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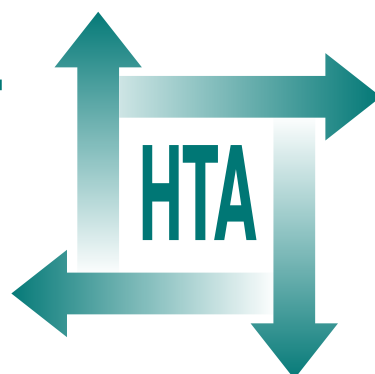
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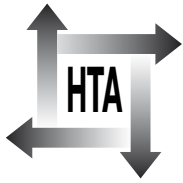
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Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation

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Abstract

Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation

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Objectives: To systematically review the effectiveness and cost-effectiveness of palivizumab for the prevention of respiratory syncytial virus (RSV) in children and examine prognostic factors to determine whether subgroups can be identified with important differences in cost-effectiveness.

Data sources: Bibliographic databases were searched from inception to March 2007 for literature on the effectiveness and cost-effectiveness of prophylaxis with palivizumab.

Review methods: The literature was systematically reviewed and current economic evaluations were analysed to identify which parameters were driving the different cost-effectiveness estimates. A probabilistic decision-analytical model was built to assess the cost-effectiveness of prophylaxis with palivizumab for children at risk of RSV infection and the parameters populated with the best estimates thought most applicable to the UK. We also constructed a new model, the Birmingham Economic Evaluation (BrumEE). Cost-effectiveness analyses were undertaken from both NHS and societal perspectives.

Results: Two randomised controlled trials (RCTs) were identified. Prophylaxis with palivizumab for preterm infants without chronic lung disease (CLD) or children with CLD resulted in a 55% reduction in RSV hospital admission: 4.8% (48/1002) in the palivizumab group and 10.6% (53/500) in the no prophylaxis group ($p = 0.0004$). Prophylaxis with palivizumab was associated with a 45% reduction in hospitalisation rate RSV among children with coronary heart disease (CHD). Hospitalisation rates for RSV were 5.3% (34/639) in the palivizumab group and 9.7% (63/648) in the no prophylaxis group ($p = 0.003$). Of existing economic evaluations, 3 systematic reviews and 18 primary studies were identified. All the systematic reviews concluded

that the potential costs of palivizumab were far in excess of any potential savings achieved by decreasing hospital admission rates, and that the use of palivizumab was unlikely to be cost-effective in all children for whom it is recommended, but that its continued use for particularly high-risk children may be justified. The incremental cost-effectiveness ratios (ICERs) of the primary studies varied 17-fold for life-years gained (LYG), from £25,800/LYG to £404,900/LYG, and several hundred-fold for quality-adjusted life years (QALYs), from £3200/QALY to £1,489,700/QALY for preterm infants without CLD or children with CLD. For children with CHD, the ICER varied from £5300/LYG to £7900/LYG and from £7500/QALY to £68,700/QALY. An analysis of what led to the discrepant ICERs showed that the assumed mortality rate for RSV infection was the most important driver. The results of the BrumEE confirm that palivizumab does not reach conventional levels of cost-effectiveness in any of the licensed indications if used for all eligible children.

Conclusions: Prophylaxis with palivizumab is clinically effective for the reducing the risk of serious lower respiratory tract infection caused by RSV infection and requiring hospitalisation in high-risk children, but if used unselectively in the licensed population, the ICER is double that considered to represent good value for money in the UK. The BrumEE shows that prophylaxis with palivizumab may be cost-effective (based on a threshold of £30,000/QALY) for children with CLD when the children have two or more additional risk factors. Future research should initially focus on reviewing systematically the major uncertainties for patient subgroups with CLD and CHD and then on primary research to address the important uncertainties that remain.



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Glossary and list of abbreviations

Glossary

Adverse effect An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Chronic lung disease Chronic lung disease is defined as oxygen dependency for at least 28 days from birth. It is caused by prolonged supplemental oxygen therapy and ventilation and usually develops in the first 4 weeks after birth, most often affecting babies born prematurely. It is caused by the pressure and high concentrations of oxygen which, when prolonged, can cause lung tissue to become inflamed and scarred.

Confidence interval A measure of the precision of a statistical estimate; quantifies the uncertainty in measurement. Usually reported as 95% CI, i.e. the range of values within which one can be 95% sure that the true values for the whole population lie.

Discounting This refers to the process of adjusting the value of costs or benefits that occur at different points of time in the future so that they may all be compared as if they had occurred at the same time.

Incremental cost-effectiveness ratio An expression of the additional cost of health gain associated with an intervention relative

to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean health gain.

Infant A child up to 1 year old (up to and including 365 days from birth).

Meta-analysis The statistical pooling of the results of a collection of related individual studies, to increase statistical power and synthesise their findings.

Quality of life A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity and also other factors that might affect their physical, mental and social well-being.

Quality-adjusted life-year (QALY) An index of health gain in which survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Odds A ratio of the number of people incurring an event to the number of people who do not have an event.

Odds ratio Ratio of odds of a specified characteristic in the treated group to the odds in the control group.

Risk ratio The ratio of risk in the treated group to the risk in the control group.

List of abbreviations

BrumEE	Birmingham Economic Evaluation	ICU	intensive care unit
BNF	<i>British National Formulary</i>	IEA	infection episode avoided
BPD	bronchopulmonary dysplasia	JCVI	Joint Committee on Vaccination and Immunisation
CBA	cost–benefit analysis	MTRAC	Midlands Therapeutic Review and Advisory Committee
CEA	cost-effectiveness analysis	NHS	National Health Service
CEAC	cost-effectiveness acceptability curve	NIC	net ingredient cost
CUA	cost–utility analysis	NICU	neonatal intensive care unit
CLD	chronic lung disease	LYG	life-year gained
CHD	congenital heart disease	LRTI	lower respiratory tract infection
CRD	Centre for Review and Dissemination	ONS	Office for National Statistics
CRIB	clinical risk index for babies	OR	odds ratio
DARE	Database of Abstracts of Reviews of Effects	PICU	paediatric intensive care unit
EED	Economic Evaluation Database	PSA	probabilistic sensitivity analysis
ESRC	Economic and Social Research Council	QALY	quality-adjusted life-year
GA	gestational age	RCT	randomised controlled trial
HAP	hospital admission prevented	RDS	respiratory distress syndrome
HDS	hospital day saved	RNA	ribonucleic acid
HEED	Health Economic Evaluation Database	RSV	respiratory syncytial virus
HRQoL	health-related quality of life	SAS	siblings at school
HUI	Health Utility Index	SD	standard deviation
ICER	incremental cost-effectiveness ratio	UK	United Kingdom
		USA	United States

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.



Executive summary

Background

Respiratory syncytial virus (RSV) causes outbreaks of respiratory tract infection in the winter months in the UK. It is the leading cause of lower respiratory tract infection (LRTI) in infants and can lead to hospitalisation, particularly in those who are premature or who have chronic lung disease (CLD) or congenital heart disease (CHD). There are currently two licensed specific therapies in the UK: ribavirin and palivizumab. Palivizumab is a monoclonal antibody designed to provide passive immunity against RSV and thereby prevent or reduce the severity of RSV infection. It is licensed for the prevention of serious lower LRTI caused by RSV in children at high risk. While it is recognised that a policy of using palivizumab for all children who meet the licensed indication does not meet conventional UK standards of cost-effectiveness, most clinicians feel that its use is justified in some children. The purpose of this review is to determine if we can identify subgroups in whom palivizumab is cost-effective.

Objective

This review aims to systematically examine the scientific evidence about the effectiveness and cost-effectiveness of palivizumab for the prevention of RSV in children and to look at prognostic factors to determine if it is possible to identify subgroups among which there are important differences in cost-effectiveness.

Methods

We systematically reviewed the literature about the effectiveness and cost-effectiveness of prophylaxis with palivizumab. Bibliographic databases were searched from inception to March 2007 with no date limits or language restrictions. Current economic evaluations were analysed to identify which parameters were driving the different cost-effectiveness estimates. A probabilistic decision-analytical model was built to assess the cost-effectiveness of prophylaxis with palivizumab for children at risk of RSV infection and the parameters populated with the best available

estimate thought to be most applicable to the UK context. Data to inform parameters in our model were systematically sought from the identified trial data and pragmatically identified from observational studies in the wider literature. Meta-analyses were carried out where appropriate.

Results

Clinical effectiveness

Two randomised controlled trials (RCTs) were identified. Prophylaxis with palivizumab for preterm infants without CLD or children with CLD resulted in a 55% reduction in RSV hospital admission: 4.8% (48/1002) in the palivizumab group and 10.6% (53/500) in the no prophylaxis group ($p = 0.0004$).

Prophylaxis with palivizumab was associated with a 45% reduction in RSV hospitalisation rate among children with CHD. Hospitalisation rates for RSV were 5.3% (34/639) in the palivizumab group and 9.7% (63/648) in the no prophylaxis group ($p = 0.003$). A slightly higher mortality in the control group was found in both RCTs, but this was not statistically significant. However, the trials were not powered to demonstrate a difference. Palivizumab had a relatively safe adverse event profile.

Cost-effectiveness

Existing economic evaluations

Three systematic reviews and 18 primary studies were identified. All the systematic reviews stated that the potential costs of palivizumab were far in excess of any likely savings achieved by decreasing hospital admission rates, and that the use of palivizumab was unlikely to be cost-effective in all children for whom it is recommended, but that continued use of palivizumab for particularly high-risk children may be justified. The incremental cost-effectiveness ratios (ICERs) of the primary studies varied 17-fold for life-years gained (LYG), from £25,800/LYG to £404,900/LYG, and several hundred-fold for quality-adjusted life-years (QALYs), from £3200/QALY to £1,489,700/QALY for preterm infants without CLD or children with CLD. For children with CHD, the ICER varied

from £5300/LYG to £7900/LYG and from £7500/QALY to £68,700/QALY.

An analysis of what led to the discrepant ICERs showed that the assumed mortality rate for RSV infection was the most important driver. The rates of hospital and paediatric intensive care unit (PICU) admissions and sequelae of RSV also had measurable effects.

Birmingham Economic Evaluation (BrumEE)

We undertook an independent economic evaluation. The resource use and unit cost were obtained from the trial studies, *British National Formulary* (BNF), Office for National Statistics (ONS), Economic and Social Research Council (ESRC) and previous economic evaluation studies. The utilities were obtained from a UK cohort study. Cost-effectiveness analyses were undertaken from both NHS and societal perspectives. Estimates from an NHS perspective derived using different methods confirm that palivizumab does not reach conventional levels of cost-effectiveness in any of the licensed indications if used for all eligible children – the lowest ICER being £64,000/QALY.

When additional risk factors for RSV hospitalisation derived from observational studies (gestational age, age at the start of the RSV season, having siblings who are in day care or at school) were modelled using the BrumEE, prophylaxis against RSV infection with palivizumab was within

the willingness-to-pay threshold of £30,000/QALY in a number of important subgroups of children with CLD. There was insufficient data to undertake a similar risk group analysis for children with CHD.

Conclusion

Prophylaxis with palivizumab is clinically effective for reducing the risk of serious LRTI caused by RSV infection and requiring hospitalisation in high-risk children, but if used unselectively in the licensed population the ICER is over £60,000/QALY, which is double that considered to represent good value for money in the UK (the current willingness-to-pay threshold is about £30,000/QALY). The BrumEE shows that prophylaxis with palivizumab may be cost-effective (based on a threshold of £30,000/QALY, but the threshold for decision-makers may vary, particularly for this type of patient group) for children with CLD when the children have two or more additional risk factors.

Our economic evaluation is limited by the quality and quantity of the primary data available and the pragmatic rather than systematic methods used to identify parameter values. Future research should initially focus on reviewing systematically the major uncertainties for patient subgroups with CLD and CHD (e.g. mortality rates for RSV infection in children not given palivizumab prophylaxis) and then on primary research to address the important uncertainties that remain.

Chapter I

Introduction

Aim of this health technology assessment

This assessment aims

- to review systematically the scientific evidence on the effectiveness and cost-effectiveness of palivizumab for the prevention of respiratory syncytial virus (RSV) infection in children
- to model the cost-effectiveness of palivizumab for prevention of RSV infection in children
- to look at prognostic factors for RSV infection with a view to the identification of subgroups of children for whom there may be important differences in cost-effectiveness.

Background

Description of underlying health problem

RSV causes outbreaks of respiratory tract infection in the UK, especially in the winter months. It can affect people of any age and is usually a mild, self-limiting illness. It is most serious in infants and young children, in whom it is the single most important cause of lower respiratory tract infection (LRTI). RSV infection can present with a wide range of severity from mild respiratory symptoms, to rhinitis and otitis media, through to bronchiolitis, tracheobronchiolitis and pneumonia with significant morbidity and a very small increased risk of death.

RSV is an RNA virus that is highly communicable. Humans are the only known reservoir. The virus is spread by contaminated nasal secretions via respiratory droplets, so close contact with an infected individual or contaminated surface is required for transmission. RSV can persist for several hours on toys or other objects. Risk factors for RSV infection include crowding, low socioeconomic status, exposure to tobacco smoke and admission to hospital during the RSV season (late autumn to early spring).

Immunity to RSV following infection is not complete or enduring, and recurrent infection is frequent. In children followed up from birth in the Houston Family Study, the infection rate was

68.8% in children aged less than 12 months, of whom 82.6% were reinfected in their second year and 46% were reinfected during their third year.¹ The fact that older children and adults are usually protected against RSV-related LRTIs suggests that primary infections may protect against later severe disease. Approximately 50% of infants and young children become infected each year. In a study from the USA, about 0.5–2% of children infected with RSV required hospital admission.² All but one child had been infected at least once by 24 months of age, and about one half had experienced two infections. LRTI was common (22.4% during year 1 and 13.0% during year 2). Most children had only one LRTI.¹ The risk of reinfection was inversely related to the level of neutralising antibodies in the serum. Reinfection illnesses tended to be mild and risk of reinfection decreased to 33.3% during year 4.¹ Other studies suggest that 40% of primary RSV infections lead to clinical bronchiolitis.³

Those most at risk from severe disease if infected with RSV are infants under 6 weeks old or who have chronic lung disease (CLD), congenital heart disease (CHD) or immunodeficiency, and those born prematurely (at 35 weeks gestational age or before).

The definition of chronic lung disease accepted by the Department of Health's Joint Committee on Vaccination and Immunisation (JCVI) is oxygen dependency for at least 28 days from birth.⁴ CLD is caused by prolonged supplemental oxygen therapy and ventilation. It usually develops in the first 4 weeks after birth and most often affects babies born prematurely. It is caused by the pressure and high concentrations of oxygen which, when prolonged, can cause lung tissue to become inflamed and scarred. Since the lungs do not work properly, babies with CLD may have trouble breathing and are at increased risk of LRTI. Moreover, as they develop problems more quickly than other children, when pulmonary infection does occur, they are more likely to be admitted to hospital.

As a child grows and gets older, the area of tissue damage becomes less important and their condition improves. Children with CLD are therefore most vulnerable during their first 2 years

of life. This condition was previously known as bronchopulmonary dysplasia (BPD).

Children from high-risk groups constitute 53% of all children hospitalised with RSV. Mortality is less than 1% in children without underlying illness. Mortality in those with heart and lung disease who are hospitalised is estimated to be around 3–5%.⁵

Although many potential vaccines have been tested or are under development, there is currently no vaccine available. One of the challenges to developing a vaccine is the fact that the host immune responses play a role in the pathogenesis of the disease: early studies showed that children vaccinated with a formalin-inactivated RSV vaccine suffered from more severe disease on subsequent exposure to the virus than did unvaccinated control subjects and the trials resulted in the hospitalisation of 80% of vaccinees and two deaths.⁶

There are currently only two licensed specific therapies in the UK: ribavirin, which is licensed for the treatment of severe bronchiolitis caused by RSV, and palivizumab.

