The cost-effectiveness of palivizumab in the prevention of respiratory syncytial virus bronchiolitis;

a systematic review

MSc Health Economics, Policy and Law
MSc Thesis

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This HEPL thesis is an updated and improved version of a previously published paper by the student, Maarten Blanken (first author). A short version of this paper was published in Current Respiratory Medicine Reviews Volume 7, Number 3, June 2011, a peer-reviewed Journal. The research and development of this paper was performed as an extension and during the course of the HEPL master study and adapted according to thesis guidelines.

Abstract

Background: RSV bronchiolitis is the most common cause of infant morbidity during the winter season and is associated with a large burden of disease and high costs. The cost-effectiveness of RSV immunoprophylaxis with the only available preventive treatment, palivizumab is subject of vigorous debate. It is recognised that a policy of using palivizumab for all children who meet the licensed indication is not cost-effective, but most clinicians feel that its use is justified in certain subgroups.

Objective: To systematically review the literature on the cost-effectiveness of palivizumab prophylaxis in the following subgroups: 1) preterm infants born before 32 weeks gestational age (WGA), 2) preterm infants born between 32 and 35 WGA, 3) children with chronic lung disease, and 4) children with congenital heart disease.

Methods: We searched Pubmed, EMBASE, and the latest versions of the DARE, NHS EED and HTA databases from inception to June 2012. Relevant studies were first selected on title and abstract and full text of the selected papers was reviewed.

Results: Nineteen studies evaluating the cost-effectiveness of palivizumab performed in 13 different countries were included. The cost-effectiveness of palivizumab for the subgroups of children born before 32 WGA, children born between 32 and 35 WGA, children with chronic lung disease (CLD), and children with congenital heart disease was studied in 9, 9, 8, and 7 studies, respectively. The incremental cost-effectiveness ratios varied considerably both within and between subgroups. Sensitivity analyses showed that cost-effectiveness was mainly driven by the mortality rate due to RSV infection. Differences in hospitalisation rates, industry sponsoring and study year were also associated with differences in cost-effectiveness, but these differences could be attributed to differences in mortality rates.

Conclusion: The cost-effectiveness of prophylactic treatment of RSV infection with palivizumab in subgroups varies considerably. The cost-effectiveness is mainly sensitive to mortality rates of RSV infection. This systematic review indicates that future research should focus on the major uncertainties in cost-effectiveness, particularly RSV-related mortality rate, high-risk populations and long term sequelae. Interpretation of RSV cost-effectiveness studies should be done cautiously due to transferability issues.

Key Words: Respiratory syncytial virus, palivizumab, prophylaxis, cost-effectiveness

LIST OF DEFINITIONS

Economic evaluation: Economic evaluation is the comparison of two or more alternative courses of action in terms of both their costs and consequences (1). Economists usually distinguish several types of economic evaluation, differing in how consequences are measured: cost-minimization analysis, cost-effectiveness analysis and cost-utility analysis.

Cost-effectiveness analysis (CEA): is a form of economic analysis that compares the relative costs and outcomes (effects) of two or more courses of action. Typically the CEA is expressed in terms of a ratio where the denominator is a gain in health from a measure (years of life, premature births averted, sight-years gained) and the numerator is the cost associated with the health gain. The most commonly used outcome measure is quality-adjusted life years (QALY).

Cost-utility analysis (CUA): is a form of economic analysis used to guide budget decisions. The purpose of CUA is to estimate the ratio between the cost of a health-related intervention and the benefit it produces in terms of the number of years lived in full health by the beneficiaries.

Payer's perspective: a perspective that can be used in a health economic evaluation to count all costs that are relevant from the viewpoint of the health payer. In an analysis conducted from the payer's perspective for example, the patients travel costs are excluded as well as indirect costs due to production losses. For example, this viewpoint is used in the study by Reeve et al. where only direct medical cost are considered(2).

Societal perspective: a perspective from which an economic evaluation is conducted that takes into account all costs to society as a whole, regardless who incurs them. It includes all costs and effects that are relevant as seen from the viewpoint of society, including indirect costs caused by the disease under investigation, such as production losses. For example, this viewpoint is used in the study by Nuijten et al. where not only direct medical cost but also costs associated with asthma, non medical costs and long term indirect costs are taken into account(3).

Discounting: Economic concept to handle time-preference, using a method of calculation by which costs and benefits occurring at different moments in time can be compared. Discounting converts the value of future costs and benefits into their present value to account for positive time preferences for benefits (preference for current benefits as compared to future benefits) and negative time preferences for costs (preference for future costs as compared to current costs).

Incremental cost-effectiveness ratio (ICER): is defined as the ratio of the change in costs of a therapeutic intervention (compared to the alternative, such as doing nothing or using the best available alternative treatment) to the change in effects of the intervention.

Hospital admission prevented (HAP): is used to describe the prevention of a single hospital admission by a given intervention. This outcome is regarded inferior to both QALY and LYG and mainly used as surrogate outcome due to relevance to clinical practice.

Quality adjusted life year (QALY): is a measure of disease burden and is based on the number of years of life that would be added by the intervention. Each year in perfect health is assigned the value of 1.0 down to a value of 0.0 for death. If the extra years would not be lived in full health, for example if the patient would be blind or have to use a wheelchair, then the extra life-years are given a value between 0 and 1 to account for this.

Life year gained (LYG): refers to a single year prolongation of a patient's life by means of a certain intervention. In contrast with QALY morbidity is not included in this measure.

Introduction

RSV bronchiolitis is the most common cause of infant morbidity during the winter season and is associated with a large burden of disease and high costs. Most children are infected with RSV during the first year of life. A recent population-based study showed that 30-50% of all children require medical attention for RSV bronchiolitis in the first year of life(4). RSV infection is worldwide the most common cause of infant morbidity during the winter season and is associated with a large burden of disease and high costs. Each year, 10-14% of all children below 1 year of age require medical care for RSV bronchiolitis in the Netherlands adding up to about 25,000 infants each year (5). A total of 1,500-2,000 of these children are hospitalised with RSV bronchiolitis in the Netherlands annually, with corresponding mean hospitalisation costs of € 3,000-4,000 per patient (6-8).

The disease typically begins with signs of common cold, followed after a few days by coughing, dyspnoea and an expiratory wheeze (9). Hospitalization in Europe and the United States is estimated to be 1-3%(10) of all infants aged less than 13 months. Of these hospitalized children, about 10% of infants require mechanical ventilation at a Paediatric Intensive Care Unit(11-13). After the acute illness, approximately 50% of children with RSV bronchiolitis will develop recurrent episodes of wheeze up to school age which is associated with reduced health-related quality of life(14;15). Although the burden of disease is considerable, RSV-associated mortality in healthy term infants is probably low, but published estimates vary between 0 and 8% (16-19).

Important risk factors for RSV bronchiolitis are prematurity with or without chronic lung disease, congenital heart disease, Down syndrome and immunodeficiencies (20-23). Long-term airway morbidity during childhood occurs in 30-70% of hospitalized infants with RSV LRTI, which is referred to as post-bronchiolitis wheeze. The clinical picture of post-bronchiolitis wheeze is recurrent episodes of wheezing, generally associated with viral upper respiratory tract infection (14). It has been shown that post-bronchiolitis wheeze is associated with decreased health-related quality of life over a broad range of domains, including lung, gastrointestinal tract and sleeping domain (24).

The only effective intervention to prevent RSV bronchiolitis is passive immunoprophylaxis with palivizumab, a monoclonal antibody against the F-protein of RSV. However, this is costly and requires monthly intramuscular injections. Due to high costs RSV immunoprophylaxis is only registered for use in selected populations during the first year of life with the exception of children with chronic lung disease (CLD) on home oxygen (2 years). The average medical cost of palivizumab prophylaxis at the recommended dose of 15 mg/kg is 4,600 Euro during a 5 month prophylaxis period per patient, which currently leads to a total of 14 million Euro for RSV prevention annually (online GIPdatabank). The efficacy of

palivizumab depends on the risk groups and varies from 39 to 80% in chronic lung disease and late preterms, respectively(25;26). The average medical cost of palivizumab prophylaxis at the recommended dose of 15 mg/kg is 4400 Euro during a 5 month prophylaxis period per patient(27).

Due to these high costs, the cost-effectiveness of palivizumab is subject of vigorous debate(28;29). Most countries, like The Netherlands, have therefore restricted this treatment to specific high risk groups, i.e. preterm infants born before 32 weeks gestational age and younger than 6 months at the start of the RSV season, children with hemodynamically significant congenital heart disease (CHD), and children with CLD.

