5979
S24 TI random* OR AB random* 85911
S23 TI (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or trebl* mask* or tripl* mask*) OR AB (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or trebl* mask* or tripl* mask*) 12936
S22 TI clinic* trial* OR AB clinic* trial* 24108
S21 PT clinical trial 48680
S20 (MH "Clinical Trials+") 96829
S19 S11 and S18 473
S18 S12 or S13 or S14 or S15 or S16 or S17 17036
S17 (MH "Antiviral Agents") 7987
S16 (MH "Antibodies, Viral") 1337
S15 TI (monoclonal antibod* or mab or mabs) OR AB (monoclonal antibod* or mab or mabs) 2004
S14 (MH "Antibodies, Monoclonal+") 7068
S13 TI (palivizumab or synagis) OR AB (palivizumab or synagis) 108
S12 (MH "Palivizumab") 61
S11 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 14405
S10 (MH "Pneumonia, Viral") 182

S9 TI pneumon* OR AB pneumon* 8786
S8 (MH "Pneumonia") 4052
S7 TI bronchiolit* OR AB bronchiolit* 622
S6 (MH "Bronchiolitis+") 558
S5 TI (acute respiratory infection* or acute respiratory tract infection* or lower respiratory tract infection* or lrti) OR AB (acute respiratory infection* or acute respiratory tract infection* or lower respiratory tract infection* or lrti) 836
S4 (MH "Respiratory Tract Infections") 2921
S3 TI (respiratory syncytial vir* or rsv) OR AB (respiratory syncytial vir* or rsv) 748
S2 (MH "Respiratory Syncytial Viruses") 241
S1 (MH "Respiratory Syncytial Virus Infections") 701

Appendix 4. LILACS search strategy

> Search > (MH:"Respiratory Syncytial Virus Infections" OR "Infecciones por Virus Sincitial Respiratorio" OR "Infecções por Vírus Respiratório Sincicial" OR MH:"Respiratory Syncytial iruses" OR "Virus Sincitiales Respiratorios" OR "Vírus Sinciciais Respiratórios" OR MH:"Respiratory Syncytial Virus, Human" OR "Virus Sincitial Respiratorio Humano" OR "Vírus sincicial Respiratório Humano" OR "respiratory syncytial virus" OR "respiratory syncytical viruses" OR rsv OR MH:"Respiratory Tract Infections" OR "Infecciones del Sistema Respiratorio" OR "Infecções Respiratórias" OR "respiratory infection" OR "respiratory infections" OR "respiratory tract infections" OR "respiratory tract infection" OR "Infecciones del Tracto Respiratorio" OR "Infecciones Respiratorias" OR "Infecções do Trato Respiratório" OR "Infecções do Sistema Respiratório" OR MH:Bronchiolitis OR bronchiolit$ OR Bronquiolitis OR Bronquiolite OR MH:C08.127.446.135$ OR MH:C08.381.495.146.135$ OR C08.730.099.135$ OR MH:Pneumonia OR Neumonía OR pneumon$ OR Pulmonía OR "Inflamación Pulmonar" OR "Inflamação Pulmonar") AND (palivizumab OR synagis OR MH:"Antibodies, Monoclonal" OR "Anticuerpos Monoclonales" OR "Anticorpos Monoclonais" OR MH:D12.776.124.486.485.114.224$ OR MH:D12.776.124.790.651.114.224$ OR MH:D12.776.377.715.548.114.224$ OR "monoclonal antibodies" OR "monoclonal antibody" OR mab OR mabs OR MH:"Antiviral Agents" OR Antivirales OR Antivirais OR MH:"Antibodies, Viral" OR "Anticuerpos Antivirales" OR "Anticorpos Antivirais") > clinical_trials

Appendix 5. Adverse effects search strategy in MEDLINE and EMBASE

MEDLINE (Ovid)

1 palivizumab.tw,nm. (502)
2 synagis.tw,nm. (74)
3 1 or 2 (507)
4 (ae or de or po or to).fs. (3302629)
5 (safe or safety or side effect* or undesirable effect* or treatment emergent or tolerability or toxicity or adrs).tw. (634946)
6 (adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).tw. (176894)
7 4 or 5 or 6 (3675600)
8 3 and 7 (155)