Description of new intervention

Palivizumab (Synagis®) is an antibody designed to provide passive immunity against RSV by preventing RSV entry in host cells and thereby preventing or reducing the severity of RSV infection. It is a humanised murine monoclonal antibody produced by recombinant technology and directed against the surface RSV fusion protein. This protein is essential for RSV to enter the host target cell.

Palivizumab was first licensed in the USA in June 1998 and across Europe in 1999 with a licensing extension in November 2003. It is currently licensed for the prevention of serious RSV-related LRTI requiring hospitalisation in children who are:

- born at ≤ 35 weeks' gestation and are less than 6 months of age at the start of the RSV season
- < 2 years of age and have required treatment for BPD within the last 6 months
- < 2 years of age and have haemodynamically significant congenital heart disease.

Current usage in the NHS

It is difficult to obtain accurate data about current practice in the UK. We first outline below some of the important UK guidance that is available and then give data on prescribing practice.

UK guidance on use of palivizumab

The *British National Formulary for Children* (BNFC) acknowledges that 'many areas of paediatric practice have suffered from inadequate information on effective medicines' and provides guidance based on information validated against emerging evidence, best practice guidelines and advice from clinical experts. Its advice on prescribing, therefore, may go beyond the licensed paediatric indications. In the case of palivizumab, the BNFC indicates that local guidelines should be consulted and states that palivizumab should be prescribed under specialist supervision and on the basis of the likelihood of hospitalisation and that the first dose should be administered before the RSV season.⁷ Hence, clinicians are recommended to take a risk-based approach in line with local guidelines.

Examples of local guidance from the West Midlands Region (where the authors are based) are given below. The Midlands Therapeutic Review & Advisory Committee (MTRAC), which makes recommendations about the appropriate use of drugs in primary care, recommended in 2000:

Restricted Use: The decision to use palivizumab should be made by a specialist. It is then appropriate for general practitioners to prescribe and administer the course of intramuscular injections.⁸

This advice is still current. The recommendation of the West Midlands Regional Advisory Panel (which advises healthcare commissioners about the appropriate use of technologies) in 2001 was:

Borderline: It is reasonable to assume that if hospital admission can be prevented then mortality may fall also. However, although the trial results were consistent with such a fall, the trial was not large enough to demonstrate a statistically significant reduction in death rates in high risk infants. The panel do not see any reason to change the current usage in high risk cases at tertiary centres.⁹

The Scottish Intercollegiate Guidelines Network has produced a guideline on bronchiolitis that concludes that palivizumab is effective but not cost-effective (based on the UK ICER threshold of £30,000/QALY). It therefore recommends that it should not be used routinely. It may, however, be used on a case-by-case basis in infants under 12 months of age with extreme prematurity, acyanotic

congenital heart disease, congenital or acquired significant lung diseases or immune deficiency. A local lead specialist should work with clinical teams to identify who might benefit from palivizumab.¹⁰

A working group of the British Paediatric Cardiac Association has developed expert group recommendations intended to assist clinicians in prescribing palivizumab to young children with CHD. They suggest that prophylaxis should be offered to infants with haemodynamically significant lesions, particularly increased pulmonary blood flow with or without cyanosis, pulmonary venous congestion, pulmonary hypertension or long-term pulmonary complications, residual haemodynamic abnormalities following medical or surgical intervention or cardiomyopathy requiring treatment, and to children likely to need admission for cardiac interventions in the RSV season. Prophylaxis at the clinician's discretion might be indicated in children with complex cardiac conditions aged over 1 year.¹¹ This is a different risk stratification to that used in the RCT of palivizumab in children with CHD.¹²

The Joint Committee on Vaccination and Immunisation (UK) recommends the use of palivizumab for children under 2 years with CLD on home oxygen or with prolonged use of oxygen; infants under 6 months old with left-to-right shunt, haemodynamically significant CHD, or pulmonary hypertension; and children under 2 years with severe congenital immunodeficiency.¹³ It should

be noted that the last recommendation is based on clinical judgement rather than research evidence and is outside the licensed indication.

It can be seen that the guidance available to clinicians recommends prescribing to children who are at particularly high risk but not to all children meeting the indication. The guidance is based more on the poor cost-effectiveness of palivizumab prophylaxis when given to all those eligible for treatment under the licensed indication than on high-quality evidence of increased effectiveness within the suggested risk groups.

Prescribing of palivizumab

We were unable to identify an audit or obtain up-to-date data on prescribing of palivizumab across the UK for secondary or tertiary care. However, worldwide, palivizumab is increasingly used, and sales generated a revenue of about US\$1.2 billion in 2005.¹⁴ In England and Wales there is no specific funding for palivizumab.

Anecdotally, secondary care clinicians we spoke to told us they would like to use this drug more because it is effective but they actually do so rarely because the very high opportunity cost would have a detrimental effect on their prescribing budgets. Such anecdotal reports, however, may reflect a biased view of clinical opinion. Therefore, we sought data on prescribing in primary and secondary care. Data for both the West Midlands and for England were provided to us by colleagues

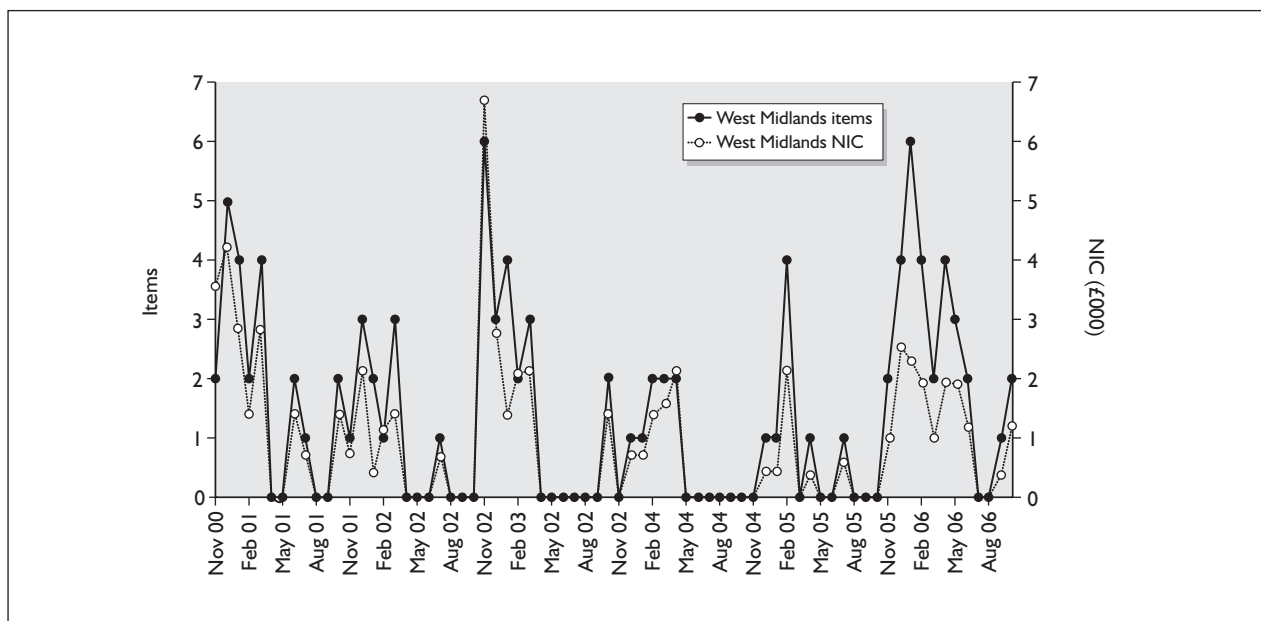


FIGURE 1 Palivizumab prescribing by item and net ingredient cost (NIC) in the West Midlands.

at the Department of Medicines Management at Keele University and are presented graphically in *Figures 1* and *2*. Primary care prescribing shows a predictable seasonal pattern and highly restricted use. The net ingredient cost (NIC) of palivizumab prescribed in primary care in England was £39,000 in 2005 and £44,000 in the first 10 months of 2006.¹⁴ The figure suggests that the West Midlands has high levels of primary care prescribing, but without national data on secondary care prescribing

it is impossible to tell whether the region has high overall palivizumab prescribing.

Figure 3 shows secondary care prescribing by item in the West Midlands (excluding FP10 prescriptions written by hospital prescribers but dispensed in the community) provided by the Department of Medicines Management, Keele University. It can be seen that most prescribing originates in secondary care and there was an approximate doubling of palivizumab prescribing in 2007 over 2006.

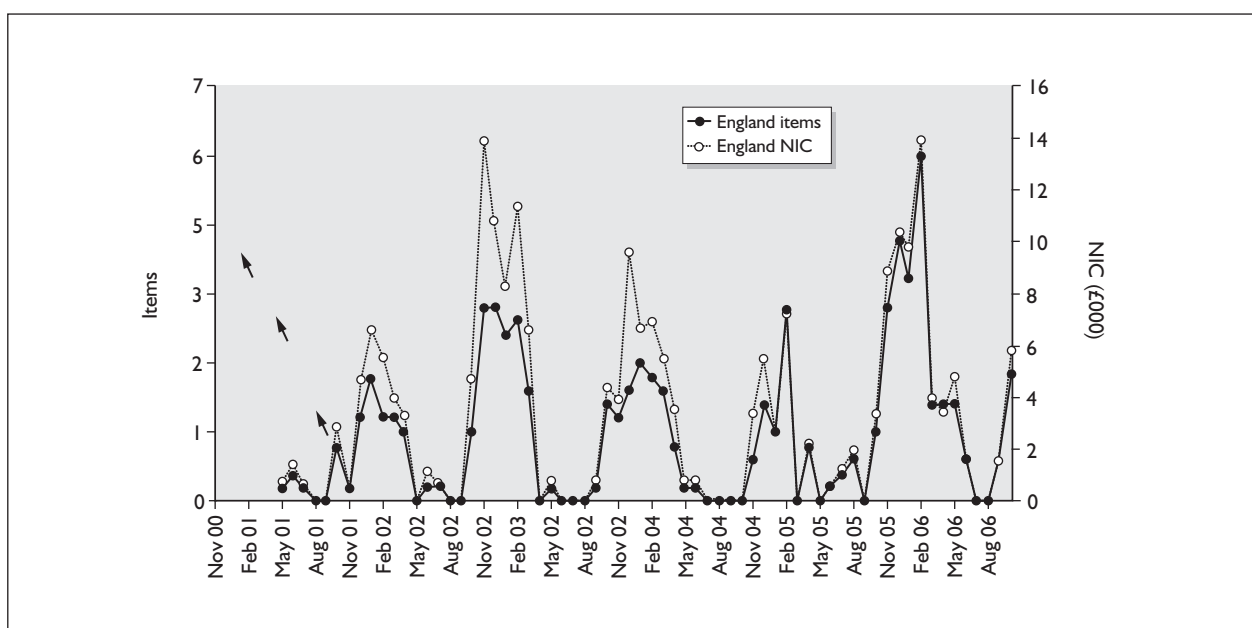


FIGURE 2 Palivizumab prescribing by item and net ingredient cost (NIC) in England.

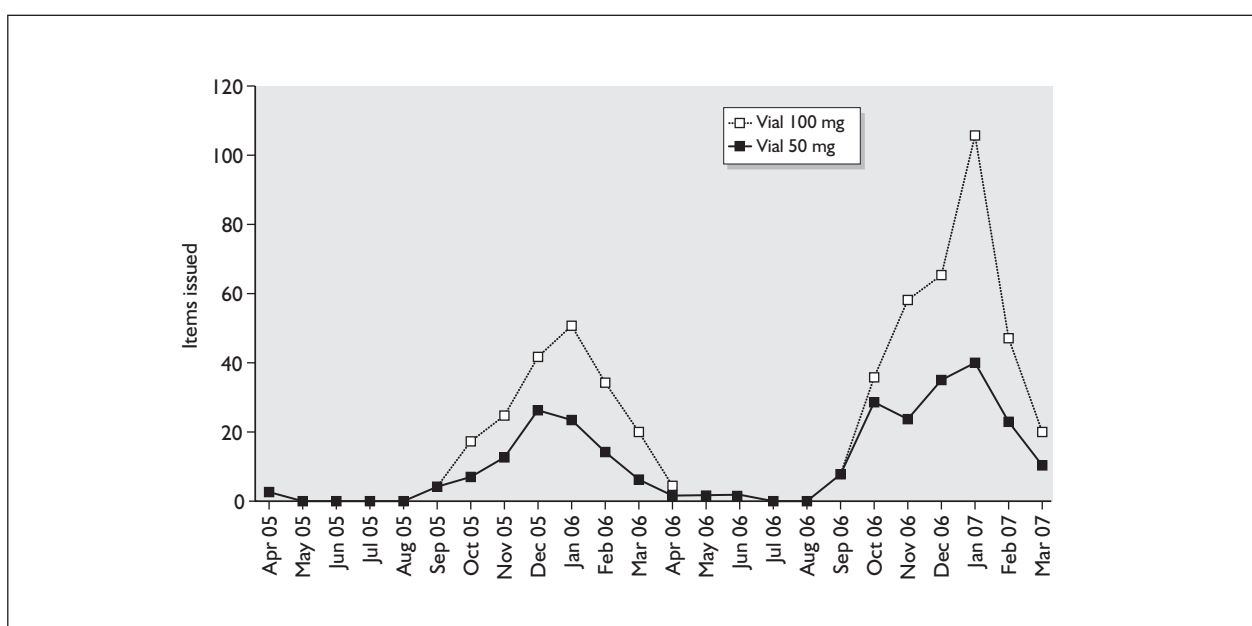


FIGURE 3 Palivizumab secondary care prescribing by item in the West Midlands.

Chapter 2

Clinical effectiveness

Methods for reviewing effectiveness

Search strategy

The following sources were searched:

- bibliographic databases: Cochrane Library (Wiley internet version) 2007 Issue 1, MEDLINE (Ovid) 1950 to March Week 2 2007, MEDLINE In-Process (Ovid) at March 26, 2007, EMBASE (Ovid) 1980 to 2007 Week 12, CINAHL (Ovid) 1982 to March 2007, Science Citation Index (Web of Knowledge) at 26 March 2007
- research registries of ongoing trials including National Research Register, Current Controlled Trials metaRegister and ClinicalTrials.gov
- reference lists of relevant studies
- relevant internet sources

No date limits or language restrictions were applied. Details of search strategies are given in Appendix 1, Search strategies – effectiveness.

Inclusion and exclusion criteria

Studies were included if they were RCTs *or* systematic reviews of RCTs that:

- included at least some high-risk children
- used palivizumab in a preventative setting at a dose and frequency comparable to that described in the licence.

Where a mixed population of high-risk and non-high risk children was reported, data were extracted for the relevant subgroups where possible. High-quality observational studies were also retrieved for consideration of adverse events, prognostic factors and other parameters required for the decision-analytical model where these were not obtainable from RCTs. Titles and were examined for inclusion by two reviewers independently. Disagreement was resolved by consensus.

Studies were excluded if they were:

- non-randomised studies

- trials conducted exclusively in non-high-risk children
- trials using a single dose of palivizumab or a dose that is not comparable to that currently used in clinical practice
- animal models
- preclinical and biological studies or
- narrative reviews, editorials, opinions.

Reports published as meeting abstracts only were also excluded if there were insufficient methodological details to allow the study quality to be appraised.

Data extraction strategy

Data were extracted independently by one reviewer using a standardised data extraction form and checked by a second reviewer. Discrepancies were resolved by discussion.

Quality assessment strategy

The quality of included studies has been assessed according to guidelines proposed in NHS CRD (Centre for Review and Dissemination) Report No. 4¹⁵ by one reviewer, and independently checked for agreement by a second reviewer. Disagreements were resolved by discussion.

Results for clinical effectiveness

Search results for clinical effectiveness

The searches for studies of effectiveness identified 601 citations, and 17 papers were retrieved after elimination of duplicate citations and exclusions made on scanning the title and abstract (*Figure 4*). Of these 17 papers, 14 were excluded on reading the paper. Excluded studies included early-phase palivizumab studies with intravenous, rather than intramuscular, administration and two open-label safety studies (these included adverse event data; Appendix 5, *Table 43*).