However, even the cost-effectiveness studies performed within these high risk groups used different perspectives, outcomes (HAP, QALY or LYG), populations, follow-up, and extra risk factors. The objective of this study therefore is to systematically review the literature on the cost-effectiveness of palivizumab prophylaxis in the following subgroups: 1) preterm infants born before 32 weeks gestational age (WGA), 2) preterm infants born between 32 and 35 WGA, 3) children with CLD, and 4) children with CHD.

Methods

Search strategy

We searched Pubmed and EMBASE from inception to week 15 2012 and the latest versions of the DARE, NHS EED and HTA databases using the terms cost, cost-effectiveness, respiratory syncytial virus and palivizumab (see Appendix for the complete search syntax) to identify articles reporting on the cost-effectiveness of palivizumab. In addition, a reference and related article search was performed.

Study selection

We screened identified titles and abstracts without blinding to authorship or journal. Potentially relevant studies were obtained and the full text examined. Criteria for inclusion in this survey were:

- Respiratory syncytial virus
- Palivizumab
- Children
- Cost-utility analysis using quality adjusted life years (QALY) or cost-effectiveness analysis using either life years gained (LYG) or hospitalization prevented (HAP)
- Analysis with comparator
- ICER

Data extraction and synthesis

Information was gathered for each study on study design, population, and ICER outcomes measured. Because there was significant heterogeneity between the identified studies, pooling of the major outcomes was not possible. The results of the studies are therefore described separately. Where possible ICER values where used which included direct medical and non-medical costs and mortality consequences. The following subgroups where analysed separately 1) preterm infants born before 32 WGA, 2) preterm infants born between 32 and 35 WGA, 3) children with CLD, and 4) children with CHD.

Study quality

Two authors (MB, MR) independently assessed the quality of all included studies using Drummond's check-list for assessing economic evaluations(1)**.** Ten specific domains were addressed, i.e. research question, competing alternatives, effectiveness, relevant cost and consequences, cost and consequence measures, unit measures, values, discounting, incremental analysis, sensitivity analysis and overall considerations. By answering pre-specified questions we reported the execution of the study and judged the quality for each domain. The original quality scores, between brackets, were adapted to Good (Yes),

Acceptable (Yes) and Poor (No/Can't tell) to be able to make a further quality assessment possible for the quality score "Yes" in the original Drummond score model. The new quality scores for each domain was 1) good, 2) acceptable, or 3) poor or unclear. Disagreement was resolved by discussion (MB, MR).

Analyses

All ICER values were inflated to 2009 values using country specific inflation rates, and converted to Euro values using mean conversion rates for the currency in the year of publication with foreign exchange databases(30-36).

To study the influence of some important factors we performed sensitivity analyses with these factors, i.e. hospitalisation rates, mortality rates and sponsoring, study year and country of origin. For the comparison analyses, only the ICER values for the preterm children born before 35 WGA are shown because the number of studies focusing on the CLD and CHD subgroup were too low. Because no internationally accepted threshold for cost-effectiveness is available no threshold was adopted but cost-effectiveness levels were derived from the conclusions of the authors in the selected papers.

Results

Study selection

Our search retrieved a total of 339 articles. A total of 19 articles were included in this review (Figure 1). No additional studies were identified by checking the bibliographies of the selected studies. Main reasons to exclude studies were that the articles did not cover respiratory syncytial virus or palivizumab or because the articles did not include an economic evaluation. Other studies that were not included were studies about elderly and replicate studies.

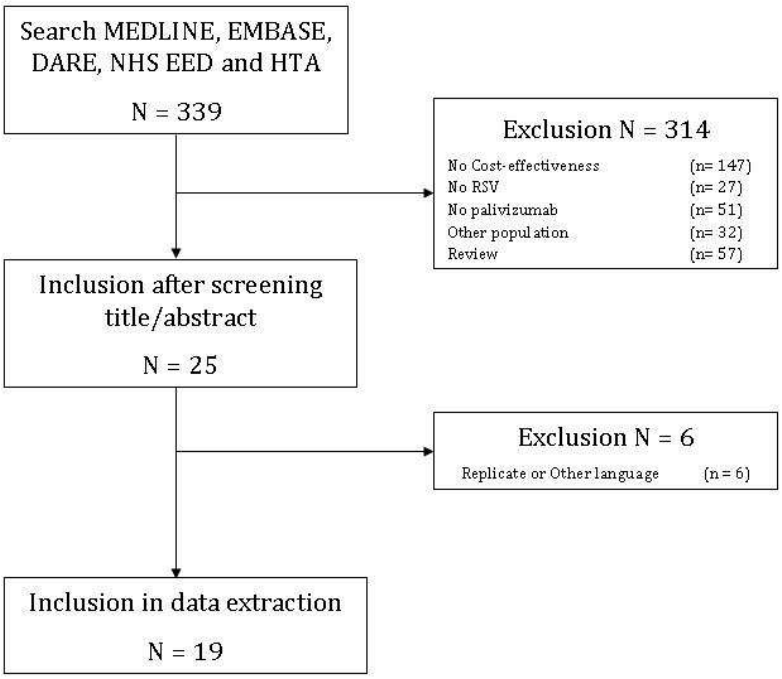

Figure 1. Flow chart showing identification of economic evaluations.

Study quality

Figure 2 shows the results of the quality assessment according to Drummond's check-list for assessing economic evaluations. All studies performed incremental analysis as this was an inclusion criterion. In 3 out of 19 studies (16%) the research question was not accurately described. In two studies (10%) the effectiveness of palivizumab was not adequately covered. Different cost and consequences were well described by most studies (69%). Only three studies (16%) did not use discounting, and two other studies did not describe it properly.

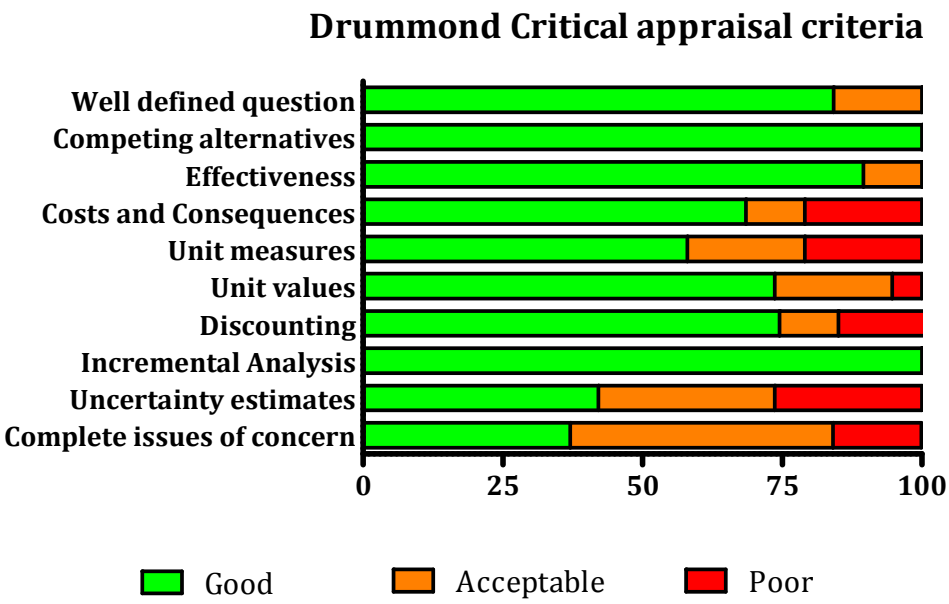

Figure 2. Critical appraisal of the included studies using Drummond criteria (n=19) adapted to Good (Yes), Acceptable (Can't tell) and Poor (No/Can't tell) (1)**.**

The reported outcomes of the included studies differed considerably. Of the 19 articles, 8 reported ICER per HAP, 2 reported ICER per QALY, 1 reported both ICER per HAP and ICER per LYG and 8 reported both ICER per QALY and ICER per LYG. The ICERs vary from € 7,372 to 344,617/HAP, from € 7,067 to € 104,532/QALY and from € 4,332 to € 985,485/LYG.

Effectiveness

Eleven studies derived the clinical effectiveness of palivizumab from the previously performed phase III trials (25;26). For preterm children, children with CHD and children with CLD they reported a reduction of the hospitalisation rate of 78%, 45% and 39% with palivizumab treatment versus no-prophylaxis, respectively. The effectiveness used in the other 8 studies was based on longitudinal birth cohort studies.