EMBASE.com

#9. #7 OR #8 273 1 Aug 2011
#8. 'palivizumab'/exp/dd_ae,dd_to AND [embase]/lim 131 1 Aug 2011
#7. #3 AND #6 219 1 Aug 2011
#6. #4 OR #5 822,846 1 Aug 2011
#5. (adverse NEAR/2 (effect OR effects OR reaction OR reactions OR event OR events OR outcome OR outcomes)):ab,ti AND [embase]/lim 206,008 1 Aug 2011
#4. safe:ab,ti OR safety:ab,ti OR 'side effect':ab,ti OR 'side effects':ab,ti OR 'undesirable effect':ab,ti OR 'undesirable effects':ab,ti OR 'treatment emergent':ab,ti OR tolerability:ab,ti OR toxicity:ab,ti OR adrs:ab,ti AND [embase]/lim 700,278 1 Aug 2011
#3. #1 OR #2 1,426 1 Aug 2011
#2. palivizumab:ab,ti OR synagis:ab,ti AND [embase]/lim 495 1 Aug 2011
#1. 'palivizumab'/de AND [embase]/lim 1,410 1 Aug 2011

Appendix 6. Quality assessment of included economic evaluations by using the adapted Drummond checklist

Study ID	Well-defined question?	Competing alternatives described?	Effectiveness established?	Relevant costs and consequences (conseq.) identified?	Costs and conseq. measured accurately?	Costs and conseq. valued credibly?	Discounting performed?	Incremental analysis of costs and conseq. performed?	Sensitivity analysis performed?
Bentley 2011	Yes	Can't tell	Yes	Can't tell	Can't tell	Can't tell	Can't tell	Yes	Yes
Chirico 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Chiroli 2005	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
ElHassan 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Embleton 2007	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Garcia-Altes 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Hampp 2011	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Harris 2011	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Hascoet 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Joffe 1999	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Kang 2009	Yes	Can't tell	Can't tell	Yes	Can't tell	Can't tell	Yes	Yes	Yes
Lanctot 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lazaro y de Mercado 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lazaro y de Mercado 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Lofland 2000	Yes	Yes	Yes	Yes	Can't tell	Can't tell	No	Yes	Yes
Mayen-Herrera 2011	Yes	Yes	Yes	Can't tell	Can't tell	Can't tell	Yes	Yes	Can't tell
Neovius 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nuijten 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

(Continued)

Nuijten 2009a	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Nuijten 2009b	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Nuijten 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ravasio 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Raya Ortega 2006	Yes	Yes	Yes	No	No	No	No	Yes	Yes
Resch 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Resch 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Rietveld 2010	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Roeckl-Wiedmann 2003	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Salinas-Escudero 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Smart 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Can't tell
Tam 2009	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Vogel 2002	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Yes
Wang 2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Weiner 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Yount 2004	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Appendix 7. GRADE approach for quality assessment of included RCTs

The GRADE approach specifies four levels of quality.

1. High quality for randomised trials or double-upgraded observational studies.
2. Moderate quality for downgraded randomised trials or upgraded observational studies.
3. Low quality for double-downgraded randomised trials or observational studies.
4. Very low quality for triple-downgraded randomised trials or downgraded observational studies or case series/case reports.

Authors could downgrade randomised trial evidence by one or two levels depending on the presence of five factors.

1. Serious (- 1) or very serious (- 2) limitation to study quality.
2. Important inconsistency across the studies (- 1 or - 2).
3. Some (- 1) or major (- 2) uncertainty about directness.
4. Imprecise or sparse data (- 1 or - 2).
5. High probability of reporting bias (- 1).

Appendix 8. Money exchange rates

World currency	Base year of the evaluation	Exchange rate to Euros
Canadian dollar (CAD)	2007	0.6994194213
	2010	0.7927647938
Great British pound (GBP)	2003	1.4194561843
	2005	1.5060315583
	2006	1.4639767907
New Zealand dollar (NZD)	2000	0.4961650904
Swedish krona (SEK)	2009	0.0920369376
United States dollar (USD)	1995	Not available
	1999	0.9704846756
	2002	1.0583130490
	2009	0.7205825931
	2010	0.8114656949

Appendix 9. GDP deflators for present value calculations

Country	Base year of the evaluation	GDP deflator for 2011 adjustment
Austria	2006	1.114357
	2010	1.032669

(Continued)

Canada	2007	1.075445
	2010	1.029121
France	2006	1.082785
Germany	2002	1.154669
	2006	1.089589
Italy	2004	1.151798
	2005	1.129224
	2006	1.106326
	2007	1.086535
Mexico	2009	1.077065
Netherlands	2000	1.249521
	2006	1.092226
New Zealand	2000	1.340948
Spain	2006	1.120584
	2008	1.04751
Sweden	2009	1.041534
UK	2003	1.237114
	2005	1.196183
	2006	1.168906
USA	1999	1.350378
	2002	1.25053
	2010	1.031568

Appendix 10. Methods for present value calculations

Present value calculations are used to provide a unique measure to compare cash flows at different times. If the payments were made in the past, their value is enhanced to reflect that those payments could have earned interest in the elapsed time. The most common way of inflation adjustment uses the gross domestic product (GDP) deflator. The GDP is a monetary value of all the finished goods and services produced within country's borders in a specific time period, though GDP is usually calculated on an annual basis. It includes all of private and public consumption, government outlays, investments and exports less imports that occur within a defined territory.