Two RCTs of palivizumab (Impact¹⁶ and Feltes¹²) and one systematic review¹⁷ that met the

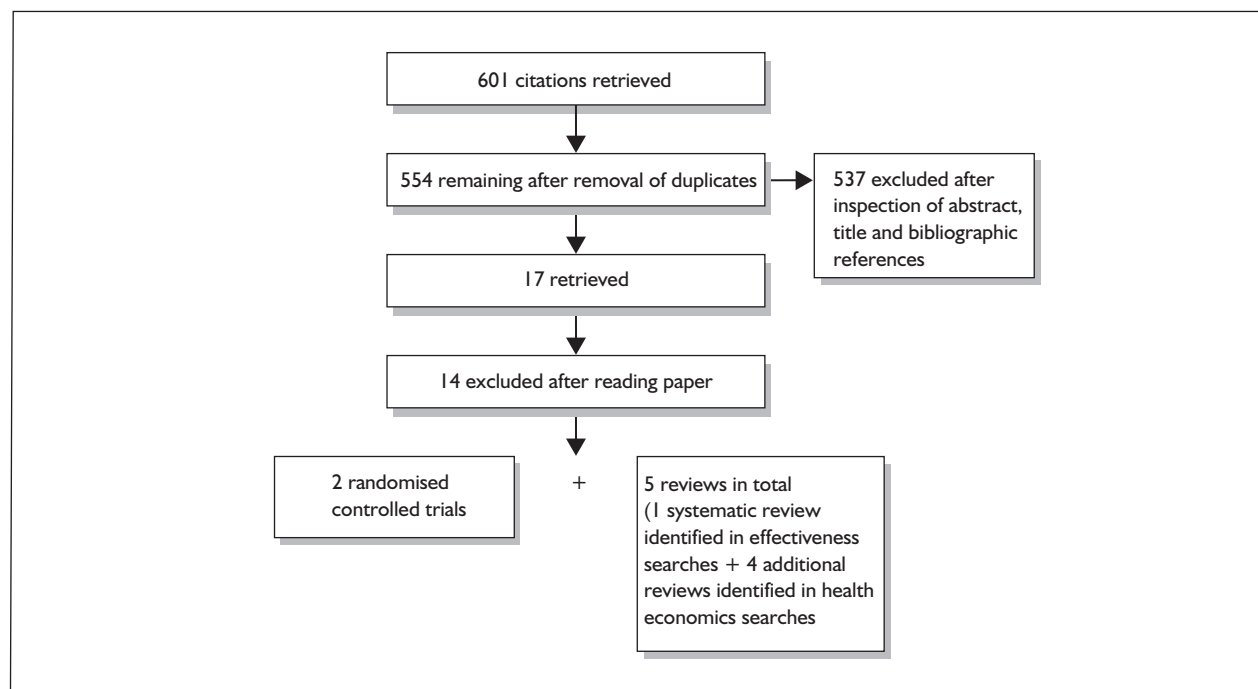


FIGURE 4 Flow chart showing identification of effectiveness studies.

inclusion criteria were identified from the clinical effectiveness searches. Additional systematic reviews were identified in the economic searches (see *Table 1* for details) and were read to see if they contained additional useful information on effectiveness. None of these systematic reviews, however, included any trials other than those identified in the searches or included formal meta-analyses.

Summary of included RCTs

Data on study quality, design and results was abstracted from the two included RCTs. Both

studies were of high quality. They were randomised with adequate concealment of allocation, double-blind and with loss to follow-up clearly reported and high level of follow-up of trial patients.

Trial populations

The patient population of one trial (IMpact) was premature infants aged ≤ 6 months or children aged ≤ 2 years with bronchopulmonary dysplasia (BPD) that had required treatment in the last six months. The population of the other trial was children aged ≤ 2 years with haemodynamically or partially corrected congenital heart disease (*Table 2*).

TABLE 1 Systematic reviews

Study	Comments
Raya <i>et al.</i> , 2006 ¹⁸	Update. Systematic review as part of cost-effectiveness study. Population: preterm babies. One trial and one cohort study included
Dunfield and Mierzwinski-Urban, 2007 ¹⁷	Postdates effectiveness searches. Includes IMpact and Feltes
Viswanathan <i>et al.</i> , 2003 ¹⁹	Cited in Dunfield and Mierzwinski-Urban, 2007 ¹⁷
Embleton <i>et al.</i> , 2005 ²⁰	Cited in Dunfield and Mierzwinski-Urban, 2007, ¹⁷ Population: preterm children. Included IMpact, Subramanian, 1998, ²¹ and Saez-Llorens, 1998 ²²
Simpson and Burls, 2001 ^{9a}	Health technology assessment
a Identified in the health economics searches.	

TABLE 2 Characteristics of the randomised control trials

Study	Population	Inclusion/exclusion criteria	Intervention	Comparator
IMpact-RSV Study Group 1998 ¹⁶	≤ 35 weeks' gestation and aged 6 months or younger or 24 months old or younger with clinical diagnosis of BPD requiring ongoing medical treatment in last 6 months	Exclusion: hospitalisation anticipated to last > 30 days or mechanic ventilation at time of entry; life expectancy < 6 months; active or recent RSV infection; hepatic or renal dysfunction or seizure disorder or immunodeficiency or allergy to IgG products; receipt of RSV immunoglobulin within 3 months; previous receipt of RSV vaccines, palivizumab, other monoclonal antibodies or other investigational agents; congenital heart disease except patient ductus arteriosus or uncomplicated and haemodynamically insignificant septal defect	Palivizumab 15 mg/kg i.m. every 30 days for five doses; 2:1 randomisation	Placebo
Feltes et al., 2003 ¹²	≤ 24 months old, haemodynamically significant CHD and unoperated or partially corrected CHD	Exclusion: cardiac respiratory instability; survival not expected; cardiac transplant planned/anticipated; hospitalised (unless discharge anticipated within 21 days); anticipated cardiac surgery within 2 weeks of randomisation; mechanical cardiac or respiratory support; anomalies/end-organ dysfunction so anticipate survival < 6 months; unstable; HIV/RSV/other acute infection/illness; investigational agents within the previous 3 months; uncomplicated small atrial or ventricular septal defects or patient ductus arteriosus	Palivizumab 15 mg/kg i.m. every 30 days for five doses	Placebo

CHD, congenital heart disease; HIV, human immunodeficiency virus; IgG, immunoglobulin G; i.m., intramuscularly; RSV, respiratory syncytial virus.

Intervention and comparator

Both trials compared palivizumab 15 mg/kg i.m. every 30 days for five doses with placebo.

Outcome measures

The primary outcome in both studies was hospitalisation with proven RSV infection. Secondary outcomes are listed in *Table 3*.

Summary of studies

The design and baseline characteristics of the two RCTs are described in *Tables 2, 3* and *4*.

IMpact-RSV

The IMpact-RSV¹⁶ trial was conducted in 1998 for infants born at ≤ 35 weeks of gestation or children with CLD using the now outdated clinical term and definition BPD. However, it is likely that the BPD patient population is very similar to the CLD population. A total of 1502 children who were born at ≤ 35 weeks gestational age and who were ≤ 6 months old at the beginning of RSV season, or who were diagnosed with CLD and were ≤ 2 years old at the beginning of RSV season, were included in the study.

TABLE 3 Study characteristics: outcomes and follow-up

Study	Primary outcome	Secondary outcomes	Length of follow-up
IMpact-RSV Study Group, 1998 ¹⁶	(1) Hospitalisation for respiratory illness and positive RSV antigen in respiratory secretions or (2) hospitalised for other reasons and positive RSV test and LRI score ≥ 3 and at least one point higher than last pre-illness visit	Days hospitalised; RSV hospitalisation days with increased supplemental oxygen; total days moderate/severe respiratory infection (LRI score); frequency and total days in ICU and mechanical ventilation; clinically diagnosed otitis media; adverse events	150 days
Feltes et al., 2003 ¹²	Incidence of RSV hospitalisation including primary (acute cardiorespiratory illness, RSV antigen positive within 48 h before/after admission) and nosocomial hospitalisations; deaths outside hospital demonstrated to be associated with RSV	Total days hospitalised; days on supplemental oxygen; days in ICU; days on mechanical ventilation; adverse events	150 days

ICU, intensive care unit; LRI, lower respiratory illness/infection; RSV, respiratory syncytial virus.

TABLE 4 Results: recruitment and baseline

Study	n, intervention	n, control	Baseline characteristics	Dosing	Follow-up
IMpact-RSV Study Group, 1998 ¹⁶	1002	500	Balanced except number of smokers in household: 69% palivizumab, 63% control	Five injections: 92% palivizumab and 94% placebo	1486 completed follow-up: 99% palivizumab, 99% placebo
Feltes <i>et al.</i> , 2003 ¹²	639	648	Balanced	Five injections: 93.0% palivizumab and 91.8% placebo	95.6% of palivizumab and 95.5% of placebo group completed the study

The children were randomised to receive 15 mg/kg palivizumab (1002 infants) or placebo (500 infants) every 30 days during the RSV season. A total of five doses were administered over 4 months. The infants were followed up for 150 days from randomisation in order to cover the first RSV season the babies were exposed to. The primary end point was hospital admission for respiratory illness and a positive test for RSV or, in the case of children who were already hospitalised, a positive RSV test with a moderate lower respiratory tract illness score of 3.¹⁶ (Lower respiratory illness score: 0 = no respiratory illness, 1 = upper respiratory tract illness, 2 = mild lower respiratory tract illness, 3 = moderate lower respiratory tract illness, 4 = severe lower respiratory tract illness, 5 = mechanical ventilation.) Prophylaxis with palivizumab resulted in a 55% reduction in RSV hospital admission, with 4.8% (Table 5) in palivizumab group and 10.6% (Table 5) in the no prophylaxis group ($p = 0.0004$). The study also reported RSV hospital admissions for subgroups of children. For preterm infants without CLD, the reduction in RSV hospital admission was 78% (Table 5) ($p = 0.001$). For children with CLD, the reduction in RSV hospital admission was 39% (Table 5) ($p = 0.038$). The reported subgroup analysis does not in itself demonstrate a difference in effect sizes for the two groups. Using the values reported, a test for interaction is marginally significant ($p = 0.05$), suggesting that palivizumab may be more effective in reducing hospitalisations for premature children than for those with CLD.

The number of children reporting adverse events judged by the blinded investigator to be related to the treatment was similar in the placebo and palivizumab groups. The reported adverse events included injection site reactions, fever and rash. These events were generally mild and of short duration. None was serious. Four deaths (0.4%) were reported in the palivizumab group and five deaths (1%) were reported in the placebo

group. No deaths were judged to be related to palivizumab. Two studies^{23,24} reported the mortality rates for those who were admitted to hospital due to RSV infection. Meta-analysis of these studies gives a mortality rate of 6.68% for RSV hospital admission. However, this mortality rate might not be RSV related. The study by Nuijten *et al.*²⁵ used a mortality rate of 8.11% for RSV hospitalisation group (taken from the Sampalis and Sampalis²³ study, which is discussed below), which is the main reason that the study reported a lower ICER.

Feltes *et al.*

The RCT by Feltes *et al.*¹² was conducted for children with CHD. A total of 1287 children aged ≤ 24 months were randomised to receive 15 mg/kg palivizumab (639 children) or placebo (648 children) every 30 days during the RSV season. The children were followed up for 150 days from randomisation to cover exposure to the relevant RSV season. The results showed that monthly prophylaxis with palivizumab was associated with a 45% reduction in RSV hospitalisation rate. RSV hospitalisation rates were 5.3% (Table 5) in the palivizumab group and 9.7% (Table 5) in the no prophylaxis group. The reduction was statistically significant with a p -value of 0.003. The RCT reported RSV hospitalisation rates of 5.6% (Table 5) for prophylaxis with palivizumab and 7.9% (Table 5) for no prophylaxis in the cyanotic stratum (pulmonary atresia with ventricular/intact septum, tetralogy of Fallot, single ventricle including hypoplastic right/left heart, tricuspid atresia, double-outlet right ventricle with transposed arteries, Ebstein anomaly, D-transposition of great arteries) with a p -value of > 0.05 , and 5% vs 11.8% in the acyanotic stratum with a p -value of 0.003. These correspond to a 29% reduction in RSV hospitalisation for children with cyanotic CHD, and a 58% reduction in RSV hospitalisation for children with acyanotic CHD. A test for interaction suggests that there is no evidence of a difference in effects between cyanotic and acyanotic CHD ($p > 0.1$).

The external validity of this study is questionable – a cohort study in Switzerland by Duppenenthaler *et al.*²⁶ reported that RSV hospitalisation rates in CHD patients less than 24 months of age varied from 0.5% to 2.5%, rates that are much lower than that reported by Feltes *et al.*¹², suggesting that the RCT may have recruited patients with particularly serious conditions. Switzerland is the same continent as the UK and is at similar latitude. Hence, RSV seasons are likely to be comparable.

The reported adverse events included injection site reactions, fever, conjunctivitis, arrhythmia and cyanosis. The numbers of adverse events reported were similar in the palivizumab group and the no prophylaxis group. Twenty-one deaths (3.3%) were reported in the palivizumab group and 27 deaths (4.2%) were reported in the placebo group. No deaths were attributed to palivizumab.

Recruitment and baseline characteristics of the two studies are reported in *Table 4*. The IMPact study had a 2:1 palivizumab–placebo randomisation, whereas the CHD trial had a 1:1 randomisation. There were few differences in the distribution of baseline characteristics between trial arms. As the baseline characteristics were balanced, confounding factors were unlikely to have influenced the outcomes of palivizumab.

As the populations of the two trials were different, premature infants and children with BPD and children with congenital heart disease, quantitative synthesis was not attempted.

In both trials, around 10% of patients in the placebo arm were hospitalised with RSV infection. There was a significant reduction in the risk of hospitalisation with palivizumab, 55% (95% CI 38–72%) in premature infants and children with CLD and 45% (95% CI 23–67%) in children with CHD (*Table 5*).

Secondary outcome results are reported in *Table 6*. Both trials reported a reduction in the days hospitalised. The risk of ICU admission and ICU days were significantly reduced in premature infants and children with CLD, but not in children with CHD. In the IMPact study, days hospitalised and days hospitalised for respiratory infections were reduced, but days of mechanical ventilation and non-respiratory hospitalisation and the incidence of otitis media were not reduced. In the Feltes *et al.*¹² study, days with supplemental oxygen in the course of an RSV admission were significantly reduced, but ICU admissions, ICU days, mechanical ventilation and mechanical ventilation days were not significantly reduced.

TABLE 5 Results: primary outcomes

Study	Primary outcome result: intervention	Primary outcome result: control	Primary outcome result: intervention vs control
IMPact-RSV Study Group, 1998 ¹⁶	RSV hospitalisation: 48/1002 (4.8%)	RSV hospitalisation: 53/500 (10.6%)	Reduction in RSV hospitalisation with palivizumab 55% (95% CI 38–72%) ($p = 0.0004$)
	With CLD: 39/496 (7.9%)	With CLD: 34/266 (12.8%)	With CLD: 39% (95% CI 20–58) ($p = 0.038$)
	Premature no CLD: 9/506 (1.8%)	Premature no CLD: 19/234 (8.1%)	Premature no CLD 78% (95% CI 66–90) ($p < 0.001$)
Feltes <i>et al.</i> , 2003 ¹²	RSV hospitalisation: 34/639 (5.3%)	RSV hospitalisation: 63/648 (9.7%)	Reduction in RSV hospitalisation with palivizumab: 45% (95% CI 23–67) ($p = 0.003$)
	Cyanotic (pulmonary atresia with ventricular septum defect/intact septum, tetralogy of Fallot, single ventricle including hypoplastic right/left heart, tricuspid atresia, double-outlet right ventricle with transposed arteries, Ebstein anomaly, D-transposition of great arteries): $n = 339$ (5.6%)	Cyanotic (pulmonary atresia with ventricular septum defect/intact septum, tetralogy of Fallot, single ventricle including hypoplastic right/left heart, tricuspid atresia, double-outlet right ventricle with transposed arteries, Ebstein anomaly, D-transposition of great arteries): $n = 343$ (7.9%)	29% ($p = 0.285$)
	Non-cyanotic: $n = 300$ (5.0%)	Non-cyanotic: $n = 305$ (11.0%)	58% ($p = 0.003$)
CLD, chronic lung disease; RSV, respiratory syncytial virus.			