Costs

Nine studies did only report on direct costs associated with respiratory syncytial virus infection. The other nine studies reported on both direct and indirect costs.

Comparison of subgroups

Figure 3a-d and Table 1 show the ICER values of the different subgroups. Eight studies (2;37-43) assessed the cost-effectiveness of palivizumab for the subgroup of children born before 32 WGA. The ICER values varied from €9,380 to €1,041742/QALY. Of these eight studies

only two studies considered treatment with palivizumab to be cost-effective with an ICER of respectively €9,380 and 12,814/QALY (Table 1). Nine studies assessed the cost-effectiveness for the subgroup of children born between 32 and 35 WGA. Five studies(3;37;41;44;45) considered treatment with palivizumab for this subgroup to be cost-effective with ICER values ranging from €11,759 to €23,060/QALY. The other five studies(39;46-49) concluded that prophylactic treatment is not cost-effective with ICER values varying from €31,522 to €985,485/LYG (Table 2). Eight studies (37;39;41-44;48;49) assessed the cost-effectiveness of palivizumab for the subgroup of children with chronic lung disease. The ICER values varied from €2,731 to €32,465/QALY, €4,332 to €167,168/LYG and €7,372 to €68,448/HAP. Four studies considered palivizumab prophylaxis in this subgroup cost-effective (Table 3). Seven studies assessed the cost-effectiveness of palivizumab for the subgroup of children with congenital heart disease(3;41;44;50-53). Four studies considered treatment with palivizumab to be cost-effective with ICER values varying from €7,067 to 22,955/QALY. The other three studies reported that palivizumab for this subgroup is not cost-effective with ICER of €165,545/HAP , 188.900/HAP and 104,532/QALY, respectively (Table 4).

	<32 WGA	32-35 WGA	CHD	BPD
HAP	38 404-130 591	37 427-344617	165 545-188 906	7 372-68 448
LYG	17 886-362 755	16 780-985 485	12 139-91 743	4 332-167 168
QALY	9 380-104 1742	11 759-20 236	7067-104 532	2 731-32 465

Table 1.ICER ranges of the selected subgroups. All values in 2009 € values. WGA: weeks gestational age; CHD: congenital heart disease; BPD: bronchopulmonary dysplasia.

Author, publication year	country	N	CEA / CUA	hospitalisation palivizumab group	hospitalisation control group	reduction hospitalisation	hospital mortality	time horizon	perspective	ICER	Conversion and inflation to 2009 € values
Chirico, 2009	Italy	model	CEA/CUA	2.0%	10.3%	80.0%	4.0%	2 years	payers	€17,886/LYG^ €9,380/QALY^	€17,886/LYG^ €9,380/QALY^
Elhassan, 2006‡	USA	model	CUA	2.9%	13.2%	78.0%	n.a.	8 years	societal	$1,228,260/QALY	€1,041,742/QALY
Joffe, 1999§	USA	1721	CEA	2.5%	5.5%	55.0%	1.2%	lifetime	societal	$108,000/HAP $300,000/LYG	€130,591/HAP €362,755/LYG
Nuijten, 2009	Spain	model	CEA/CUA	3.9%	13.4%	71.0%	1.4%	lifetime	payers	€18,872/LYG €12,814/QALY	€18,872/LYG €12,814/QALY
Reeve, 2006	Australia	12171	CEA	0.8%	4.0%	80.0%	n.a.	1 year	payers	A$98,818/HAP	€64,659/HAP
Resch, 2008	Austria	model	CEA/CUA	1.8%	8.1%	78.0%	8.1%	lifetime	payers	€41,242/LYG €28,939/QALY	€41,406/LYG €29,054/QALY
Salinas, 2012	Mexico	model	CUA	4.9%	10.1%	51.5%	0.23% / 0.99%°	lifetime	payers	$27,333/LYG $19,146/QALY	
Stevens, 2000	USA	1029	CEA	4.1%	9.2%	55.0%	n.a.	1 year	payers	$32,792/HAP	€44,326/HAP
Vogel, 2002	New Zealand	437	CEA	2.9%	13.4%	78.0%	n.a.	1 year	societal	NZ$65,000/HAP	€38,404/HAP

Table 1. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children born before 32 weeks gestational age.

§= ≤32WGA values derived from the mean of groups C and D ‡= values derived from mean values of groups 26 WGA, 27-28WGA, 29-30WGA and 31-32WGA. ^= asthma costs were included in the ICER. ° different mortality rates adopted for palivizumab and control group respectively (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

Author, publication year	country	N	CEA / CUA	hospitalisation palivizumab	hospitalisation control	reduction hospitalisation	hospital mortality	time horizon	perspective	ICER	Conversion and inflation to 2009 € values
Chirico, 2009	Italy	model	CEA/CUA	1.5%	9.8%	85.0%	4.0%	2 years	payers	€28,417/LYG^ €14,937/QALY^	€28,417/LYG^ €14,937/QALY^
Joffe, 1999 §	USA	1721	CEA	1.0%	2.2%	55.0%	1.2%	lifetime	societal	$285,000/HAP $815,000/LYG	€344,617/HAP €985,485/LYG
Lanctot, 2008	Canada	model	CEA/CUA	1.8%	10.0%	80.0%	8.1%	lifetime	payers	CAN$ 44,237/LYG CAN$ 30,618/QALY	€29,053/LYG €20,109/QALY
Resch, 2008	Austria	model	CEA/CUA	1.8%	8.1%	78.0%	8.1%	lifetime	payers	€16,714/LYG €11,713/QALY	€16,780/LYG €11,759/QALY
Lofland, 2000†	USA	model	CEA	5.0%	12.0%	59.0%	n.a.	1 year	payers	$53,777/HAP	€72,693/HAP
Nuijten, 2009	Netherlands	model	CUA	4.8%	10.6%	55.0%	8.1%	lifetime	societal	€20,236/QALY^	€20,236/QALY^
Nuijten, 2007	UK	model	CEA/CUA	1.8%	8.1%	78.0%	8.1%	lifetime	payers	£20,344/LYG^ £14,883/QALY^	€31,522/LYG^ €23,060/QALY^
Rodriguez, 2008	Argentina	159	CEA	3.5%	16.5%	79.0%	n.a.	1 year	payers	$51,550/HAP	€37,427/HAP
Roeckl-Wiedmann, 2003^^	Germany	model	CEA	5.8%	12.8%	55.0%	1.2%	1 year	societal	€94,270/HAP	€104,691/HAP

Table 2. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children born before between 32 and 35 weeks gestational age.

Data described are derived from the subgroups of children born <35 WGA and children born between 32 and 35 WGA. §= 32-35 values derived from the mean of groups G and H, CLD values derived from groups A, B, E and F. †= ≤35WGA values used most comparable to 55% efficacy rate for the preterm subgroup; ICER values included indirect medical costs (asthma costs). ^= asthma costs were included in the ICER. ^^= all children had one of the risk factors: male, siblings or birth month Oct-Dec., ≤35WGA values were derived from the mean of groups B to D. (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

Author, publication year	country	N	CEA / CUA	hospitalisation palivizumab group	hospitalisation control group	reduction hospitalisation	hospital mortality	time horizon	perspective	ICER	Conversion and inflation to 2009 € values
Chirico, 2009	Italy	model	CEA/CUA	5.6%	18.4%	70.0%	4.0%	2 years	payers	€4,332/LYG^ €2,731/QALY^	€4,332/LYG^ €2,731/QALY^
Joffe, 1999*	USA	1721	CEA	5.7%	12.7%	55.0%	1.2%	lifetime	societal	$49,750/HAP $138,250/LYG	€55,319/HAP €167,168/LYG
Nuijten, 2007	UK	model	CEA/CUA	7.9%	12.8%	39.0%	8.1%	lifetime	payers	£28,569/LYG^ £20,953/QALY^	€44,266/LYG^ €32,465/QALY^
Resch, 2008	Austria	model	CEA/CUA	7.9%	12.8%	39.0%	8.1%	lifetime	payers	€45,369/LYG €31,867/QALY	€45,550/LYG €31,994/QALY
Rodriguez, 2008	Argentina	159	CEA	16.5%	28.0%	41.0%	n.a.	1 year	payers	$32,089/HAP	€23,297/HAP
Roeckl-Wiedmann, 2003^^	Germany	model	CEA	24.3%	53.9%	55.0%	1.2%	1 year	societal	€6,639/HAP	€7,372/HAP
Stevens, 2000	USA	1029	CEA	14.8%	24.4%	39.0%	n.a.	1 year	payers	$16,851/HAP	€22,778/HAP
Vogel, 2002	New Zealand	437	CEA	10.0%	16.5%	39.0%	n.a.	1 year	societal	NZ$115,850/HAP	€68,448/HAP

Table 3. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children with bronchopulmonary dysplasia (BPD) or chronic lung disease (CLD).