In order to calculate the ICER present values at 2011 Euros, we performed two main steps: currency conversion and inflation adjustment.

Firstly, we converted the values reported in the study in their original currency to Euros at the same price year. When the information about the price year used was not stated by the authors, we took one year prior to the year of publication as a referent year. To be consistent

through studies, all the exchange rates used were taken at the same month and day: 16 June (e.g. if value was reported in 2003 USD, to convert it in Euros we used the exchange rate for 16 June 2003). To do this, we used the XE Universal Currency Converter, as it contains historical rate tables for every world currency since 1995 to present date, and is available at http://www.xe.com/ucc/. Money exchange rates used for currency conversions are presented in Appendix 8.

Once the currencies were converted to Euros, we performed the inflation adjustments by using the following formula.

Present value in 2011 EUR = Reported value converted to EUR at base year x GDP deflator

The GDP deflator is the ratio of nominal GDP (the value of aggregate final output at current market prices) to real GDP (its value at base year prices) and can be considered the most comprehensive measure of inflation, since a wide array of goods and services are included in its construction.

GDP deflator = Nominal GDP/Real GDP

For calculating the GDP deflators, we considered not only the price years reported by authors, but also the country where the economic analysis was carried out. We retrieved the World Bank Consumer Price Indexes for these calculations (available at http://data.worldbank.org/indicator/FP.CPI.TOTL). GDP deflators used for inflation adjustments are given in Appendix 9.

WHAT'S NEW

Date	Event	Description
9 June 2013	Amended	Results on mortality now included in the Abstract.

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 4, 2013

Date	Event	Description
11 August 2010	New citation required and major changes	A new review team took over this previously withdrawn protocol.
7 September 2009	Amended	Withdrawn from *The Cochrane Library* 2010, Issue 1.
13 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

TA conceived the idea for the review and searched for articles for the background section. TA and JWN completed the literature search and extracted the data for the efficacy and safety analysis. TA and BB conducted the statistical analysis of the efficacy and safety data, and interpreted the results from RCTs. BB contributed to the conception of the idea for the review, defined the statistical methods for efficacy and safety data, and contributed to analysing the results from RCTs. TA and JDR completed the literature search and extracted the data for the economic analysis. MXRR defined the methods for the review of economic evidence, verified study selection and data extraction from economic evaluations, and contributed to analysis of economics data. TA and MXRR performed present value calculations and interpreted the results from economic studies. TA and MXRR wrote the results, discussion and conclusions. All review authors critically edited and approved the review.

DECLARATIONS OF INTEREST

This review is in no way funded by commercial entities that could possibly benefit financially from its results. The review authors have no financial interest in the subject matter of the review (e.g. private clinical practice, stocks, legal advice, consultancies, employment).

TA is employed at Allergan.

BB is involved in consultancies for an international epidemiological study on the incidence and characteristics of RSV infections sponsored by Abbott (H09 - 116: RSV Survey in CEE).
MXRR has participated as co-investigator of independent clinical research studies supported in part by Abbott Laboratories, MSD, Astra-Zeneca, GlaxoSmithKline and Sanofi-Aventis.
JWN has received scholarships from the Canadian Society of Respiratory Therapists, Ikaria and the Ontario Graduate Scholarship program (none of which had any role in this review).
JDR and VBV have no potential conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol, we prespecified that we would analyse the number of children with secondary complications as one of the main outcomes. However, since different studies assessed different secondary complications (e.g. otitis media in IMpact-RSV 1998, cardiac surgery/interventional catheterisation earlier than planned in Feltes 2003), the data were not comparable and we discarded this outcome. Due to this, the main outcomes included in the final 'Summary of findings' tables differ to some extent from those prespecified by the protocol. Also, two RCTs assessed RSV-specific outpatient medically attended lower respiratory tract infections (Carbonell-Estrany 2010; Feltes 2011) and we decided to add this outcome in the review, even though we did not prespecify it in the protocol.

In the protocol, we prespecified including not only full, but also partial economic evaluations. However, we included in the review only full economic evaluations assessing cost-effectiveness or cost-utility of palivizumab prophylaxis compared to no intervention taken, due to the fact that a large number of these high-quality studies was available. With the intention of being concise, we did not report specific costs (resources) identified and considered in the obtained total cost per patient in each of the 34 included economic evaluations.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibodies, Monoclonal, Humanized [*therapeutic use]; Antiviral Agents [*therapeutic use]; Hospitalization [statistics & numerical data]; Palivizumab; Randomized Controlled Trials as Topic; Respiratory Syncytial Virus Infections [*prevention & control]

MeSH check words

Child, Preschool; Humans; Infant; Infant, Newborn