Subgroups

In the IMpact trial, pre-specified subgroups were premature infants and children with CLD. There was a reduction in the risk of RSV hospitalisation in both groups, with a greater reduction in the premature (78%; 95% CI 66–90%) than in the CLD group (39%; 95% CI 20–58%) (Table 5). This is a

marginally significant difference in effect between the two groups ($p = 0.05$).

In the trial by Feltes *et al.*¹², pre-specified subgroups were cyanotic and non-cyanotic heart disease (see Table 5 for precise definition), with a non-significant 29% reduction in RSV hospitalisation in

TABLE 6 Results: secondary outcomes

Study	Secondary outcomes results: intervention	Secondary outcomes results: control	Secondary outcomes results: intervention vs control
IMpact-RSV Study Group, 1998 ¹⁶	Days per 100 children	Days per 100 children	
	Hospitalised: 36.4	Hospitalised: 62.6	$p < 0.001$
	Increased oxygen: 30.3	Increased oxygen: 50.6	$p < 0.001$
	LRI ≥ 3 : 29.6	LRI score ≥ 3 : 47.4	$p < 0.001$
	ICU admission: 1.3%	ICU admission: 3%	$p = 0.026$
	Total ICU days: 13.3	Total ICU days: 12.7	$p = 0.023$
	Mechanical ventilation: 0.7%	Mechanical ventilation: 0.2%	$p = 0.280$
	Total mechanical ventilation days: 8.4	Total mechanical ventilation days: 1.7	$p = 0.210$
	Hospitalisation	Hospitalisation	
	Total 24%	Total 31%	$p = 0.011$
	Respiratory: 16%	Respiratory: 22%	$p = 0.008$
	Unrelated to RSV: 13%	Unrelated to RSV: 14%	$p = 0.470$
	Hospitalisation days per 100 children	Hospitalisation days per 100 children:	
	Total: 191	Total: 242	$p = 0.005$
	Respiratory: 124	Respiratory: 180	$p = 0.004$
	Unrelated to RSV: 88	Unrelated to RSV: 118	$p = 0.369$
Feltes <i>et al.</i> 2003 ¹²	Otitis media: 42%	Otitis media: 40%	$p = 0.505$
			Relative reduction: % (p-value)
	Days RSV hospitalisation	Days RSV hospitalisation	
	Total days: 367	Total days: 836	
	Total days/100 children: 57.4	Total days/100 children: 129.0	56% ($p = 0.003$)
	RSV hospital days of increased supplemental oxygen therapy	RSV hospital days of increased supplemental oxygen therapy	
	Total days: 178	Total days: 658	
	Total days/100 children: 27.9	Total days/100 children: 101.5	73% ($p = 0.014$)
	ICU admission: 13 (2%)	ICU admission: 24 (3.7%)	46% ($p = 0.094$)
	Days of ICU stay	Days of ICU stay	
	Total: 101	Total: 461	
	Total days/100 children 15.9	Total days/100 children: 71.2	78% ($p = 0.080$)
	Mechanical ventilation: 8 (1.3%)	Mechanical ventilation: 14 (2.2%)	41% ($p = 0.282$)
	Days of mechanical ventilation	Days of mechanical ventilation	
	Total days: 42	Total days: 354	
	Total days/100 children: 6.5	Total days/100 children: 54.7	88% ($p = 0.224$)
ICU, intensive care unit; RSV, respiratory syncytial virus.			

the cyanotic group and a 58% reduction in the non-cyanotic group ($p = 0.003$). A test for interaction suggested no evidence of a difference in effect between the two groups.

Overall adverse events

Adverse effects are given in *Table 7*. There was no evidence that palivizumab was associated with greater frequency of adverse events or associated with serious adverse events. The most frequently reported events believed to be related to palivizumab were injection site reactions, fever and nervousness. Events were generally mild and of short duration. Antibodies to palivizumab were detected in about 1% of infants in the IMpact study. There were no differences in death rates but the trials were not statistically powered to show such a difference.

A small study of 88 infants from IMpact evaluated the safety of palivizumab for a second season.²⁷ Of the 88 infants studied, 56 received palivizumab for a second season. Mean age at entry to this study was 16 months, and approximately 20% of infants had CLD. Palivizumab was administered at the same dose and frequency as before. The researchers reported no local or systemic reactions suggestive of a possible immune-mediated response.

Summary of effectiveness results

There is limited good-quality evidence from two trials that palivizumab reduces the need for hospitalisation due to RSV by around 50% in the trial populations and is relatively safe.

Subgroup analysis suggested that palivizumab may be more effective in premature babies than in children with CLD. It could be speculated that this may be related to a greater need for hospitalisation with milder infection in the CLD group.

The reduction in RSV hospitalisation was also slightly greater in children with non-cyanotic rather than cyanotic congenital heart disease (see *Table 5*), but this trial was underpowered to detect a difference between these subgroups and there is no evidence of a true underlying difference in effect size.

Although we outlined in the protocol that other high-risk groups, for example children with cystic fibrosis or immune deficiency, would be assessed, we have not found the relevant data for cystic fibrosis or immune deficiency subgroups.

TABLE 7 Results: adverse events

Study	Adverse event	Intervention	Comparator
IMpact-RSV Study Group, 1998 ¹⁶	Children reporting adverse events	11%	10%
	Deaths (not considered related to intervention)	4 (0.4%, two during RSV admission)	5 (1.0%)
	Fever	2.8%	3.0%
	Nervousness	2.5%	2.6%
	Injection site reaction	2.3%	1.6%
	No statistically significant differences in prevalence of other adverse events (prevalence $\leq 1\%$)		
Feldes et al., 2003 ¹²	Children reporting adverse events	611 (95.6%)	625 (96.5%)
	Deaths ($p = 0.463$)	21 (3.1%)	27 (4.2%)
	Cardiovascular ($p = 0.180$)	286 (44.8%)	315 (48.6%)
	Respiratory ($p = 0.296$)	525 (82.2%)	547 (84.4%)
	Requiring medical intervention ($p = 0.392$)	588 (92.0%)	605 (93.4%)
	Related ($p = 0.914$)	46 (7.2%)	45 (6.9%)
	Serious ($p = 0.005$)	354 (55.4%)	409 (63.1%)
	Related serious ($p = 0.249$)	0	3 (0.55%)

Chapter 3

Existing economic evaluations

The aim of this section is to estimate the cost-effectiveness of palivizumab for immunoprophylaxis of RSV in high-risk children or particular subgroups of children at even higher risk. This section contains two components: (1) systematic review and analysis of published economic evaluations and reviews of economic evaluations; (2) economic analysis of palivizumab using a decision model developed by the authors.

Systematic review of economic evaluations

Methods

Search strategy

A comprehensive search for literature on the cost and cost-effectiveness of palivizumab versus no prophylaxis for immunoprophylaxis of RSV in high-risk children was conducted.

Studies on costs, quality of life, cost-effectiveness and modelling were identified from the following sources:

- bibliographic databases: MEDLINE (Ovid), 1950 to January, week 3, 2007; EMBASE (Ovid), 1980 to 2007, week 03; Cochrane Library (Wiley internet version) [NHS Economic Evaluation Database (EED) and Database of Abstracts and Reviews of Effects], 2006, Issue 4; and Office of Health Economics Health Economic Evaluation Database (HEED), January 2007 issue
- internet sites.

Searches were not limited by date and there were no language restrictions. Details of search strategies can be found in Appendix 2.

Inclusion and exclusion criteria

Inclusion criteria applied for economic searches are summarised below.

- **Study design:** cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis.
- **Population:** children at high risk of hospitalisation, morbidity or death due to RSV infection.

- **Intervention:** immunoprophylaxis with palivizumab.
- **Comparator:** no prophylactic treatment.

Cost analysis was excluded.

Study selection and quality assessment

One reviewer applied the inclusion and exclusion criteria and extracted data. These were checked by a second reviewer. The quality of included primary economic evaluations was assessed using an adapted version of the Drummond criteria for economic evaluations.²⁸ A modified version of the Oxman and Guyatt²⁹ assessment tool and scale was used to assess the quality of reviews. Disagreements were resolved by discussion. The main characteristics, quality assessment and results of included economic evaluations were tabulated (see below).

Analysis

In order to make different ICERs comparable, they were converted from their currencies to pounds sterling (£) using an online currency converter.³⁰ Once converted to pounds sterling, the cost data were inflated to 2006 prices using the NHS Executive Hospital and Community Health Services Pay and Prices inflation index.³¹ For those studies that did not report price year, the incremental cost-effectiveness ratios were converted to pounds sterling using the rate in their study year.

Results of review of economic evaluations

The searches produced 240 citations, of which 207 citations were excluded on the basis of the title and abstracts as they did not fulfil one or more of the inclusion criteria in terms of the population, the intervention or design of the studies. The full text was obtained for 33 citations for further assessment. Twelve studies were excluded. The details of the studies and reasons for exclusion are given in Appendix 5, *Table 44*. Twenty-one studies reached the final stage of our review and were considered for data extraction (*Figure 5*). Three of the included studies are systematic reviews of economic evaluations (*Table 8*) and the remaining

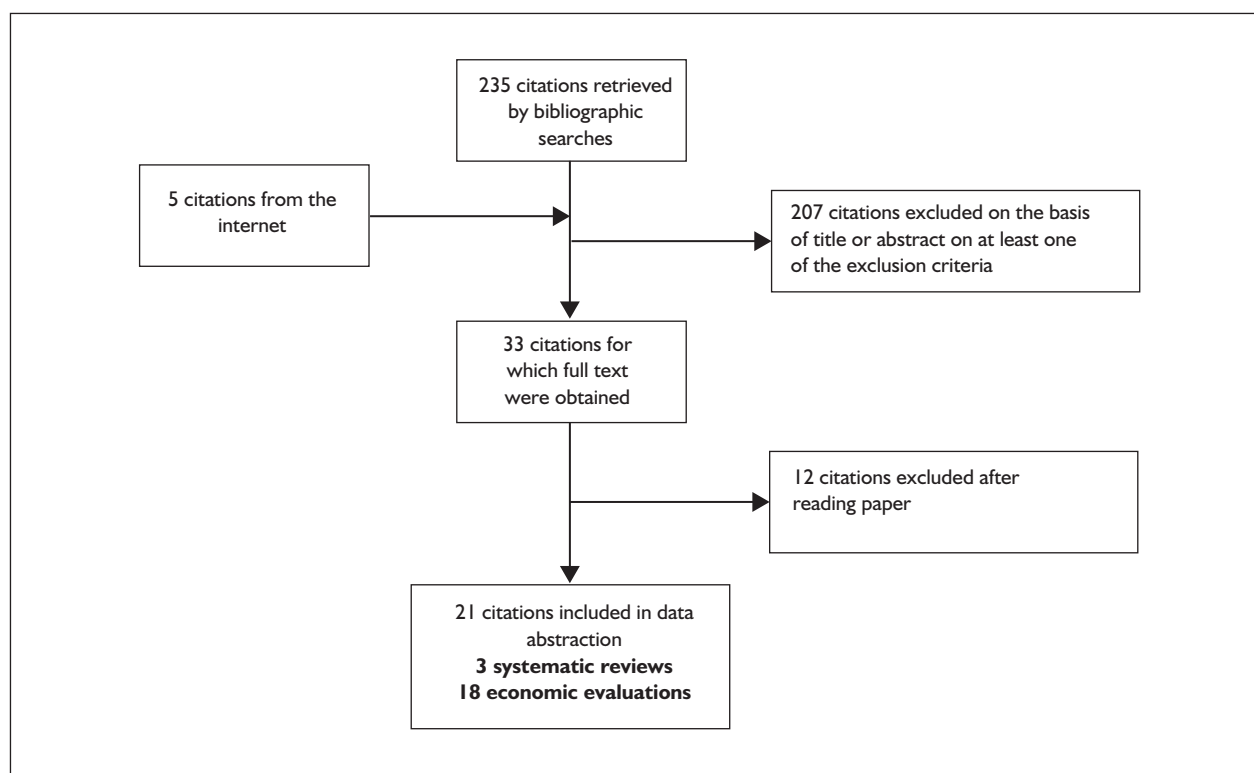


FIGURE 5 Flow chart of identification of existing economic evaluations.

18 are primary economic evaluation studies (*Table 9*).

The quality of the systematic reviews was moderate: none assessed the quality of the included primary economic evaluation studies. Details of the quality assessments are given in *Table 45* (see Appendix 6). The three systematic reviews encompassed two, four and four primary economic evaluations that were identified in this report, respectively. All the reviews qualitatively summarised the results of the included economic evaluations and did not develop decision-analytical models to estimate the cost-effectiveness of prophylaxis with palivizumab.

All the systematic reviews stated that the potential costs of palivizumab were far in excess of any likely savings achieved by decreasing hospital admission rates, and that palivizumab is not cost-effective when used in all children for whom it is licensed at a willingness-to-pay threshold of £60,000/QALY or less, and that continued use of palivizumab for very high risk children may be justified. Details of the main findings of the systematic reviews are summarised in *Table 8*.

The 18 primary economic evaluation studies included were assessed and found to be of

variable quality. Most of the studies clearly defined questions and described the competing alternatives, correctly established clinical effectiveness, performed incremental analysis of both costs and consequences, and clearly presented the results. However, some studies did not identify all relevant costs and consequences and others did not accurately measure or value the costs and consequences. More than half of the included studies did not consider discounting of costs and consequences for differential timing adjustment. Most of the studies did not carry out an adequate sensitivity analysis. Fewer than half of the studies used a lifetime time horizon; others did not specify the time horizon or used a time horizon of 1 year. Half of the studies did not report the price year. Full details of the quality of assessments can be found in *Table 47* (see Appendix 8).

The characteristics of the included primary economic evaluations are summarised in *Table 9*. Most studies performed cost-effectiveness or cost-utility analyses, the remaining studies performed cost-benefit analysis. Most studies ($n = 10$) reported the ICER in terms of cost per hospital admission prevented (HAP), some studies ($n = 5$) reported the incremental cost per life-year gained (LYG), and others ($n = 4$) reported the incremental cost

TABLE 8 Summary results of systematic reviews of economic evaluations

Study	Country	Population	Intervention	Comparator	Main findings
Dunfield and Mierzwinski-Urban, 2007 ¹⁷	Canada	Premature children with or without CLD or children with CHD	Palivizumab	No prophylaxis	The results of the included studies were variable; this may be due to different cost data sources Palivizumab was not cost-effective when used in all children for whom it is recommended Owing to the high cost of palivizumab, only children at very high risk of RSV should be administered palivizumab None of the identified studies was a comprehensive economic analysis
Embleton <i>et al.</i> , 2005 ²⁰	UK	Premature infants with or without CLD	Palivizumab	No prophylaxis	All studies noted that true societal costs could not be addressed. None of the UK cost studies showed economic benefit for palivizumab prophylaxis The costs of prophylaxis were far in excess of any likely savings achieved by decreasing hospital admission rates In the absence of a comprehensive economic assessment, continued use of palivizumab for high-risk children, such as those with CLD, may appear justified The potential cost of palivizumab prophylaxis far exceeded the actual cost of hospitalisation The reported divergent results may be explained by differences in the study methods, assumptions and the poor quality of some economic evaluations Policy-makers, or providers or payers, need to critically appraise and judiciously interpret the cost-effectiveness of palivizumab
Kamal <i>et al.</i> , 2002 ³²	USA	Premature infants with or without CLD	Palivizumab	No prophylaxis	
CHD, congenital heart disease; CLD, chronic lung disease.					