§= CLD values derived from groups A, B, E and F. *= defined as ≥ 28 days oxygen. ^= asthma costs were included in the ICER. ^^= all children had one of the risk factors: male, siblings or birth month Oct-Dec. Children in the CLD group had all three risk factors. CLD values were derived from group A. (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

Author, publication year	country	N	CEA / CUA	hospitalisation palivizumab group	hospitalisation control group	reduction hospitalisation	hospital mortality	time horizon	perspective	ICER	Conversion and inflation to 2009 € values
Harris, 2011	Canada	704	CEA	1.7%	2.9%	41.4%	5.9%	1 year	societal	$188,906/HAP ~	$188,906/HAP ~
Meberg, 2006	Norway	43470	CEA	5.0%	9.2%	45.0%	n.a.	1 year	payers	$195,000/HAP	€165,545/HAP
Nuijten, 2009	Germany	model	CEA/CUA	5.3%	9.7%	45.0%	4.5%**	lifetime	societal	€19,391/LYG €18,266/QALY	€19,391/LYG €18,266/QALY
Nuijten, 2009	Netherlands	model	CUA	5.3%	9.7%	45.0%	4.5%**	lifetime	societal	€7,067/QALY^	€7,067/QALY^
Nuijten, 2007	UK	model	CEA/CUA	5.6%	7.9%	29.0%	4.5%	lifetime	payers	£15,575/LYG^ £14,816/QALY^	€24,132/LYG^ €22,955/QALY^
Resch, 2008	Austria	model	CEA/CUA	5.3%	9.7%	45.0%	4.5%**	lifetime	payers	€12,091/LYG €11,390/QALY	€12,139/LYG €11,435/QALY
Yount, 2004	USA	model	CEA/CUA	5.3%	9.7%	45.0%	3.0%	lifetime	societal	$100,338/LYG $114,337/QALY	€91,734/LYG €104,532/QALY

Table 4. Summary of study characteristics of the systematic review of economic evaluations of palivizumab for the subgroup of children with congenital heart disease (CHD)

**= based on analysis by Nuijten et al. (Nuijten et al. Pharmacoeconomics 07). ~ derived from the mean hospitalisation duration and the incremental cost to prevent 1 day of hospitalisation ^= asthma costs were included in the ICER. (model= decision analytical model; n.a.= not applicable; CEA= cost-effectiveness analysis, CUA= cost-utility analysis, ICER= incremental cost-effectiveness ratio, LYG= life years gained, QALY=quality adjusted life year, HAP= hospital admission prevented)

Sensitivity analyses

The results of our sensitivity analyses are shown in figures 4-9. Figure 4 shows the relation between the hospitalisation rate and the cost-effectiveness for the subgroup of children born before 32 WGA and children born between 32 and 35 WGA. Studies adopting an efficacy rate of approximately 80% for prophylactic treatment tend to be more cost-effective than studies using an efficacy rate of 55% as derived from the IMpact trial(25).

Figure 5 shows the relation between the mortality rate and cost-effectiveness. The mortality rates for children hospitalized with RSV infection varied from 0.5 to 8.1 %, and especially the latter rate has a tremendous effect on the cost-effectiveness. Studies with 8.1% mortality rate tend to be more cost-effective than studies using lower mortality rates. Figure 6 shows the relation between potential sponsoring by pharmaceutical companies and the cost-effectiveness. Sponsored studies show a tendency to be more cost-effective. Figure 7 shows the relation between year of publication and cost-effectiveness. Economic evaluations from recent years tend to be more cost-effective. Figure 8 shows the geographic location of the various economic evaluations and the outcome of the analyses. The majority of studies performed in Europe appear to show more cost-effectiveness than the studies from America.

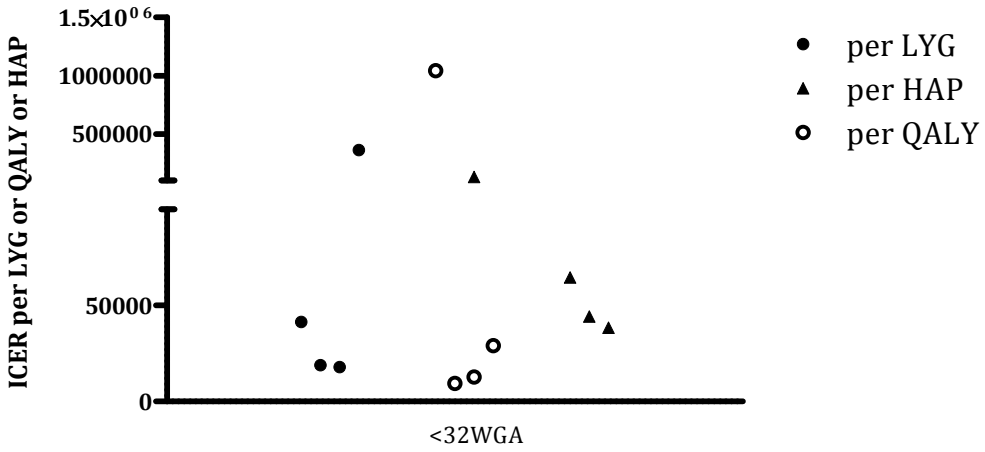

Figure 3a. The cost-effectiveness of palivizumab for the subgroup of children born before 32 weeks gestational age.

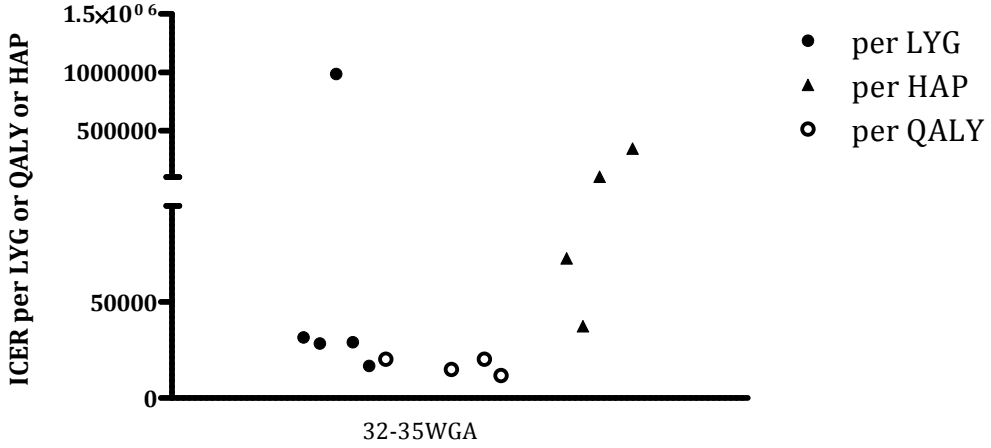

Figure 3b. The cost-effectiveness of palivizumab for the subgroup of children born at 32 - 35 weeks gestational age.

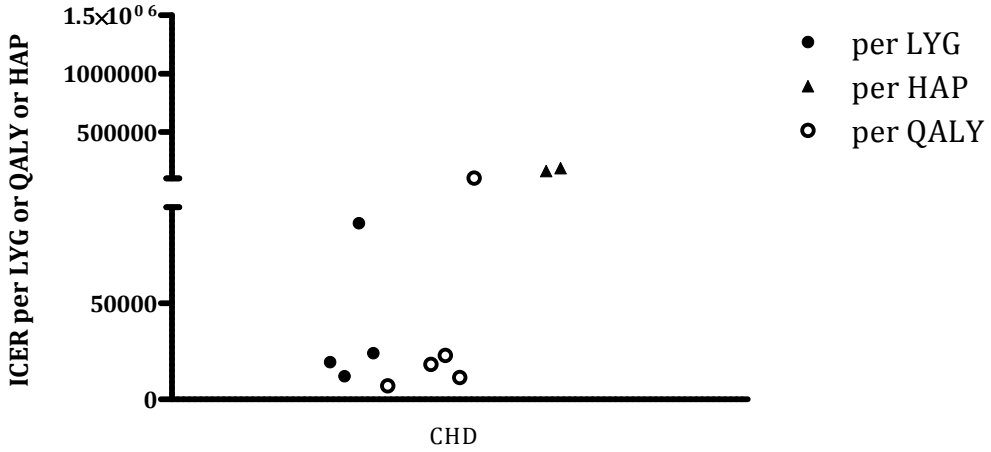

Figure 3c. The cost-effectiveness of palivizumab for the subgroup of children with congenital heart disease.

