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 GIP databank). 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.

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.
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).

<table>
<thead>
<tr>
<th></th>
<th>&lt;32 WGA</th>
<th>32-35 WGA</th>
<th>CHD</th>
<th>BPD</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAP</td>
<td>38,404-130,591</td>
<td>37,427-344,617</td>
<td>165,545-188,906</td>
<td>7,372-68,448</td>
</tr>
<tr>
<td>LYG</td>
<td>17,886-362,755</td>
<td>16,780-985,485</td>
<td>12,139-91,743</td>
<td>4,332-167,168</td>
</tr>
<tr>
<td>QALY</td>
<td>9,380-104,1742</td>
<td>11,759-20,236</td>
<td>7067-104,532</td>
<td>2,731-32,465</td>
</tr>
</tbody>
</table>

Table 1.ICER ranges of the selected subgroups. All values in 2009 € values.
WGA: weeks gestational age; CHD: congenital heart disease; BPD: bronchopulmonary dysplasia.
<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>country</th>
<th>N</th>
<th>CEA / CUA</th>
<th>hospitalisation palivizumab group</th>
<th>hospitalisation control group</th>
<th>reduction hospitalisation</th>
<th>hospital mortality</th>
<th>time horizon</th>
<th>perspective</th>
<th>ICER</th>
<th>Conversion and inflation to 2009 € values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chirico, 2009</td>
<td>Italy</td>
<td>model</td>
<td>CEA/CUA</td>
<td>2.0%</td>
<td>10.3%</td>
<td>80.0%</td>
<td>4.0%</td>
<td>2 years</td>
<td>payers</td>
<td>€17,886/LYG^</td>
<td>€17,886/LYG^</td>
</tr>
<tr>
<td>Elhassan, 2006‡</td>
<td>USA</td>
<td>model</td>
<td>CUA</td>
<td>2.9%</td>
<td>13.2%</td>
<td>78.0%</td>
<td>n.a.</td>
<td>8 years</td>
<td>societal</td>
<td>$1,228,260/QALY</td>
<td>$1,041,742/QALY</td>
</tr>
<tr>
<td>Joffe, 1999§</td>
<td>USA</td>
<td>1721</td>
<td>CEA</td>
<td>2.5%</td>
<td>5.5%</td>
<td>55.0%</td>
<td>1.2%</td>
<td>lifetime</td>
<td>societal</td>
<td>$18,872/LYG</td>
<td>$18,872/LYG</td>
</tr>
<tr>
<td>Nuijten, 2009</td>
<td>Spain</td>
<td>model</td>
<td>CEA/CUA</td>
<td>3.9%</td>
<td>13.4%</td>
<td>71.0%</td>
<td>1.4%</td>
<td>lifetime</td>
<td>payers</td>
<td>€18,872/LYG</td>
<td>€18,872/LYG</td>
</tr>
<tr>
<td>Reeve, 2006</td>
<td>Australia</td>
<td>12171</td>
<td>CEA</td>
<td>0.8%</td>
<td>4.0%</td>
<td>80.0%</td>
<td>n.a.</td>
<td>1 year</td>
<td>payers</td>
<td>A$98,818/HAP</td>
<td>€64,659/HAP</td>
</tr>
<tr>
<td>Resch, 2008</td>
<td>Austria</td>
<td>model</td>
<td>CEA/CUA</td>
<td>1.8%</td>
<td>8.1%</td>
<td>78.0%</td>
<td>8.1%</td>
<td>lifetime</td>
<td>payers</td>
<td>€41,242/LYG</td>
<td>€41,406/LYG</td>
</tr>
<tr>
<td>Salinas, 2012</td>
<td>Mexico</td>
<td>model</td>
<td>CUA</td>
<td>4.9%</td>
<td>10.1%</td>
<td>51.5%</td>
<td>0.23% / 0.99%*</td>
<td>lifetime</td>
<td>payers</td>
<td>$27,333/LYG</td>
<td>$29,054/QALY</td>
</tr>
<tr>
<td>Stevens, 2000</td>
<td>USA</td>
<td>1029</td>
<td>CEA</td>
<td>4.1%</td>
<td>9.2%</td>
<td>55.0%</td>
<td>n.a.</td>
<td>1 year</td>
<td>payers</td>
<td>$32,792/HAP</td>
<td>€44,326/HAP</td>
</tr>
<tr>
<td>Vogel, 2002</td>
<td>New Zealand</td>
<td>437</td>
<td>CEA</td>
<td>2.9%</td>
<td>13.4%</td>
<td>78.0%</td>
<td>n.a.</td>
<td>1 year</td>
<td>societal</td>
<td>NZ$65,000/HAP</td>
<td>€38,404/HAP</td>
</tr>
</tbody>
</table>