TABLE 9 Characteristics of included primary economic evaluations

Author	Country	Study design	Population	Female (%)	Intervention	Comparator	Perspective	Model	Time horizon
Farina <i>et al.</i> , 2002 ³¹	Argentina	CEA	Born at ≤ 35 weeks GA (≤ 6 months) or at ≤ 28 weeks GA (≤ 12 months) or CLD ≤ 2 years	29	Palivizumab	No prophylaxis	Societal (stated, but not strictly)	Not specified	2 years
Numa, 2000 ³⁸	Australia	CBA, CEA	Born at ≤ 35 weeks GA (≤ 6 months) or CLD ≤ 2 years	43	Palivizumab	No prophylaxis	Provider	Not specified	Not specified
Reeve <i>et al.</i> , 2006 ³⁵	Australia	CEA	Hospitalised children positive for RSV either born at < 33 weeks GA or with birth weight < 2500 g (and/or of indigenous origin or with siblings) or with CLD or CHD, ex-NICU	Not specified	Palivizumab	No prophylaxis	Provider	Not specified	Not specified
Roeckl-Wiedmann <i>et al.</i> , 2003 ³⁶	Germany	CEA	Born at ≤ 35 weeks GA with or without CLD	0	Palivizumab	No prophylaxis	Societal	Decision-analytical model	1 year
Chiroli, 2005 ³⁷	Italy	CEA	CHD ≤ 2 years	46	Palivizumab	No prophylaxis	Third payer	Decision-analytical model	Life time
Vogel <i>et al.</i> , 2002 ³⁸	New Zealand	CEA	Born at ≤ 32 weeks GA	Not specified	Palivizumab	No prophylaxis	Societal	Not specified	Not specified
de Armentia, 2003 ³⁹	Spain	CEA	Born at ≤ 32 weeks GA	Not specified, about 50% because of cohort	Palivizumab	No prophylaxis	Health service	Not specified	2 years
Lazaro <i>et al.</i> , 2006 ⁴⁰	Spain	CUA	Born at 32–35 weeks GA	Not specified	Palivizumab	No prophylaxis	Provider, societal	Decision-analytical model	Life time

Author	Country	Study design	Population	Female (%)	Intervention	Comparator	Perspective	Model	Time horizon
Raya <i>et al.</i> , 2006 ¹⁸	Spain	CEA	Born at 32–35 weeks GA inclusive and two or more risk factors ^a	Not specified	Palivizumab	No prophylaxis	Hospital	Decision-analytical model	1 year
Simpson and Burls, 2001 ⁹	UK	CEA	Born at ≤ 35 weeks GA (≤ 6 months), or CLD ≤ 2 years	43	Palivizumab	No prophylaxis	Provider	Decision-analytical model	Lifetime
Nuijten <i>et al.</i> , 2007 ²⁵	UK	CUA	Born at ≤ 35 weeks GA (≤ 6 months), or CLD ≤ 2 years or CHD ≤ 2 years	43–46	Palivizumab	No prophylaxis	Provider, societal	Decision-analytical model	Lifetime
Joffe, 1999 ⁴¹	USA	CEA	Born at ≤ 36 weeks GA	Not specified	Palivizumab	No prophylaxis	Societal, clinician, policy-maker	Decision-analytical model	Lifetime
Lofland <i>et al.</i> , 2000 ⁴²	USA	CEA	Born at ≤ 35 weeks GA (≤ 6 months)	43	Palivizumab	No prophylaxis	Provider	Decision-analytical model	1 year
Stevens <i>et al.</i> , 2000 ⁴³	USA	CEA	Born at ≤ 32 weeks GA	Not specified	Palivizumab	No prophylaxis	Provider	Not specified	Not specified
Shireman and Braman, 2002 ⁴⁴	USA	CBA	Born during RSV season ≤ 10 months	39	Palivizumab	No prophylaxis	Provider	Not specified	1 year
Strutton and Stang, 2003 ⁴⁵	USA	CEA	Born at ≤ 35 weeks GA	Not specified	Palivizumab	No prophylaxis	Payer, societal	Not specified	Not specified
Yount <i>et al.</i> , 2004 ⁴⁶	USA	CUA	CHD ≤ 2 years	46	Palivizumab	No prophylaxis	Societal	Decision-analytical model	Life time
ElHassan <i>et al.</i> , 2006 ⁴⁷	USA	CBA, CUA	Hypothetical cohort of children born at 26–32 weeks GA without CLD	Not specified	Palivizumab	No prophylaxis	Societal	Decision-analytical model	1 year without asthma, 8 years with asthma

CEA, cost-effectiveness analysis; CBA, cost-benefit analysis; CLD, chronic lung disease; CUA, cost-utility analysis; GA, gestational age; NICU, neonatal intensive care unit; RSV, respiratory syncytial virus.
a Breast feeding for less than 2 months, age < 10 weeks at start of season, sibling of school age, live with four or more adults, family history of allergy.

per quality-adjusted life-year (QALY). About half of the studies employed a societal perspective; others employed provider, or payer, or third-party perspectives.

The summary results of the included primary economic evaluations are given in *Table 10*.

The results of the included economic evaluation studies show that the ICERs vary from £5307/HAP to £69,240/HAP with mean of £33,190/HAP (SD £17,807/HAP), from £5288/LYG to £1,104,351/LYG with mean £202,104/LYG (SD £78,066/LYG), and from £3,164/QALY to £1,489,668/QALY with mean £547,817/QALY (SD £169,082/QALY).

In the UK study by Simpson and Burls⁹ values of £55,000/HAP and £122,800/LYG were reported for preterm infants or children with CLD (less than 2 years old). The most recent economic evaluation (2007) is a UK study by Nuijten *et al.*²⁵ funded by the manufacturer of palivizumab. This reported ICERs of £25,800/LYG and £18,900/QALY for preterm infants or children (less than 2 years old) with CLD, and £7900/LYG and £7,500/QALY for children with CHD.

An analysis of existing economic evaluations

The ICERs vary a lot from study to study. This makes it difficult for decision-makers to decide whether prophylaxis with palivizumab is effective. In order to find what is driving the differences between the ICERs we looked at the results for systematic differences in the populations, interventions, metrics, outcomes, time horizons and other parameters. These differed; for example, doses of palivizumab used in the economic evaluations were different, varying from four to six, while two studies did not specify dose. Studies also used different perspectives: half of the studies estimated ICERs from a societal perspective and others from a provider or hospital perspective. The time horizons were different, most varying from 1 year to 2 years, while two of the studies did not specify time horizon.

Population

The studies by Simpson and Burls⁹, Raya *et al.*¹⁸, Farina *et al.*³³, Reeve *et al.*³⁵, Roeckl-Wiedmann *et al.*³⁶, Vogel *et al.*³⁸, de Armentia³⁹, Lofland *et al.*⁴² and Stevens *et al.*⁴³ assessed the cost-effectiveness of palivizumab in terms of cost per hospital admission prevented (HAP). Although the populations of

these studies were preterm infants with gestational age less than 36 weeks, some studies reported cost-effectiveness for different subpopulations, such as preterm children with CLD and those born at different gestational ages, or with different risk factors, such as having a sibling in a day-care group. In general, prophylaxis with palivizumab was more cost-effective in those children with a higher risk of being admitted to hospital due to an RSV infection than in children from populations at lower risk. For example, Roeckl-Wiedmann *et al.*³⁶ reported that the ICER for preterm children born at a gestational age of less than 35 weeks and without other risk factors was £162,800/HAP and that the ICER for preterm children born at a gestational age of less than 35 weeks and with siblings in day-care groups was £42,200/HAP. It can be seen that 'having a sibling in day care' contributed to the 74% ICER reduction. Discharge between October and December reduced the ICER to £20,200/HAP, contributing to the 52% ICER reduction. CLD further reduced the ICER to £5300/HAP, contributing to the 74% of ICER reduction. Vogel *et al.*³⁸ reported that CLD increased the ICER from £13,300/HAP to £27,000/HAP for preterm children with a gestational age of less than 32 weeks, an increase of 103%, and from £40,600/HAP to £69,200/HAP for preterm children with a gestational age between 29 and 31 weeks, an increase of 70%. Stevens *et al.*⁴³ showed that the ICER was less than £30,000/HAP for those who were born at a gestational age of below 31 weeks, but was £57,500/HAP for those born at between 31 and 32 weeks gestational age. These risk factors were reflected in the RSV hospitalisation rates. These are listed in *Table 10*. The values of ICERs decrease as the risk difference of RSV hospitalisation between no prophylaxis and palivizumab become large (shown in *Figure 6*).

Outcomes and other model parameters

The studies by Simpson and Burls⁹, Nuijten *et al.*²⁵, Chirolì³⁷, Joffe⁴¹ and Strutton and Stang⁴⁵ assessed the cost-effectiveness of palivizumab in terms of cost per life-year gained. The cost-effectiveness for children with CHD was £4300/LYG in the study by Chirolì³⁷ and £7900/LYG in the study by Nuijten *et al.*²⁵. The two studies used the same provider perspective and the same RSV hospitalisation rates, which was obtained from the RCT by Feltes *et al.*¹², the same time horizon. The study by Nuijten *et al.*²⁵ applied a discount of 3.5% and the price year was specified as 2003, whereas the study by Chirolì³⁷ did not specify the price year and did not apply discounting. The studies by Simpson and Burls⁹,

TABLE 10 Summary of results of economic evaluations^{sw}

Author	Country	Price Year	Number of doses	Discount rate (%)	Hospitalisation rates (%)			Population	Reported in price year	Converted to £ (sterling) 2006
					Palivizumab	No prophylaxis				
Farina et al., 2002 ³³	Argentina	2000	4	Not specified	10.71	23.8		Born at ≤ 35 weeks GA (≤ 6 months), or at ≤ 28 weeks GA (≤ 12 months), or CLD ≤ 2 years	\$15,358/HAP	£8000/HAP
Numa, 2000 ³⁴	Australia	Not specified	5	Not specified	4.8	10.6		Born at ≤ 35 weeks GA (≤ 6 months), or CLD ≤ 2 years, weight < 6.7 kg	A\$27,786/HDS	£14,400/HDS ^a
								Born at ≤ 35 weeks GA (≤ 6 months), or CLD ≤ 2 years, weight ≥ 6.7 kg	A\$55,572/HDS	£28,900/HDS ^a
Reeve et al., 2006 ³⁵	Australia	Not specified	5	Not specified	2.0	4.0		Hospitalised children positive for RSV or born at ≤ 33 weeks GA	A\$98,818/HAP	£42,000/HAP ^a
					2.3	4.4		Birth weight < 2500 g	A\$88,547/HAP	£37,700/HAP ^a
					2.2	5.0		Indigenous and birth weight < 2500 g	A\$73,294/HAP	£31,200/HAP ^a
					1.8	4.8		Birth weight < 2500 g and with siblings	A\$69,861/HAP	£29,700/HAP ^a
					2.3	5.1		E-NICU	A\$79,619/HAP	£33,900/HAP ^a
Roeckl-Wiedmann et al., 2003 ³⁶	Germany	2000	5	No discounting	24	54		Born at ≤ 35 weeks GA with CLD, siblings in day-care groups and discharge between October and December	€6639/HAP	£5300/HAP
					10	23		Born at ≤ 35 weeks GA with siblings in day-care groups and discharge between October and December	€25,288/HAP	£20,200/HAP
					6	12		Born at ≤ 35 weeks GA with siblings in day-care groups	€52,838/HAP	£42,200/HAP
					2	3		Born at ≤ 35 weeks GA without CLD, siblings in day-care groups and discharge between October and December	€204,68/4HAP	£162,800/HAP
Chiroli, 2005 ³⁷	Italy	2004	5	No discounting	5.3	9.7		CHD ≤ 2 years	€7186/LYG	£4300/LYG

continued

TABLE 10 Summary of results of economic evaluations

Author	Country	Price Year	Number of doses	Discount rate (%)	Hospitalisation rates (%)			Reported in price year	Converted to £ (sterling) 2006
					Palivizumab	No prophylaxis	Population		
Vogel et al., 2002 ³⁸	New Zealand	2000	5	Not specified	Not specified	42.1	Discharged home on oxygen	NZ\$29,000/HAP	£12,000/HAP
					14.0	22.9	Born at ≤ 32 weeks GA, with CLD	NZ\$65,000/HAP	£27,000/HAP
					4.1	18.5	Born at ≤ 32 weeks GA, without CLD	NZ\$32,000/HAP	£13,300/HAP
					6.1	10	Born at 29–31 weeks GA, with CLD	NZ\$167,000/HAP	£69,200/HAP
					1.8	8.2	Born at 29–31 weeks GA, without CLD	NZ\$98,000/HAP	£40,600/HAP
de Armentia, 2003 ³⁹	Spain	Unclear	Unclear; up to 50 mg, full five doses in total	N/A	Unclear		Born at ≤ 30 weeks GA	€12,915/HAP	£9500/HAP
								€20,900/HAP	£15,400/HAP; appears to be data driven, states with 35 weeks GA, then treats only ≤ 32 weeks GA
Lázaro et al., 2006 ⁴⁰	Spain	2006	15 mg/kg, mean of 3.88 doses	3	1.8	8.1	Born at 32–35 weeks GA	€4605/QALY (societal)	£3200/QALY (societal)
Raya et al., 2006 ¹⁸	Spain	2005	3.8 doses (mean), sharing vials	N/A	2.7	6.6	Born at 32–35 weeks GA	€13,849/QALY (provider)	£9500/QALY (provider)
								€42,761/HAP to €68,104/HAP	£29,400–46,800/HAP
Simpson and Burris ⁹	UK	2000	6	1.5 for benefit	4.8	10.6	Born at ≤ 35 weeks GA (≤ 6 months), or CLD ≤ 2 years	£43,000/HAP, £96,000/LYG	£55,000/HAP, £122,800/LYG
Nuijten et al., 2007 ²⁵	UK	2003	4.87	3.5 for both cost and benefit	4.8	10.6	Born at ≤ 35 weeks GA (≤ 6 months), CLD ≤ 2 years	£16,720/QALY, £22,826/LYG	£18,900/QALY, £25,800/LYG
								£6664/QALY, £7002/LYG	£7500/QALY, £7900/LYG