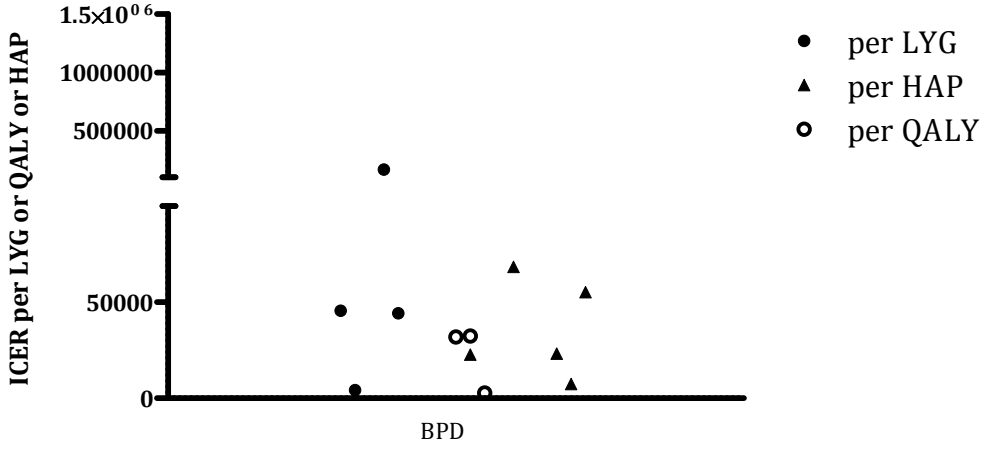

Figure 3d. The cost-effectiveness of palivizumab for the subgroup of children with bronchopulmonary dysplasia.

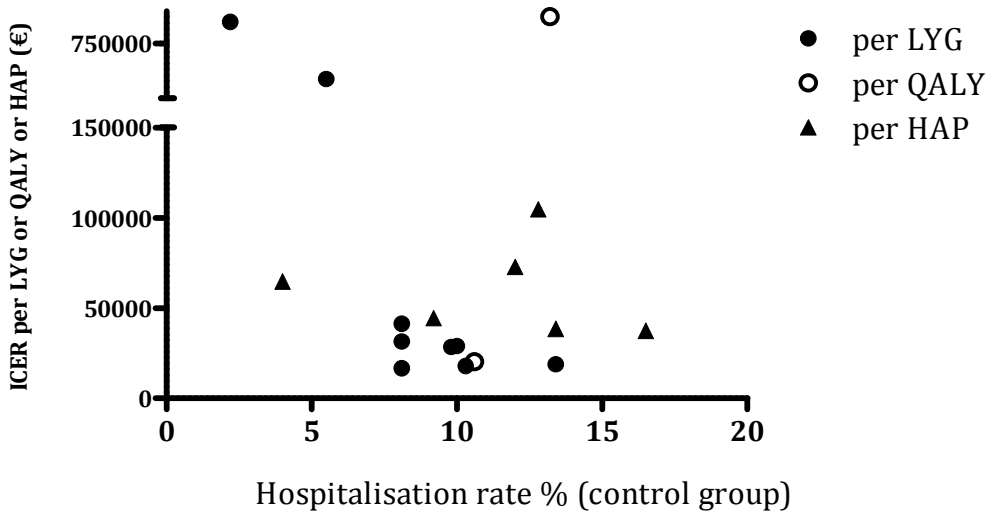

Figure 4. The relation between the hospitalisation rates used in the economic analyses and the measured ICER values for the subgroup of children born before 35 weeks gestational age.

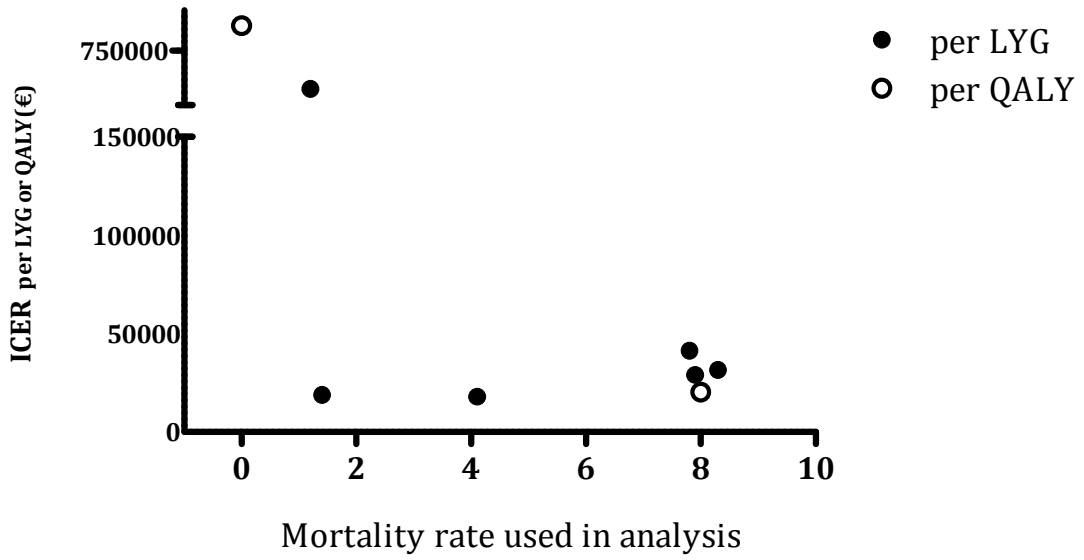

Figure 5. The relation between the mortality rate for hospitalised children in the economic analysis and the measured ICER values for the subgroup of children born before 35 weeks gestational age.

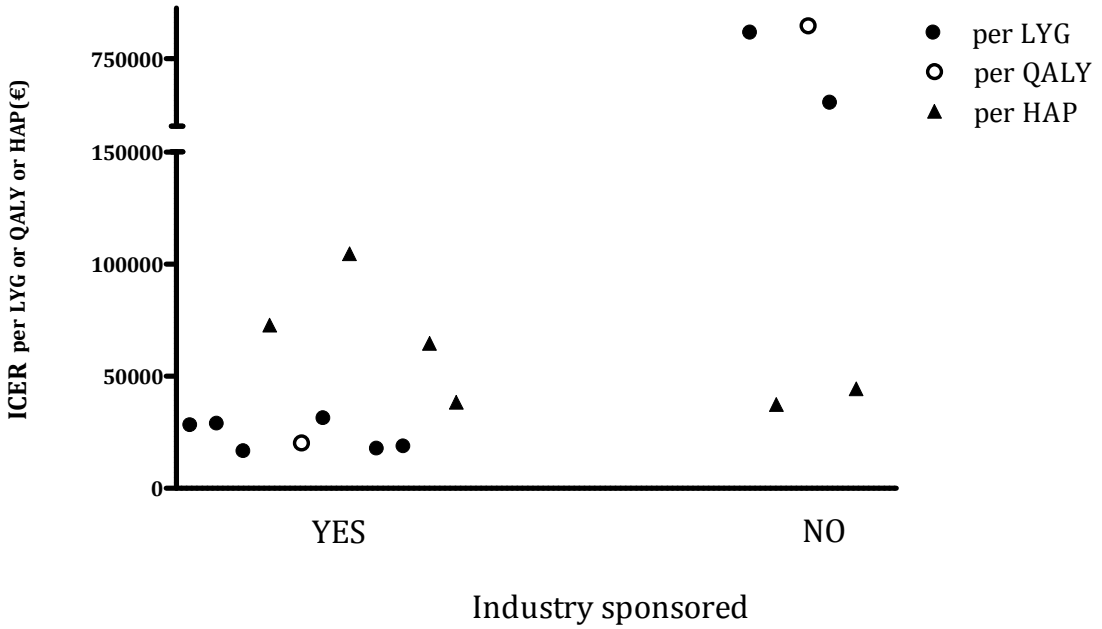

Figure 6. The relation between the economic analysis sponsored by the pharmaceutical industry and the measured ICER values for the subgroup of children born before 35 weeks gestational age.