**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.  \(^\ast\)= asthma costs were included in the ICER.  \(^\ast\)= 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)
<table>
<thead>
<tr>
<th>Author, publication year</th>
<th>country</th>
<th>N</th>
<th>CEA / CUA</th>
<th>Hospitalisation palivizumab</th>
<th>Hospitalisation control</th>
<th>Reduction hospitalisation</th>
<th>Hospital mortality</th>
<th>Time horizon</th>
<th>Perspective</th>
<th>ICER</th>
<th>Conversion and inflation to 2009 € values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chirico, 2009</td>
<td>Italy</td>
<td>model</td>
<td>CEA/CUA</td>
<td>1.5%</td>
<td>9.8%</td>
<td>85.0%</td>
<td>4.0%</td>
<td>2 years</td>
<td>payers</td>
<td>€28,417/LYG&lt;sup&gt;+&lt;/sup&gt; €14,937/QALY&lt;sup&gt;+&lt;/sup&gt;</td>
<td>€28,417/LYG&lt;sup&gt;+&lt;/sup&gt; €14,937/QALY&lt;sup&gt;+&lt;/sup&gt;</td>
</tr>
<tr>
<td>Joffe, 1999 §</td>
<td>USA</td>
<td>1721</td>
<td>CEA</td>
<td>1.0%</td>
<td>2.2%</td>
<td>55.0%</td>
<td>1.2%</td>
<td>lifetime</td>
<td>societal</td>
<td>$285,000/HAP $815,000/LYG</td>
<td>€34,617/HAP €985,485/LYG</td>
</tr>
<tr>
<td>Lanctot, 2008</td>
<td>Canada</td>
<td>model</td>
<td>CEA/CUA</td>
<td>1.8%</td>
<td>10.0%</td>
<td>80.0%</td>
<td>8.1%</td>
<td>lifetime</td>
<td>payers</td>
<td>CAN$ 44,237/LYG CAN$ 30,618/QALY</td>
<td>€29,053/LYG €16,780/QALY</td>
</tr>
<tr>
<td>Resch, 2008</td>
<td>Austria</td>
<td>model</td>
<td>CEA/CUA</td>
<td>1.8%</td>
<td>8.1%</td>
<td>78.0%</td>
<td>8.1%</td>
<td>lifetime</td>
<td>payers</td>
<td>€16,714/LYG €11,713/QALY</td>
<td>€16,780/LYG €11,759/QALY</td>
</tr>
<tr>
<td>Lofland, 2000†</td>
<td>USA</td>
<td>model</td>
<td>CEA</td>
<td>5.0%</td>
<td>12.0%</td>
<td>59.0%</td>
<td>n.a.</td>
<td>1 year</td>
<td>payers</td>
<td>$53,777/HAP €72,693/QALY</td>
<td>€16,780/LYG €11,759/QALY</td>
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<td>Nuijten, 2009</td>
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<td>model</td>
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<td>10.6%</td>
<td>55.0%</td>
<td>8.1%</td>
<td>lifetime</td>
<td>societal</td>
<td>€20,236/QALY^</td>
<td>€20,236/QALY^</td>
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<td>Nuijten, 2007</td>
<td>UK</td>
<td>model</td>
<td>CEA/CUA</td>
<td>1.8%</td>
<td>8.1%</td>
<td>78.0%</td>
<td>8.1%</td>
<td>lifetime</td>
<td>payers</td>
<td>£20,344/LYG^ £14,883/QALY^</td>
<td>£1,522/LYG^ £2,060/QALY^</td>
</tr>
<tr>
<td>Rodriguez, 2008</td>
<td>Argentina</td>
<td>159</td>
<td>CEA</td>
<td>3.5%</td>
<td>16.5%</td>
<td>79.0%</td>
<td>n.a.</td>
<td>1 year</td>
<td>payers</td>
<td>$51,550/HAP €37,427/QALY</td>
<td>€1,522/LYG^ £2,060/QALY^</td>
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<tr>
<td>Roeckl-Wiedmann, 2003&lt;sup&gt;^^&lt;/sup&gt;</td>
<td>Germany</td>
<td>model</td>
<td>CEA</td>
<td>5.8%</td>
<td>12.8%</td>
<td>55.0%</td>
<td>1.2%</td>
<td>1 year</td>
<td>societal</td>
<td>€94,270/HAP</td>
<td>€104,691/HAP</td>
</tr>
</tbody>
</table>

**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. <sup>^^</sup>= 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)
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).

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

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

**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
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 transparency 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 evaluation data accross 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


(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.


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**


**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))