Author	Country	Price Year	Number of doses	Discount rate (%)	Hospitalisation rates (%)			Population	Reported in price year	Converted to £ (sterling) 2006
					Palivizumab	No prophylaxis	No			
Joffe, 1999 ⁴¹	USA	1995	4	3 for both cost and benefit	11.1	24.6		Born at 23–32 weeks GA, length of oxygen ≥ 28 days, month of NICU discharge September to November	\$33,000/LYG	£30,400/LYG
					4.8	10.7		Born at 23–32 weeks GA, length of oxygen ≥ 28 days, month of NICU discharge December to August	\$110,000/LYG	£101,200/LYG
					3.6	8		Born at 23–32 weeks GA, length of oxygen < 28 days, month of NICU discharge September to November	\$160,000/LYG	£147,200/LYG
					1.4	3.1		Born at 23–32 weeks GA, length of oxygen < 28 days, month of NICU discharge December to August	\$440,000/LYG	£404,900/LYG
					5.0	11		Born at 33–36 weeks GA, length of oxygen ≥ 28 days, month of NICU discharge September to November	\$110,000/LYG	£101,200/LYG
					2.0	4.4		Born at 33–36 weeks GA, length of oxygen ≥ 28 days, month of NICU discharge December to August	\$300,000/LYG	£276,100/LYG
					1.4	3.2		Born at 33–36 weeks GA, length of oxygen < 28 days, month of NICU discharge September to November	\$430,000/LYG	£395,700/LYG
					0.5	1.2		Born at 33–36 weeks GA, length of oxygen < 28 days, month of NICU discharge December to August	\$1,200,000/LYG	£1,104,001/LYG
					5 ^b	10 ^b		Born at ≤ 35 weeks GA (≤ 6 months)	\$39,591/IEA if palivizumab therapy cost \$2500	£31,300/IEA ^a if palivizumab therapy cost \$2500
					5 ^b	10 ^b			\$79,706/IEA ^a if palivizumab therapy cost \$4500	£63,000/IEA ^a if palivizumab therapy cost \$4500
Lofland et al., 2000 ⁴²	USA	Not specified	5	Not specified						

continued

TABLE 10 Summary of results of economic evaluations

Author	Country	Price Year	Number of doses	Discount rate (%)	Hospitalisation rates (%)		Population	Reported in price year	Converted to £ (sterling) 2006
					Palivizumab	No prophylaxis			
Stevens <i>et al.</i> , 2000 ⁴³	USA	Not specified	5	Not specified	9.3	20.6	Born at ≤26 weeks GA	\$18,183/HAP	£14,400/HAP ^a
					6.6	14.6	Born at 27–28 weeks GA	\$24,113/HAP	£19,100/HAP ^a
					5.1	11.3	Born at 29–30 weeks GA	\$36,878/HAP	£29,200/HAP ^a
					2.9	6.4	Born at 31–32 weeks GA	\$72,712/HAP	£57,500/HAP ^a
Shireman and Bramer, 2002 ⁴⁴	USA	Not specified	Up to 6	Not specified	5.8	11.7	Born during RSV season ≤10 months	Cost-benefit ratio 6.67:1, drug cost \$4,687, hospitalisation cost decreased by \$703	Cost-benefit ratio 6.67:1, drug cost £3746 ^a , hospitalisation cost decreased by £559 ^a
					Not specified	Not specified	Born at ≤35 weeks GA	\$66,200/LYG (societal)	£53,200/LYG (societal)
Strutton and Stang, 2003 ⁴⁵	USA	2002	Not specified	5 for both cost and benefit	Not specified	Not specified	Born at ≤35 weeks GA	\$66,400/LYG (payer)	£53,300/LYG (payer)
Yount <i>et al.</i> , 2004 ⁴⁶	USA	2002	5	3 for both cost and benefit	5.3	9.7	CHD ≤2 years	\$114,337/QALY	£91,800/QALY
ElHassan <i>et al.</i> , 2006 ⁴⁷	USA	2002	5	3 for both cost and benefit	5.2	20.6	Hypothetical cohort of children born at 26 weeks GA without CLD	\$830,152/QALY	£666,700/QALY
					3.7	14.6	Hypothetical cohort of children born at 27 weeks GA without CLD	\$1,295,781/QALY	£1,040,600/QALY
					3.7	14.6	Hypothetical cohort of children born at 28 weeks GA without CLD	\$1,500,351/QALY	£1,204,900/QALY
					2.8	11.3	Hypothetical cohort of children born at 29–30 weeks GA without CLD	\$675,780/QALY	£542,700/QALY
					1.6	6.4	Hypothetical cohort of children born at 31 weeks GA without CLD	\$1,212,497/QALY	£973,700/QALY
					1.1	6.4	Hypothetical cohort of children born at 32 weeks GA without CLD	\$1,855,000/QALY	£1,489,700/QALY

CHD, congenital heart disease; CLD, chronic lung disease; GA, gestational age; E-NICU, ex-neonatal care unit; HAP, hospital admission prevented; HDS, hospital day saved; IEA,

infection episode avoided; LYG, life-year gained; NICU, neonatal intensive care unit; QALY, quality-adjusted life-year.

a Cost year was not clearly defined, assumed to be the same as study year.

b Incidence of RSV infection.

Nuijten *et al.*²⁵, Joffe⁴¹ and Strutton and Stang⁴⁵ estimated the cost-effectiveness of palivizumab for preterm children. The values of ICER varied from £25,800/LYG to £404,900/LYG. The minimum ICER was reported in the study by Nuijten *et al.*²⁵ and the maximum ICER was reported in the study by Joffe.⁴¹ The main variation in the ICER was caused by gestational age and NICU discharge seasons, which were reflected by RSV hospitalisation rates. The values of ICERs decrease as the risk difference of RSV hospitalisation between no prophylaxis and palivizumab becomes large (shown in *Figure 7*).

Mortality

The studies by Nuijten *et al.*²⁵, Lázaro *et al.*⁴⁰, Yount *et al.*⁴⁶, and ElHassan *et al.*⁴⁷ assessed the cost-effectiveness of palivizumab in terms of cost per QALY. The cost-effectiveness for children with CHD was £7500/QALY in the study by Nuijten *et al.*²⁵ and £91,800/QALY in the study by Yount *et al.*⁴⁶ The ICERs and the model parameters of the two studies are summarised in *Table 11*.

These two studies used the same RSV hospitalisation rates, a similar dose of palivizumab and the same time horizon. The differences

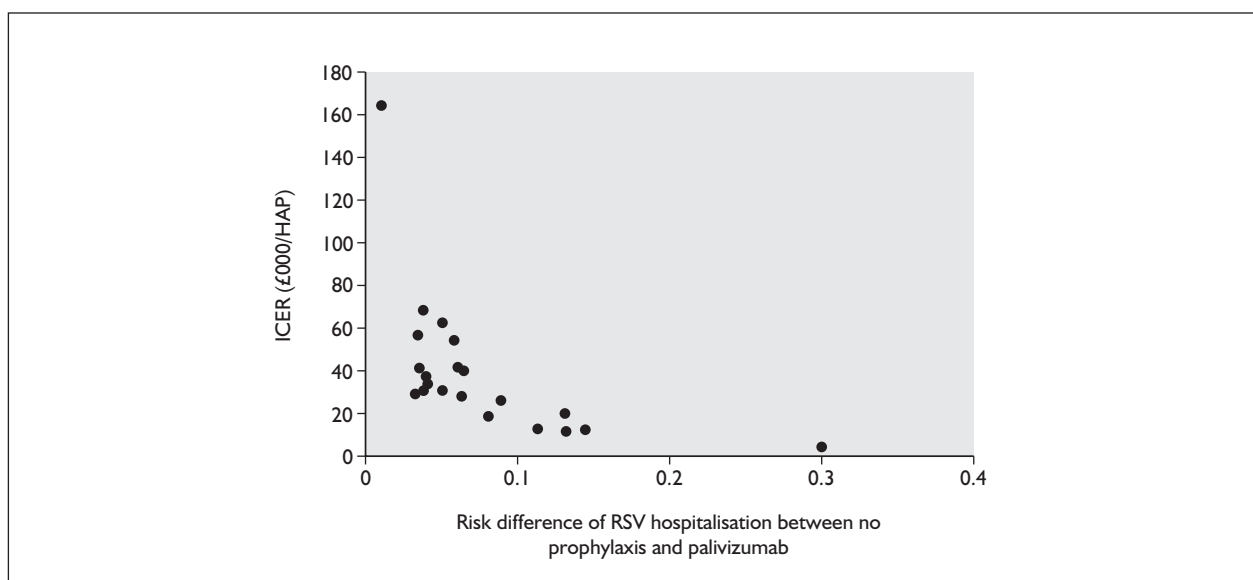


FIGURE 6 Cost-effectiveness (£/HAP).

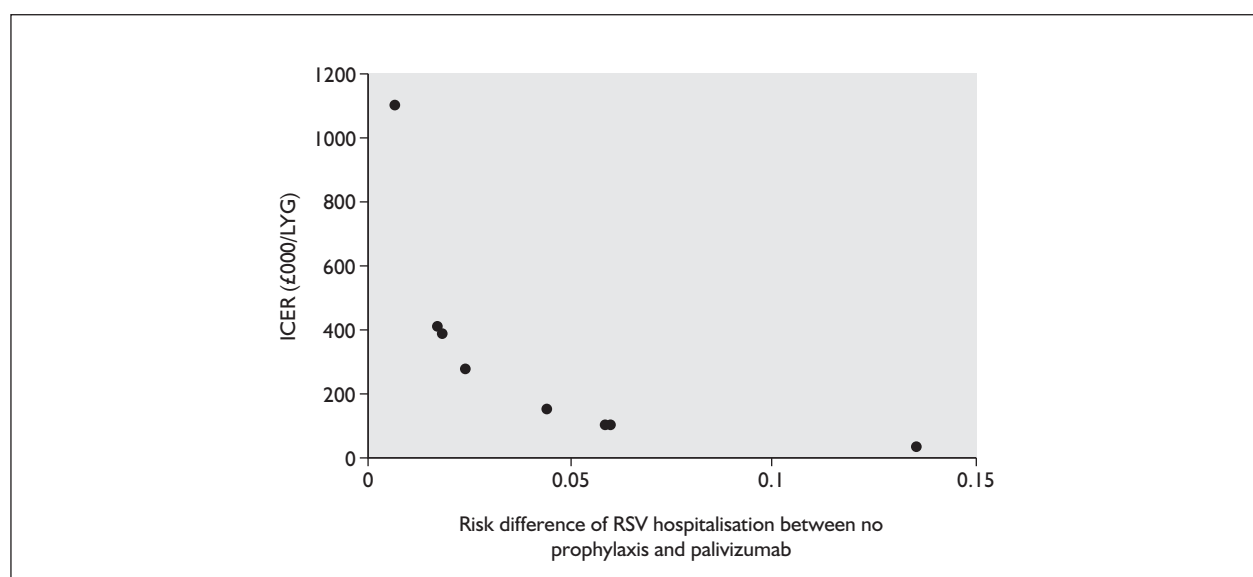


FIGURE 7 Cost-effectiveness (£/LYG).

TABLE 11 ICERs and the corresponding model parameters (children with CHD)

Author	Industry sponsored	Hospitalisation rates (%)		Population	Time horizon	Discount rate (%)	Number of doses	Mortality rate (%)	Perspective	Utility value	ICER (£/QALY)
		Palivizumab	No prophylaxis								
Nuijten et al., 2007 ²⁵	Yes	5.3	9.7	CHD ≤ 2 years	Lifetime	3.5	4.87	4.5	Provider	0.88–0.95	7500
Yount et al., 2004 ⁴⁶	No	5.3	9.7	CHD ≤ 2 years	Lifetime	3	5	3	Societal	0.71	91,800

TABLE 12 ICERs and the corresponding model parameters (preterm infants without CLD or children with CLD)

Author	Industry sponsored	Hospitalisation rates (%)		Population	Time horizon	Discount rate (%)	Number of doses	Mortality rate (%)	Perspective	Utility value	ICER (£/QALY)
		Palivizumab	No prophylaxis								
Nuijten et al., 2007 ²⁵	Yes	4.8	10.6	Born at ≤ 35 weeks GA (≤ 6 months), CLD ≤ 2 years	Lifetime	3.5	4.87	8.11	Provider	0.88–0.95	18,900
ElHassan et al., 2006 ⁴⁷	No	5.2	20.6	Hypothetical cohort of children born at 26 weeks GA without CLD	1 year without asthma, 8 years with asthma	3	5	Not considered	Societal	0.89–0.92	666,700
		3.7	14.6	Hypothetical cohort of children born at 27 weeks GA without CLD	1 year without asthma	3	5	Not considered	Societal	0.89–0.92	1,040,600
		3.7	14.6	Hypothetical cohort of children born at 28 weeks GA without CLD	1 year without asthma	3	5	Not considered	Societal	0.89–0.92	1,204,900
		2.8	11.3	Hypothetical cohort of children born at 29–30 weeks GA without CLD	1 year without asthma	3	5	Not considered	Societal	0.89–0.92	542,700
		1.6	6.4	Hypothetical cohort of children born at 31 weeks GA without CLD	1 year without asthma	3	5	Not considered	Societal	0.89–0.92	973,700
		1.1	6.4	Hypothetical cohort of children born at 32 weeks GA without CLD	1 year without asthma	3	5	Not considered	Societal	0.89–0.92	1,489,700

CLD, chronic lung disease; GA, gestational age; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

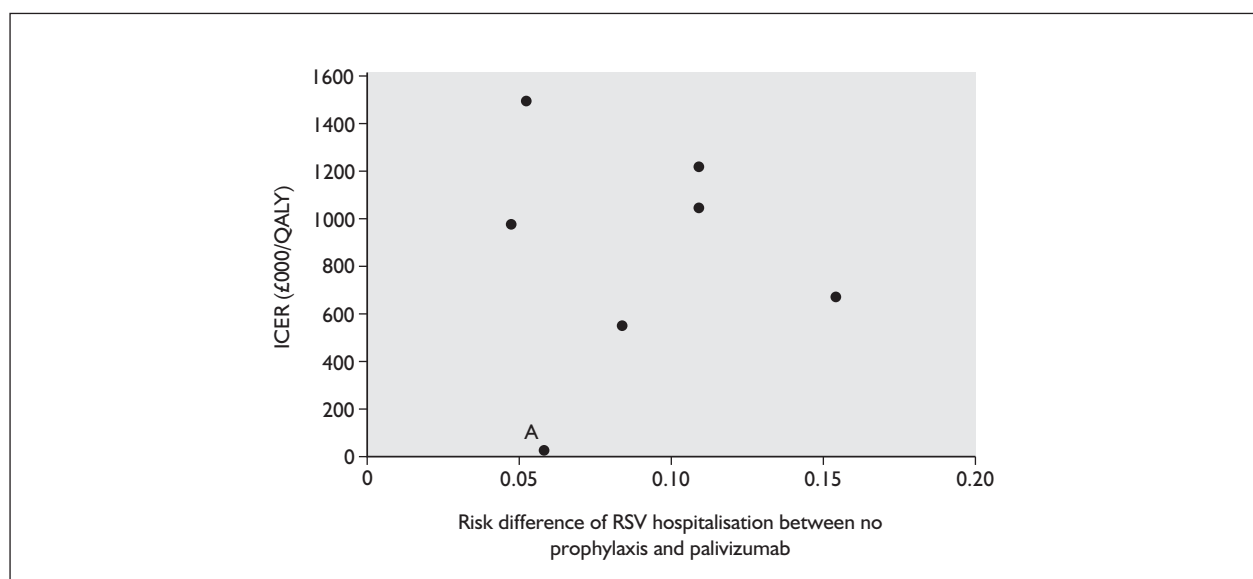


FIGURE 8 Cost-effectiveness (£/QALY).

TABLE 16 The results of cost-effectiveness versus different mortality rates using the model by Nuijten *et al.*²³

	Mortality rate (%)						
	7	6	5	4	3	2	1
ICER (£/LYG)	29,200	33,800	40,300	50,000	66,200	98,500	195,500
ICER (£/QALY)	20,200	22,000	24,200	27,000	30,500	35,200	41,700

ICER, incremental cost-effectiveness ratio; LYG, life-year gained; QALY, quality-adjusted life-year.

between the two studies are that Yount *et al.*⁴⁶ used a societal perspective, an RSV mortality rate of 3% and a utility value of 0.71, whereas Nuijten *et al.*²⁵ used a provider perspective, an RSV mortality rate of 4.5% and utility values of 0.88–0.95. The ICER values for preterm children compared with the risk difference of RSV hospitalisation, which were collected from two studies^{25,47}, are shown in *Figure 8*. The study by Lázaro *et al.*⁴⁰ was not included as the number of doses of palivizumab was too low (fewer than 4). In general, we can see that the values of ICERs decrease as the differences in RSV hospitalisation rates between no prophylaxis and palivizumab become large. However, there is an exception in the case of the study by Nuijten *et al.*²⁵, as shown at point A in *Figure 8*. The ICERs and the model parameters of the two studies are summarised in *Table 12*. Apart from the different perspectives, hospitalisation rates and time horizon, compared with the study by ElHassan *et al.*⁴⁷, the study by Nuijten²⁵ assumed

a higher mortality rate (8.11%). This is probably the main reason that Nuijten *et al.*²⁵ reported a very low ICER value. Three observational studies^{24,48,49} report mortality rates for children admitted to hospital because of RSV infection. Meta-analysis of these studies gives a mortality rate of 3.72% for RSV hospital admission, which is similar to the mortality rate of 3% used in the study by Yount *et al.*⁴⁶

In order to evaluate the effect of the high mortality rate on the cost-effectiveness, we reconstructed the model described in the study by Nuijten *et al.*²⁵ and ran it using different mortality rates. The results are summarised in *Table 13*. The ICER changes from £29,200/LYG for a mortality rate of 7% to £195,500/LYG for a mortality rate of 1%, and changes from £20,200/QALY for a mortality rate of 7% to £41,700/QALY for a mortality rate of 1%. Note that the best estimate of mortality for premature children without CLD that we could find

is smaller than any shown here and therefore the probable cost/QALY will be in excess of £41,000. Therefore, even given the other very optimistic assumptions favouring palivizumab used by

Nuijten and colleagues in their model, palivizumab would not reach conventional UK levels of cost-effectiveness when a more representative mortality rate is used.