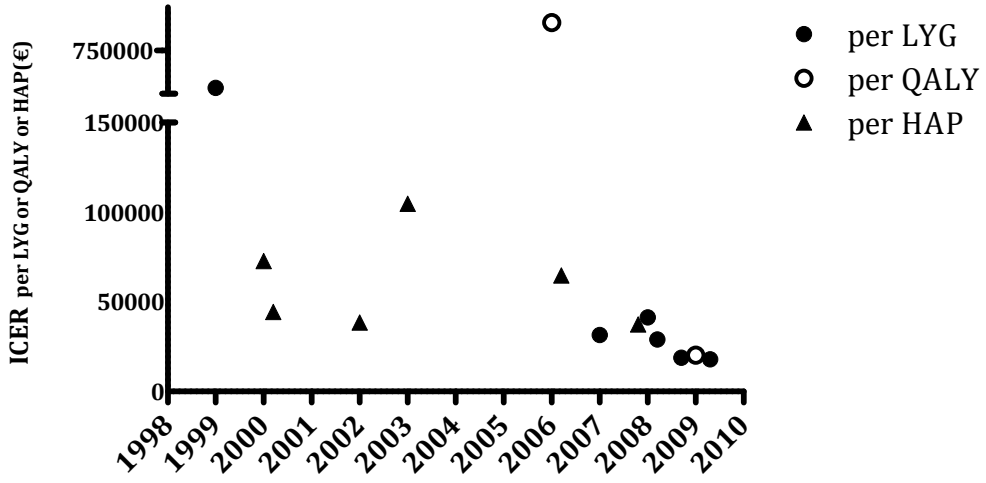

Figure 7. The relation between the cost-effectiveness of palivizumab and the year of publication for the subgroup of children born before 35 weeks gestational age.

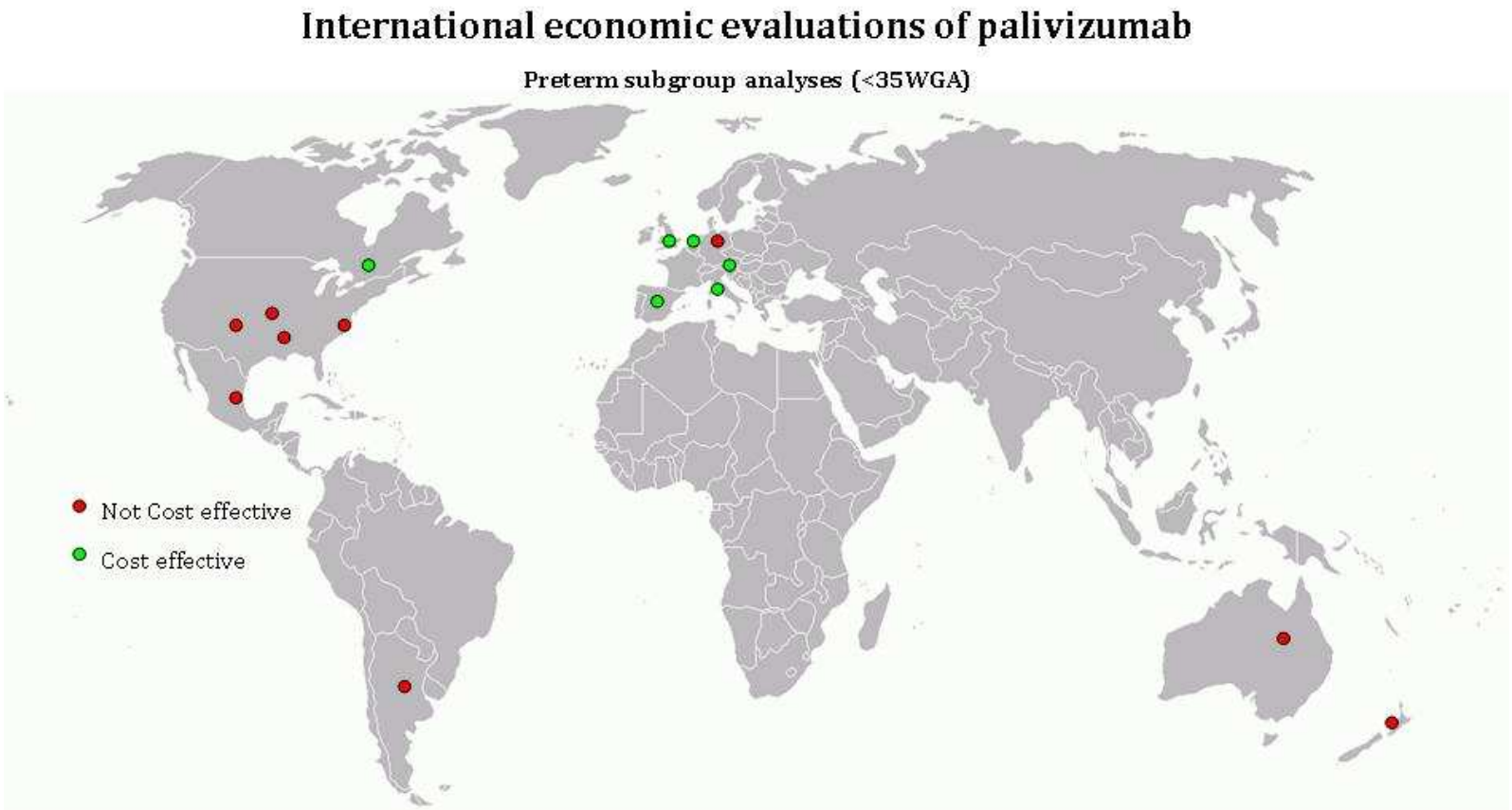

Figure 8. The presented conclusion of cost-effectiveness studies of palivizumab shown per country for subgroup of children born before 35 weeks gestational age.

Discussion

The evidence regarding the cost-effectiveness of prophylactic treatment of RSV infection with palivizumab in subgroups varies considerably. This is in agreement with the results of other reviews(54-56). Due to this high variability between studies and the broad ranges in all outcome measures conclusive recommendations are currently not possible.

The most important driver of cost-effectiveness seems the mortality rate, and even the other variations associated with cost-effectiveness, can often be attributed to differences in mortality. This is also reflected in sponsored studies, although we are not the first to describe the influence of industry sponsoring on cost-effectiveness.(57) For example, most of the sponsored studies used a high mortality rate and productivity losses of children within a life time horizon, which are also based on mortality. These high mortality rates have a large impact on cost-effectiveness when ICERs are reported for LYGs or QALYs. Every percent increase in mortality will mean that more life years or QALYs are gained despite the cost of palivizumab. As a result, the cost-effectiveness ratio will be lower. A recent study from Denmark suggests that the mortality rate of RSV probably does not exceed 1%(58). The high mortality rate used is based on the study of Sampalis, in which there was a high amount of children with sudden or otherwise unexplained death for which the causal relation with RSV infection has not been proven(59). The European studies, which are the more recent studies, also generally use the higher mortality rate. The need for solid RSV mortality rates is evident and should be an important RSV research subject.

The major strength of our systematic review is the diversity of the included studies with respect to localization, year of analysis and the subgroups studied. Nevertheless, some of our findings deserve further discussion. First, the included studies reported LYG, QALY or HAP, which cannot be compared directly. Cost per HAP as even considered an inferior outcome measure compared to cost per LYG or QALY but we included it in our systematic review as morbidity and especially hospitalisation is a much bigger issue than mortality in RSV infection and thus regarding a highly relevant outcome. Second, some studies ((3;40;41;44;51) looked at different subgroups but used identical modelling data (both costs and effects), and are therefore not independent as suggested in the figures. Third, cost data for palivizumab are generally based on 5 doses of palivizumab and no drug wastage, but in daily practice it is not unusual that more doses are given and is there considerable drug wastage because of the limited time a vial is usable after opening (3 hours). The real cost will thus often be higher than reported in most papers, although vial sharing becomes increasingly used. Fourth, one of our inclusion criteria was the presence of an ICER as outcome measure. This created a possible selection bias and we might have missed important studies for which the ICER could be calculated. Fifth, as our quality analysis shows, there were differences in study quality. Some studies used data derived from small cohort studies as a measure of effectiveness of palivizumab. The associated cost-effectiveness ratios are therefore not based on

the best available evidence. This should be taken into account when comparing these studies to cost-effectiveness studies with a better approach. The original quality scores of the Drummond Critical appraisal criteria, between brackets, were adapted to Good (Yes), Acceptable (Yes) and Poor (No/Can't tell) to be able to make a further quality assessment possible for the quality score "Yes" in the original Drummond score model. The authors chose this approach because a high variability in quality in the "Yes" area. Although this provided additional insight in study quality we don't recommend further use of this approach as domains should either be appropriately discussed, i.e. "Yes", or not, i.e. "No"/"Can't tell".

Evidence derived from cost effectiveness studies is used to inform decisions about the reimbursement of medical interventions in an increasing number of countries. Cost-effectiveness and cost-utility thresholds have either been explicitly specified by authorities or can be implicitly determined from examining past reimbursement decisions. However, the use of thresholds is disputed and alternative approaches to assess the value of a health technology have been proposed, such as the fixed budget approach, fixed trade off approach and flexible trade off approach. Although an explicit threshold approach will not be end of equity discussions within and between countries it will certainly help increase transparancy of reimbursement decisions. Currently, interpreting the results of cost effectiveness analysis can be problematic, making it difficult to decide whether to adopt an intervention. The threshold for adoption is thought to be somewhere between €20 000/QALY and €100 000/QALY, with thresholds of €50-60 000/QALY frequently proposed.(60) Because there is still no consensus regarding an international threshold we have refrained from adopting a threshold for this systematic review. Another issue that needs discussion is the transferability of cost effectiveness data across countries. Because it is not feasible to assess the cost effectiveness of every intervention in every country, reimbursement decisions in one country could be based on the results of a cost effectiveness study in another country. Unfortunately, decision-makers need to assess whether, and to what extent, the assessment and analysis from this other country applies to their own country. In a recent systematic review treatment effect were considered to have high transferability whereas especially baseline risk, resource use and unit costs have low transferability. (61) This is highly relevant for the guidelines for cost effectiveness studies regarding choices for input data. It is for example generally accepted to adopt clinical data from trials performed in another setting as the source of the relative treatment effect, while absolute risk estimates or resource consumption from these studies are difficult to transfer. There are several systems, processes and approaches for assessing the transferability of cost effectiveness studies or guidelines for transferring economic evalution data accros countries, although the proposed approached varied substantially. (62) There is general agreement on the approach to first consider critical criteria like study quality, transparency of methods the level of reporting of methods and results and the applicability of the treatment comparators to the target country followed by the assessment of non-critical criteria for

which is the list is long and diverse. A consensus on the approach of transferability in national guidelines and regularly updating these guidelines would a big step forward to cost effective use of the results of cost effectiveness studies between countries.
In this review we did not focus on targeting high risk populations with additional risk factors within preterm infants or infants with CHD or CLD. This is a main focus for future RSV research and subsequent economic evaluation studies. For example although RSV immunoprophylaxis has shown to be effective in preventing RSV LRTI in preterm children born at 32-35 WGA, it is not reimbursed in the Netherlands. Due to high costs, the willingness to pay for palivizumab is too low for use in late preterm infants 32-35 WGA in the Netherlands indiscriminately. However, cost-effectiveness of providing immunoprophylaxis to a subgroup of preterm infants 32-35 WGA at highest risk to develop RSV bronchiolitis based on individualized risk prediction may be acceptable. I have recently discovered that every year 5.1% of all late preterm infants 32-35 WGA are hospitalised for RSV infection in the Netherlands (PIDJ in review). Because 6000 preterm infants 32-35 WGA are born annually in the Netherlands, an annual country-specific RSV hospitalisation rate of 306 is estimated. RSV disease burden is not only a direct burden for the child. During the acute illness parents experience stress on both private and working life. After the acute illness the child could develop wheezing complaints with significant morbidity and decreased quality of life. This underlines the importance of developing guidelines to target the disease burden caused by RSV infection in the highest risk groups based on risk stratification.

Future RSV cost-effectiveness analyses should make use of country specific epidemiological cost and effectiveness data and describe all input data on both unit and value level. This demands both large cohort studies, accurate RSV related mortality estimates and attention for short and long term consequences with respect to morbidity and indirect costs of productivity losses of parents and future productivity losses of children. Also, to increase legitimacy and decrease potential bias, the analyses should be performed independent from the influence of pharmaceutical companies.

Conclusion

The cost-effectiveness of prophylactic treatment of RSV infection with palivizumab in subgroups varies importantly, and is certainly not always below the threshold. The cost-effectiveness is mainly affected by mortality rates of RSV infection. Future research should focus on the major uncertainties in cost-effectiveness, particularly RSV-related mortality rate.

Reference List

(1) Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. Methods for the Economic Evaluation of Health Care Programmes. 3 ed. Oxford University Press; 2005.

(2) Reeve CA, Whitehall JS, Buettner PG, Norton R, Reeve DM, Francis F. Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab. J Paediatr Child Health 2006;42(5):253-8.

(3) Nuijten M, Lebmeier M, Wittenberg W. Cost effectiveness of palivizumab for RSV prevention in high-risk children in the Netherlands. J Med Econ 2009 Oct 8.

(4) Hall CB, Weinberg GA, Iwane MK, Blumkin AK, Edwards KM, Staat MA, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009 Feb 5;360(6):588-98.

(5) Houben ML, Bont L, Wilbrink B, Belderbos ME, Kimpen JL, Visser GH, et al. Clinical prediction rule for RSV bronchiolitis in healthy newborns: prognostic birth cohort study. Pediatrics 2011 Jan;127(1):35-41.

(6) Bos JM, Rietveld E, Moll HA, Steyerberg EW, Luytjes W, Wilschut JC, et al. The use of health economics to guide drug development decisions: Determining optimal values for an RSV-vaccine in a model-based scenario-analytic approach. Vaccine 2007 Sep 28;25(39-40):6922-9.

(7) Jansen AG, Sanders EA, Hoes AW, van Loon AM, Hak E. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. Eur Respir J 2007 Dec;30(6):1158-66.

(8) Rietveld E, De Jonge HC, Polder JJ, Vergouwe Y, Veeze HJ, Moll HA, et al. Anticipated costs of hospitalization for respiratory syncytial virus infection in young children at risk. PIDJ 2004 Jun;23(6):523-9.

(9) Smyth RL, Openshaw PJ. Bronchiolitis. Lancet 2006 Jul 22;368(9532):312-22.

(10) Smyth RL, Openshaw PJ. Bronchiolitis. Lancet 2006 Jul 22;368(9532):312-22.

(11) Ermers MJ, Rovers MM, van Woensel JB, Kimpen JL, Bont LJ. The effect of high dose inhaled corticosteroids on wheeze in infants after respiratory syncytial virus infection: randomised double blind placebo controlled trial. BMJ 2009;338:b897.

(12) Bont L, Kimpen JL. Immunological mechanisms of severe respiratory syncytial virus bronchiolitis. Intensive Care Med 2002 May;28(5):616-21.

(13) Tissing WJE, Van Steensel-Moll HA, Offringa M. Risk factors for mechanical ventilation in respiratory syncytial virus infection. Eur J Pediatr 1993;152:125-7.

(14) Bont L, Aalderen vWMC, Kimpen JLL. Long-term consequences of respiratory syncytial virus (RSV) bronchiolitis. Paediatr Respir Rev 2000;1(3):221-7.

(15) Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. PIDJ 2004 May;23(5):414-7.

(16) Simon A, Ammann RA, Wilkesmann A, Eis-Hubinger AM, Schildgen O, Weimann E, et al. Respiratory syncytial virus infection in 406 hospitalized premature infants: results from a prospective German multicentre database. Eur J Pediatr 2007 Dec;166(12):1273-83.

(17) Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr 2003 Nov;143(5 Suppl):S150-S156.

(18) Prais D, Schonfeld T, Amir J. Admission to the intensive care unit for respiratory syncytial virus bronchiolitis: a national survey before palivizumab use. Pediatrics 2003 Sep;112(3 Pt 1):548-52.

(19) Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. Pediatr Infect Dis J 2003 Feb;22(2 Suppl):S21-S32.

(20) Bloemers BL, van Furth AM, Weijerman ME, Gemke RJ, Broers CJ, van den EK, et al. Down syndrome: a novel risk factor for respiratory syncytial virus bronchiolitis--a prospective birth-cohort study. Pediatrics 2007 Oct;120(4):e1076-e1081.

(21) Boyce TG, Mellen BG, Mitchel EF, Jr., Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in medicaid. J Pediatr 2000 Dec;137(6):865-70.