Chapter 4

The Birmingham Economic Evaluation

Given the disparity of results of existing economic evaluations and the fact that none of the models was suitable for addressing the questions posed in this review, we decided to construct a *de novo* model, the Birmingham Economic Evaluation (BrumEE). This chapter provides details of the BrumEE developed by our team and used to evaluate the cost-effectiveness of prophylaxis with palivizumab compared with no prophylaxis.

Methods of the BrumEE

The model was designed to estimate, from the UK NHS and societal perspectives, the incremental costs and outcomes in terms of QALYs of prophylaxis with palivizumab compared with no prophylaxis. The model also attempts to incorporate uncertainty in probabilities, resource use and utilities by incorporating the input parameters of the model as probability distributions. These distributions are used in a Monte Carlo simulation in order for uncertainty in the results of the model to be presented. The model is developed using the R programming language (<http://cran.r-project.org>). All costs are presented in 2006 UK pounds sterling (£). Both costs and benefits are discounted at 3.5%.

Structure of the model

The model structure is shown in *Figure 9*. The model follows high-risk children for their first RSV season. The high-risk children are divided into two groups: those receiving palivizumab prophylaxis and those not receiving prophylaxis. Children in either group may develop an RSV infection and be admitted to hospital. A proportion of them will require admission to a paediatric intensive care unit, the rest are managed in a general paediatric ward. A small proportion of children die. A time horizon of lifetime is used to take into account the impact of palivizumab on long-term morbidity and mortality of RSV infection. Cost-effectiveness is measured in terms of £ per QALY and £ per life-year gained. Adverse events are not taken into account in the model as the clinical trials did not show any important differences between the palivizumab and placebo groups.^{12,16}

We do not consider sequelae (such as asthma, recurrent wheezing) in the base-case model. The relationship between RSV infections and the development of wheezing and asthma in children has been the subject of much debate. Most previous cohort studies have failed to identify a link between early RSV infection and atopic asthma. Recent cohort studies have indicated that wheezing in early childhood is associated with an increased incidence of atopic asthma, but that this risk is not increased by RSV infections.⁵⁰

Estimation of model pathway parameters *Prognostic factor studies in RSV*

The limited RCT data (*Tables 5 and 6*) do not distinguish adequately between subgroups of risk within the 'high-risk' groups (e.g. groups defined by different gestational ages or age at the start of RSV season). It is therefore not possible to answer the core question of this review (For which high-risk subgroups may palivizumab be a cost-effective use of resources?) from the RCT data alone. Hence, supplementary evidence is needed to model different risk groups within the licensed indication.

Unfortunately, the scope of the commissioning brief does not permit us to undertake a full systematic review to look for studies about the development, course or outcome of infection in children with RSV so we took a pragmatic approach to seek the best available information. We systematically looked for prognostic studies identified during the search for the systematic review and undertook a further specific systematic search for prognostic studies (see Appendices for details). Based on scrutiny of title and abstract we selected those that were of most relevance to the current UK context and of highest quality. The studies selected as most relevant are summarised in *Table 15*.

Of these, the papers by Carbonell-Estrany *et al.*^{51,52} and Rietveld *et al.*⁵³ were the most useful. All include large samples of children and use an appropriate method to investigate prognostic factors. Carbonell-Estrany *et al.*⁵¹ and Rietveld *et al.*⁵³ estimate risk by gestational age (GA),

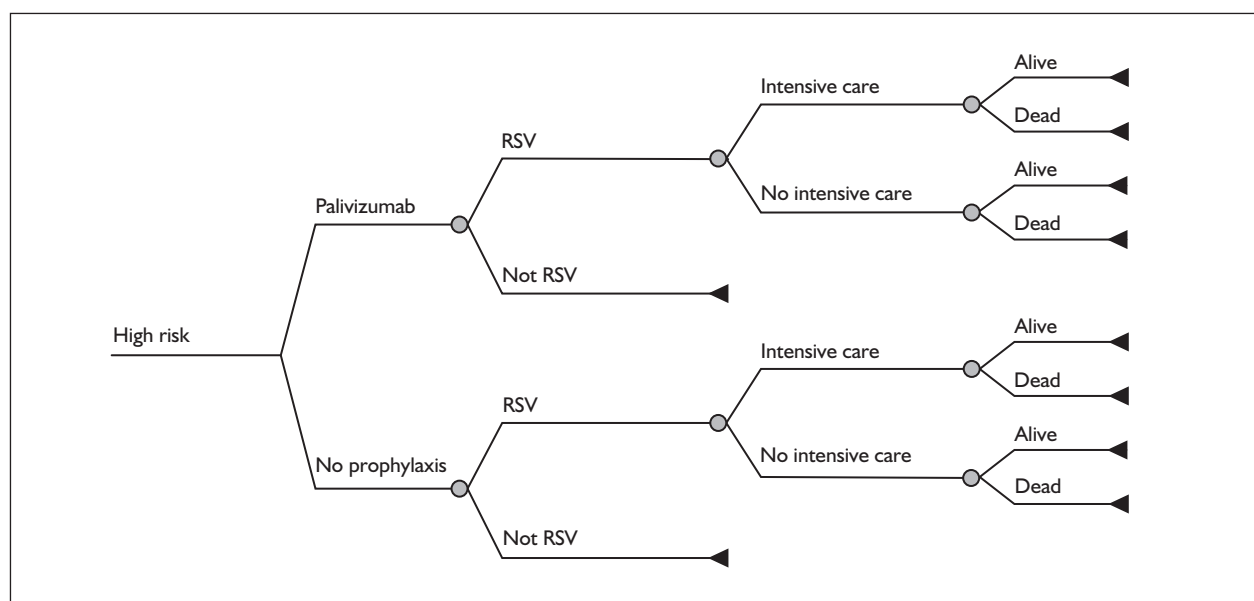


FIGURE 9 Base-case decision tree model for palivizumab versus no prophylaxis.

which is a particularly important component of risk, and allows consideration of this important subgroup in the model. Carbonell-Estrany *et al.*⁵² report a similar study for children with higher gestational age (> 32 weeks) and, along with Rietveld *et al.*⁵³, compare risk in children of different ages. Carbonell-Estrany *et al.*⁵² use birth age for this comparison, whereas Rietveld *et al.*⁵³ use post-conceptional age. These papers also reported a significant impact of CLD/BPD and of having siblings at school (SAS) on the risk of RSV hospitalisation. The ORs and their confidence

intervals for key prognostic factors are summarised in Table 14.

For modelling prognosis, we decided to use the estimates for GA, CLD and SAS from Carbonell-Estrany *et al.*⁵¹ These estimates are comparable to the odds ratios (OR) reported in the other papers, but the OR for GA in Rietveld *et al.*⁵³ is estimated by grouped GAs rather than as an OR/month, as in the Carbonell-Estrany *et al.* papers, and so is less flexible for modelling purposes; in addition, Rietveld *et al.*⁵³ report ORs to only one decimal

TABLE 14 Estimated ORs [and confidence intervals (CIs)] for key prognostic factors

Risk factor	Carbonell-Estrany <i>et al.</i> , 2000 ⁵¹	Carbonell-Estrany <i>et al.</i> , 2004 ⁵²	Rietveld <i>et al.</i> , 2006 ⁵³
Gestational age	0.85, 0.72–0.99/week	–	≤ 28 weeks: 3.2 (2.1–4.8) 29–32 weeks: 2.8 (2.1–3.8) 33–34 weeks: 2.3 (1.8–3.0) 35–36 weeks: 1.6 (1.3–1.9) 37+ weeks: 1.0
Chronic lung disease	3.1 (1.22–7.91)	–	2.2 (no CI reported)
Siblings at school	1.86 (1.01–3.4)	–	–
Age	–	0.55 (0.33, 0.92)	No BPD 0.8/month (0.8, 0.8) with BPD 0.9/month (0.9, 1.0)
BPD, bronchopulmonary dysplasia; CI, confidence interval.			

place, which introduces a high rounding error. Similarly, Carbonell-Estrany *et al.*⁵² report an OR only for age groups above and below 3 months, whereas Rietveld *et al.*⁵³ report an OR of 0.8/month for post-conceptional age without BPD and 0.9/month for post-conceptional age with BPD. The OR for birth age used in our prognostic model was 0.8, obtained by considering ORs of the correct order of magnitude according to Rietveld *et al.*⁵³ but which also corresponded well to data from the other paper.⁵⁴

Other significant prognostic factors reported by these papers include sex, birth weight, parents' level of education and overcrowding at home. With additional resources it would be possible to build a more comprehensive prognostic model that includes these and other factors.

The risk of hospitalisation due to RSV was estimated for different subgroups, cross-tabulated by GA and age, using a simple Excel spreadsheet. The OR for a specific group compared with the reference group (GA = 28 weeks, age = 3 months, no CLD or SAS) was calculated using the ORs taken from the prognostic papers using the formula:

$$\text{OR}_{\text{subgroup}} = \exp(-\ln\text{OR}_{\text{GA}}(28 - \text{GA}) - \ln\text{OR}_{\text{age}}(3 - \text{age}) + (\text{CLD} * \ln\text{OR}_{\text{CLD}}) + (\text{SAS} * \ln\text{OR}_{\text{CLD}}))$$

where CLD and SAS are indicator variables for the presence/absence of these risk factors.

Note that the lnORs for GA and age are included as negative terms because our model uses increasing risk with lower values than the reference (OR > 1), whereas the ORs in the papers are reported the other way around (OR < 1).

The absolute risk for each group was then calculated from an estimated baseline risk for the reference group of 15.1%, obtained from considering the empirical data from the UK study by Deshpande *et al.*⁵⁵ An RSV-related hospitalisation rate of 12.5% was reported for children less than 6 months with a gestational age of less than 28 weeks. We assumed that this hospitalisation rate was obtained from children with a gestational age of 26 weeks, 27 weeks and 28 weeks. The odds ratio of 0.85 was applied to gestational ages and the hospitalisation rate of children with a gestational age of 28 weeks was estimated to be 10.8%. The odds ratio of 0.8 was applied to birth ages and the hospitalisation rate of infants under 3 months with a gestational age of 28

weeks was estimated to be 15.1%, which was used to estimate the hospitalisation rates for children with different gestational ages and different birth ages.

The average of the derived absolute risks of hospitalisation for different subgroups across gestational age and birth age is estimated to be 11.3%. This is consistent with a hospitalisation rate of 10.6% reported in the RCT.¹⁶

Estimation of model pathway parameters

RSV hospitalisation for infants born at ≤35 weeks of gestation or children with CLD

The IMPact-RSV¹⁶ RCT was conducted for infants born at ≤35 weeks of gestation or children with CLD. The results of the study showed that monthly prophylaxis with palivizumab was associated with a 55% (95% CI 38–72%) reduction in RSV hospitalisation compared with no prophylaxis (Table 8). Significant reductions were observed in both children with CLD (39%, 95% CI 20–58%) and premature children without CLD (78%, 95% CI 66–90%).¹⁶ The RSV hospitalisation rate was 4.8% for prophylaxis with palivizumab and 10.6% for no prophylaxis. These rates were used in our model (Table 16).

RSV hospitalisation for CHD children

One RCT study, by Feltes *et al.*,¹² compared RSV hospitalisation rate in children with CHD receiving or not receiving prophylaxis with palivizumab. The results showed that monthly prophylaxis with palivizumab was associated with a 45% reduction in RSV hospitalisation rate (Table 5). RSV hospitalisation rates were 5.3% in the palivizumab group and 9.72% in the no prophylaxis group (Table 17). One Switzerland cohort study by Duppenenthaler *et al.*²⁴ has been identified for RSV hospitalisation rates in children < 24 months of age with CHD. This study reported that RSV hospitalisation rates in CHD patients less than 24 months of age varied from 0.5% to 2.5%, which is fourfold lower than that reported from the RCT study. The latitude and location of Switzerland suggest that RSV seasons might be expected to be similar to those experienced in the UK. However, it is unclear whether demographic characteristics were the same between the cohort study and the RCT study (Tables 2 and 4). The RSV-hospitalisation rates obtained from the RCT study are used in the base case model. The RSV-hospitalisation rates of 0.5% to 2.5% from the cohort study are used in sensitivity analysis. RSV-hospitalisation rates of 5.6% for prophylaxis with palivizumab and 7.9% for no prophylaxis in the

TABLE 15 Prognostic studies

Reference	Design	Population	Outcomes	Factors	Results
Arnold <i>et al.</i> , 1999 ⁵⁶	Prospective multicentre cohort	1516 children with lung disease (CLD, cystic fibrosis, and others) hospitalised with RSV, 1993–1995 (159 only reported)	Duration of hospitalisation, ICU, duration of ICU, mechanical ventilation, duration of ventilation	CLD, cystic fibrosis, pneumonitis, pulmonary malformation, neurogenic disorders, tracheoesophageal fistula, other	No significant differences between groups; patients using home oxygen were more likely to be admitted to ICU ($p = 0.03$)
Carbonell-Estrany <i>et al.</i> , 2000 ⁵¹	Prospective multicentre cohort	680 children born ≤ 32 weeks gestation, 1998–1999 (584 evaluable)	Hospitalisation for RSV	Gestational age, birth weight, family history of asthma, CRIB score, age at start of RSV season, month of discharge, CLD, heart disease, neurological disease, ventilation at birth, breast-feeding, smoke exposure, day care, one or more siblings, school-age siblings	Gestational age (OR 0.85, 0.72–0.99), chronic lung disease (OR 3.1, CI 1.22–7.91), school-age siblings (OR 1.86, CI 1.01–3.4)
Carbonell-Estrany <i>et al.</i> , 2004 ⁵²	Prospective multicentre cohort	1832 children born at 33–35 weeks gestation, 2000–2002	Hospitalisation for RSV	Multiple pregnancy, abnormal delivery, intubation, ICU at birth, ethnicity, month of birth, sex, small for gestational age, any chronic condition, crowding, two or more smokers at home, older siblings, preschool-age siblings in day care and not breast-feeding, eczema in a first-degree relative	Month of birth, sex, small for gestational age, any chronic condition, crowding, two or more smokers at home, older siblings, preschool-age siblings in day care and not breast-feeding, eczema in a first-degree relative
Clark <i>et al.</i> , 2000 ⁵⁷	Prospective multicentre cohort	656 high-risk children, 1998–2000 (< 36 weeks gestation, < 24 months and discharged with supplemental oxygen)	Hospitalisation for RSV	Prematurity, discharge with oxygen	Premature infants at higher risk than those discharged with oxygen
Grimaldi <i>et al.</i> , 2002 ⁵⁸	Prospective multicentre cohort	484 children admitted for RSV bronchiolitis, 1999–2000	PICU admission in children hospitalised for RSV-induced bronchiolitis	Prematurity, low birth weight, RDS, mechanical ventilation, CLD, CHD	Prematurity, low birth weight, RDS, mechanical ventilation, CLD, CHD
Holberg <i>et al.</i> , 1991 ⁵⁹	Prospective multicentre cohort	1,179 healthy children 1980–1984	RSV-LRTI	Breast feeding, maternal education, sex, shared bedroom, birth month, ethnicity, maternal smoking, day care	Breast feeding, sex, shared bedroom
Rietveld <i>et al.</i> , 2006 ⁵³	Retrospective multicentre cohort	143,130 (2469 hospitalised) children, 1996–1998	Hospitalisation for RSV	Sex, gestational age, birth weight, CLD, age	Sex, gestational age, birth weight, CLD, age
Kneyber <i>et al.</i> , 2000 ⁶⁰	Quantitative review	10 studies	Asthma	Asthma associated with RSV infection	40% vs 11% ($p < 0.001$) up to 5 years follow-up, 22% vs 10% ($p = 0.19$) 5–10 years

CLD, chronic lung disease; CRIB, clinical risk index for babies; ICU, intensive care unit; LRTI, lower respiratory tract infection; PICU, paediatric intensive care unit; RDS, respiratory distress syndrome; RSV, respiratory syncytial virus.