(22) Weisman LE. Populations at risk for developing respiratory syncytial virus and risk factors for respiratory syncytial virus severity: infants with predisposing conditions. Pediatr Infect Dis J 2003 Feb;22(2 Suppl):S33-S37.

(23) Welliver RC. Review of epidemiology and clinical risk factors for severe respiratory syncytial virus (RSV) infection. J Pediatr 2003 Nov;143(5 Suppl):S112-S117.

(24) Bont L, Steijn M, van Aalderen WM, Kimpen JL. Impact of wheezing after respiratory syncytial virus infection on health-related quality of life. PIDJ 2004 May;23(5):414-7.

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

(26) Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, Jr., et al. Palivizumab prophylaxis reduces hospitalization due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. J Pediatr 2003 Oct;143(4):532-40.

(27) GIP database, Dutch database of medical resources and medicines. GIP database, Drug Information System of the Health Care Insurance Board 2010 [cited 2010 Feb 2];Available from: URL: http://www.gipdatabank.nl/

(28) Isaacs D. Palivizumab. An example of indication creep. BMJ 2009;339:b2724.

(29) Meissner HC, Bocchini JA, Jr., Brady MT, Hall CB, Kimberlin DW, Pickering LK. The role of immunoprophylaxis in the reduction of disease attributable to respiratory syncytial virus. Pediatrics 2009 Dec;124(6):1676-9.

(30) FXHistory; Historical Exchange rates. OANDA 2010 [cited 2010 Feb 2];Available from: URL: http://www.oanda.com/currency/historical-rates

(31) Eurostat. Eurostat 2010 [cited 2010 Feb 2];Available from: URL: http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/

(32) United States Department of Labor. Bureau of Labor Statistics 2010 [cited 2010 Feb 2];Available from: URL: http://www.bls.gov/CPI/

(33) Australian Bureau of Statistics. Australian Bureau of Statistics 2010 [cited 2010 Feb 2];Available from: URL: http://www.abs.gov.au/

(34) Reserve Bank of New Zealand. Reserve Bank of New Zealand 2010 [cited 2010 Feb 2];Available from: URL: http://www.rbnz.govt.nz/statistics/

(35) Statistics Canada. Statistics Canada 2010 [cited 2010 Feb 2];Available from: URL: http://www.statcan.gc.ca/

(36) Institutio Nacional de Estadistica y Censos. Institutio Nacional de Estadistica y Censos 2010 [cited 2010 Feb 2];Available from: URL: http://www.indec.mecon.ar/

(37) 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. Ital J Pediat 2009;35(4).

(38) Elhassan NO, Sorbero MES, Hall CB, Stevens TP, Dick AW. Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. Arch Pediatr Adolesc Med 2006;160(10):1070-6.

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

(40) Nuijten MJ, Wittenberg W. Cost effectiveness of palivizumab in Spain: an analysis using observational data. Eur J Health Econ 2009;1-11.

(41) 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. Clin Ther 2008;30(4):749-60.

(42) 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. Arch Pediatr Adolesc Med 2000;154(1):55-61.

(43) Vogel AM, McKinlay MJ, Ashton T, Lennon DR, Harding JE, Pinnock R, et al. Cost-effectiveness of palivizumab in New Zealand. J Paediatr Child Health 2002;38(4):352-7.

(44) 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.

(45) 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 Mex 2012 Jan;54(1):47-59.

(46) 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. Curr Med Res Opin 2008;24(11):3223-37.

(47) 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. Clin Ther 2000;22(11):1357-69.

(48) Rodriguez SP, Farina D, Bauer G. Respiratory Syncytial Virus Prophylaxis in a High-Risk Population in Argentina: A Cost-Effectiveness Analysis. Pediatr Infect Dis J 2008;27(7):660-1.

(49) Roeckl-Wiedmann I, Liese JG, Grill E, Fischer B, Carr D, Belohradsky BH. Economic evaluation of possible prevention of RSV-related hospitalizations in premature infants in Germany. Eur J Pediatr 2003;162(4):237-44.

(50) Meberg A, Bruu AL. Respiratory syncytial virus infections in congenital heart defects - Hospitalizations and costs. Acta Paediatr Int J Paediatr 2006;95(4):404-6.

(51) Nuijten M, Lebmeier M, Wittenberg W. Cost effectiveness of palivizumab in children with congenital heart disease in Germany. J Med Econ 2009 Oct 8.

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

(53) 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. Can J Cardiol 2011 Jul;27(4):523-5.

(54) 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 Technol Assess 2008;12(36).

(55) Prescott WA, Jr., Doloresco F, Brown J, Paladino JA. Cost effectiveness of respiratory syncytial virus prophylaxis: a critical and systematic review. Pharmacoeconomics 2010 Apr 1;28(4):279-93.

(56) Embleton ND, Harkensee C, Mckean MC. Palivizumab for preterm infants. Is it worth it? Arch Dis Child Fetal Neonatal Ed 2005 Jul;90(4):F286-F289.

(57) Bell CM, Urbach DR, Ray JG, Bayoumi A, Rosen AB, Greenberg D, et al. Bias in published cost effectiveness studies: systematic review. BMJ 2006 Mar 25;332(7543):699-703.

(58) Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. Arch Dis Child 2009 Feb;94(2):99-103.

(59) Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. J Pediatr 2003 Nov;143(5 Suppl):S150-S156.

(60) Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004 Sep;7(5):518-28.

(61) Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, et al. What do international pharmacoeconomic guidelines say about economic data transferability? Value Health 2010 Dec;13(8):1028-37.

(62) Goeree R, He J, O'Reilly D, Tarride JE, Xie F, Lim M, et al. Transferability of health technology assessments and economic evaluations: a systematic review of approaches for assessment and application. Clinicoecon Outcomes Res 2011;3:89-104.

Appendix 1

Search strategy

A systematic search was conducted in Pubmed (Ovid), EMBASE(Ovid) and the DARE, NHS EED and HTA databases in week 5 2010, this search was updated in week 15 2012 . Searches were not restricted by date or language. We used the following search terms with corresponding synonyms:

- cost
- cost effectiveness
- cost utility
- cost benefit
- decision making
- palivizumab
- synagis
- monoclonal antibody
- vaccine
- prevent*
- immunotherapy
- immunoprophylaxis
- respiratory syncytial virus
- bronchiolitis

Exclusion criteria:

- not about children
- not about respiratory syncytial virus
- not about palivizumab
- no comparator
- no full text available
- other immunoprophylaxis

Specific database search strategies

PUBMED

((cost[title/abstract] OR costs[title/abstract] OR cost-effectiveness[title/abstract] OR cost-utility[title/abstract] OR cost-benefit[title/abstract] OR decision analys*[title/abstract]) AND (palivizumab[title/abstract] OR synagis[title/abstract] OR monoclonal antibod* [title/abstract] OR vaccin*[title/abstract] OR prevent*[title/abstract] OR immunotherapy[title/abstract] OR immunoprophylaxis[title/abstract]) AND (RSV[title/abstract] OR respiratory syncytial virus[title/abstract] OR bronchiolitis[title/abstract])) OR ((cost[title/abstract] OR costs[title/abstract] OR cost-effectiveness[title/abstract] OR cost-utility[title/abstract] OR cost-benefit[title/abstract] OR decision analys*[title/abstract]) AND (palivizumab[title/abstract] OR synagis[title/abstract]))

EMBASE

((cost:ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost benefit':ab,ti OR 'decision making':ab,ti) AND (palivizumab:ab,ti OR synagis:ab,ti OR 'monoclonal antibody':ab,ti OR vaccin*:ab,ti OR prevent*:ab,ti OR immunotherapy:ab,ti OR immunoprophylaxis:ab,ti) AND ('syncytial respiratory virus'/exp OR 'syncytial respiratory virus':ab,ti OR bronchiolitis:ab,ti)) OR ((cost:ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost benefit':ab,ti OR 'decision making':ab,ti) AND (palivizumab:ab,ti OR synagis:ab,ti))

CRD (DARE, NHS EED, HTA)
((cost OR costs OR cost-effectiveness OR cost-utility OR cost-benefit OR decision analys*) AND (palivizumab OR synagis OR monoclonal antibod* OR vaccin* OR prevent* OR immunotherapy OR immunoprophylaxis) AND (RSV OR respiratory syncytial virus OR bronchiolitis)) OR ((cost OR costs OR cost-effectiveness OR cost-utility OR cost-benefit OR decision analys*) AND (palivizumab OR synagis))