TABLE 16 Model pathway parameters for preterm infants without CLD or children with CLD

Parameter	Estimate	Source
RSV-related mortality rate (without CLD)	0.0043	Chater <i>et al.</i> , 2006 ⁶¹
RSV-related mortality rate (with CLD)	0.04 (0.03–0.05)	Stensballe <i>et al.</i> , 2003 ⁵
Probability of ICU admission	0.107	Deshpande <i>et al.</i> , 2003; ⁵⁵ Greenough <i>et al.</i> , 2001; ⁶² Clark <i>et al.</i> , 2000; ⁵⁷ Broughton <i>et al.</i> , 2005 ⁶³
Relative risk of RSV hospitalisation rate between palivizumab versus no prophylaxis	0.4519	The IMPact-RSV Study Group, 1998 ¹⁶
Probability of RSV hospitalisation in palivizumab prophylaxis group (without CLD)	0.018	The IMPact-RSV Study Group, 1998 ¹⁶
Probability of RSV hospitalisation in palivizumab prophylaxis group (with CLD)	0.079	The IMPact-RSV Study Group, 1998 ¹⁶
Probability of RSV hospitalisation in no prophylaxis group (without CLD)	0.081	The IMPact-RSV Study Group, 1998 ¹⁶
Probability of RSV hospitalisation in no prophylaxis group (with CLD)	0.128	The IMPact-RSV Study Group, 1998 ¹⁶

CLD, chronic lung disease; ICU, intensive care unit; RSV, respiratory syncytial virus.

TABLE 17 Model pathway parameters for children with CHD

Parameter	Estimate	Source
RSV-related mortality rate	0.0372	Wang <i>et al.</i> , 1995; ²⁴ Moler <i>et al.</i> , 1992; ⁴⁸ Navas <i>et al.</i> , 1992 ⁴⁹
Probability of ICU admission	0.387	Feltes <i>et al.</i> , 2003 ¹²
Relative risk of RSV hospitalisation rate between palivizumab and no prophylaxis	0.5473	Feltes <i>et al.</i> , 2003 ¹²
Probability of RSV hospitalisation in palivizumab prophylaxis group	0.0532	Feltes <i>et al.</i> , 2003 ¹²
Probability of RSV hospitalisation in no prophylaxis group	0.0972	Feltes <i>et al.</i> , 2003 ¹²

ICU, intensive care unit; RSV, respiratory syncytial virus.

TABLE 18 Probability of ICU stay for preterm infants

Study	N (RSV hospitalisation)	N (ICU)	%
Greenough <i>et al.</i> , 2001 ⁶²	45	6	13.33
Clark <i>et al.</i> , 2000 ⁵⁷	53	5	9.43
Broughton <i>et al.</i> , 2005 ⁶³	44	4	9.09
Deshpande <i>et al.</i> , 2003 ⁵⁵	53	6	11.32
Pooled result			10.71

ICU, intensive care unit; RSV, respiratory syncytial virus.

cyanotic stratum, and 5% vs 11.8% in the acyanotic stratum reported from the RCT study are also used for sensitivity analysis.

Probability of ICU admission

Four UK studies, by Greenough *et al.*,⁶² Clark *et al.*,⁵⁷ Broughton *et al.*⁶³ and Deshpande *et al.*,⁵⁵ were meta-analysed to estimate the ICU rate. The individual and pooled results are shown in *Table 18*.

Feltes *et al.*¹⁴ reported that 13 out of 34 palivizumab recipients who were hospitalised due to RSV infection were admitted to the ICU, compared with 24 out of 63 placebo recipients who were admitted to hospital because of RSV infection (*Table 6*). This gives an average ICU admission rate of 38.7% for CHD children. This is consistent with the ICU admission rate (38.2%) reported in the study by Chiroti.³⁷

Mortality rates for children born ≤ 35 weeks of gestation or children with CLD

Mortality rates of 0.4% in the prophylaxis with palivizumab group and 1% in the no prophylaxis group were reported in the RCT study (*Table 6*).¹⁶ However, the study was not powered to estimate mortality rates²⁵ because it was designed to evaluate RSV hospitalisation rates associated with prophylaxis with palivizumab and no prophylaxis. Furthermore, they are not the mortality rates required by the decision-analytical model. The model needs estimates of mortality rates for those who were admitted to hospital due to RSV infection. The mortality rates reported in the RCT are the total death rates for those in either arm. Therefore, these cannot be directly used in the model.

The study by Sampalis and Sampalis²³ reported a mortality rate of 8.11% (196/2415) for RSV hospitalisation. This mortality rate in a cohort of children generally considered to be less high risk (32–35 weeks' gestation) is exceptionally high, and is far greater than reported among more high-risk children. Moreover, this mortality rate is all-cause mortality during follow-up subsequent to RSV hospitalisation, and does not necessarily relate to RSV hospitalisation *per se*. The author reported a significantly higher rate of sudden or otherwise unexplained death among RSV-hospitalised children than among controls, possibly an artefact from the use of poorly coded, routinely collected discharge data or selection bias. Since the median age at RSV hospitalisation among the preterm cohort was 6.9 months, and as the risk of sudden infant death syndrome greatly reduces by 6 months

of age, use of the mortality figure from this study for model estimates is inappropriate. Wang *et al.*²⁴ reported RSV hospitalisation rates of 5.06% (4/79) for CLD and 3.38% (5/148) for gestation < 37 weeks. The subgroups in this study were not mutually exclusive, e.g. children with gestation < 37 weeks could also have had other risk factors such as CLD, cardiac disease, immunocompromise, etc. As the authors mentioned, there were only six deaths in the entire cohort of 689 hospitalised children; four of the children who died had underlying illnesses while one was premature and one was less than 6 weeks of age. Again, it is inappropriate to use these mortality rates in the model because it is not clear whether the deaths were due to RSV or to underlying disease.

The RSV-related mortality rate among preterm infants without CLD derived from the study by Chater *et al.*⁶¹ was 0.43%. Stensballe *et al.*⁵ reported high mortality rates of 3–5% among children with CLD. Therefore, a mortality rate of 4% was used in the base-case model for preterm children with CLD.

Mortality rates for CHD children

The economic evaluation study by Yount *et al.*⁴⁶ used a mortality rate of 3% for both the prophylaxis with palivizumab and no prophylaxis groups. The study by Nuijten *et al.*²⁵ used a mortality rate of 4.5% for RSV hospitalisation. The RCT by Feltes *et al.*¹² reported a total mortality rate of 3.3% for the palivizumab prophylaxis group and of 4.2% for the no prophylaxis group (*Table 6*). They are not the mortality rates required by the decision-analytical model as the model requires mortality rates of those who were admitted to hospital because of RSV infection.

Three studies^{24,48,49} that reported a mortality rate for those who were admitted to hospital due to RSV infection were identified. The study by Moler *et al.*⁴⁸ reported a mortality rate of 2.53% (2/79), that by Navas *et al.*⁴⁹ a mortality rate of 3.46% (9/260) and that by Wang *et al.*²⁴ a mortality rate of 5.26% (3/57). Meta-analysis of these studies gives a mortality rate of 3.72% for those who were admitted to hospital due to RSV infection. This value of the mortality rate was used in the base-case model for children with CHD (*Table 17*).

Resource use and costs

The UK NHS perspective is adopted for the base-case evaluation and the cost-effectiveness is expressed in terms of incremental cost per QALY or per LYG. In the non-base-case analysis,

we also include cost implications for a societal perspective which includes parent work loss costs due to infant's hospitalisation or for administering prophylaxis with palivizumab. Thus, the identification of costs for the model was conducted from both an NHS perspective and a societal perspective.

Medical costs

The utilisation of palivizumab reported in the study by Nuijten *et al.*²⁵ is used in the base-case model. It was based on assumptions about the number of 50-mg and 100-mg vials used in the RCT studies.^{12,16} Among preterm infants without CLD or children with CLD, 38.7% used a 50-mg vial and 91.3% used a 100-mg vial. Among children with CHD, 39.6% of children used a 50-mg vial and 100% of infants used 100-mg vial; in 3.8% of cases a second 100-mg vial was used.²⁵

The cost of a 50-mg vial of palivizumab is £360.40 and the cost of a 100-mg vial of palivizumab is £600.10.⁶⁴ The recommended dose of palivizumab is 15 mg/kg body weight administered once monthly throughout the RSV season. We assume that each infant received five doses. Palivizumab utilisation and unit cost for preterm infants are listed in Table 19 and for children with CHD in Table 20.

Administration costs

We assumed that palivizumab is routinely administered in a outpatient setting and that the costs of palivizumab administration consist of the following components:

- 8.4 min of GP time and 15 min of nurse time at the first visit to see the patient and discuss RSV prophylaxis with palivizumab
- 15 min of nurse time in the following visits.

The resource use for palivizumab administration and unit cost for preterm infants are listed in Table 19 and for children with CHD in Table 20.

Hospitalisation costs

The two RCT studies^{12,16} reported the number of patients who were admitted to paediatric wards and ICUs and the total of days in paediatric wards and in ICUs. For preterm infants without CLD or children with CLD, the average ICU stay is calculated to be 1.37 days and the average of non-ICU stay is calculated to be 6.47 days.²⁵ Two UK cohort studies^{57,65} reported length of stay in hospital due to RSV infection. However, the study by Clark *et al.*⁵⁷ reported only median of length of hospital stay (4 days with a range of 2–7 days), making it difficult to combine the length of stay in hospital with the RCT study. The other study

TABLE 19 NHS perspective or societal perspective resource use and costs for preterm infants

	Resource use	Source	Unit cost	Source	Total
Palivizumab	Five doses; 38.7% 50mg, 91.3% 100mg	Numa, 2000; ³⁴ Chiroli, 2005; ³⁷ Nuijten <i>et al.</i> , 2007 ²⁵	£360.40/50mg; £600.10/100mg	BNF ⁶⁴	£3436.83
Palivizumab administration	1 × 8.4 min GP	Yount <i>et al.</i> , 2004 ⁴⁶	£2.45	Curtis and Netten, 2006 ³¹	£20.58
Palivizumab administration	5 × 15 min nurse	Yount <i>et al.</i> , 2004 ⁴⁶	£0.52	Curtis and Netten, 2006 ³¹	£39.00
Hospitalisation (intensive care unit)	1.37 days	The IMPact-RSV Study Group, 1998 ¹⁶	£1723	Nuijten <i>et al.</i> , 2007 ²⁵	£3183.24
Hospitalisation (non-intensive care unit)	6.47 days	The IMPact-RSV Study Group, 1998 ¹⁶	£492	Nuijten <i>et al.</i> , 2007 ²⁵	£2360.57
Parents' work loss due to administration of prophylaxis	5 × 3 hours	Yount <i>et al.</i> , 2004 ⁴⁶	£13.98	ONS; ⁶⁶ ESRC ⁶⁷	£209.70
Parents' work loss due to children in hospital	7.84 × 8 hours	The IMPact-RSV Study Group, 1998; ¹⁶ Yount <i>et al.</i> , 2004 ⁴⁶	£13.98	ONS; ⁶⁶ ESRC ⁶⁷	£876.83
ESRC, Economic and Social Research Council; ONS, Office for National Statistics.					

TABLE 20 NHS perspective or societal perspective resource use and costs for children with CHD

	Resource use	Source	Unit cost	Source	Total
Palivizumab	Five doses, 39.6% 50 mg, 100% 100 mg. 3.8% 200 mg	Numa, 2000; ³⁴ Chirolu, 2005; ³⁷ Nuijten <i>et al.</i> , 2007 ²⁵	£360.40/50 mg; £600.10/100 mg	BNF ⁶⁴	£3736.90
Palivizumab administration	1 × 8.4 min GP	Yount <i>et al.</i> , 2004 ⁴⁶	£2.45	Curtis and Nettern, 2006 ³¹	£20.58
Palivizumab administration	5 × 15 min nurse	Yount <i>et al.</i> , 2004 ⁴⁶	£0.52	Nuijten <i>et al.</i> , 2007 ²⁵	£39.00
Hospitalisation (intensive care unit)	6.14 days	The Impact-RSV Study Group, 1998 ¹⁶	£1723	Nuijten <i>et al.</i> , 2007 ²⁵	£10,579.22
Hospitalisation (non-intensive care unit)	6.25 days	The Impact-RSV Study Group, 1998 ¹⁶	£492	Nuijten <i>et al.</i> , 2007 ²⁵	£3075
Parents' work loss due to administration of prophylaxis	5 × 3 hours	Yount <i>et al.</i> , 2004 ⁴⁶	£13.98	ONS; ⁶⁶ ESRC ⁶⁷	£209.70
Parents' work loss due to children in hospital	12.39 × 8 hours	The Impact-RSV Study Group, 1998; ¹⁶ Yount <i>et al.</i> , 2004 ⁴⁶	£13.98	ONS; ⁶⁶ ESRC ⁶⁷	£1385.70

ESRC, Economic and Social Research Council; ONS, Office for National Statistics.

by Thomas *et al.*⁶⁵ reported a total of 26 ICU days for three RSV-positive admissions and three admissions with RSV status unknown, but did not report the length of ICU stay for the three RSV-positive patients, making it difficult to estimate the average ICU days for RSV admission. We used the average number of days in a paediatric ward and in ICU estimated from the RCTs in the model. The hospitalisation resource use and unit cost for preterm children are listed in *Table 19*. For children with CHD, the average ICU stay is calculated to be 6.14 days and the average non-ICU stay was calculated to be 6.25 days.²⁵ The hospitalisation resource use and unit cost for children with CHD are listed in *Table 20*.

Parent work loss costs

Parent work loss costs consist of two parts, that due to the infant's hospitalisation and that due to administering prophylaxis with palivizumab. We assumed that in each case the infant was accompanied by one parent and that 3 hours of work was missed for each visit to administer palivizumab and 8 hours of work was lost in accompanying the infant to hospital.⁴⁶ The weekly wage in the UK in 2002 was estimated to be £442,⁶⁷ which is equivalent to £516.58 in 2006. The average number of hours worked in the UK is estimated to be 36.96 hours per week.⁶⁶ This gives a unit cost of £13.98/hour for estimating parent

work loss cost. The parent work loss and unit costs for preterm children are listed in *Table 19* and for children with CHD in *Table 20*.

Estimation of QALYs

Life expectancy

National statistics (1997–2001) reported average life expectancy to be 79.4, 77.8, 76.8, 74.6, 73.3, and 71 years for men and 82.2, 81.7, 81.3, 79.3, 78.6, and 77.6 year for women in different social classes.⁶⁸ The life expectancy for children at risk of RSV infection is calculated by averaging the life expectancies for men and women in different social classes using the assumption that men and women are equally represented in each social group. The mean life expectancy is estimated to be 77.8 with a standard deviation of 3.44. For preterm infants without CLD or children with CLD, the life expectancy at the age of 1 year was assumed to be 76.8 years. In the case of children with CHD, 95.3% of children were predicted to be survived to age 16 years if they had survived to age of 1 year.^{25,69} Therefore, life expectancy at the age of 1 year was assumed to be 76.1 years for children with CHD.

Utilities

The study by Greenough *et al.*⁷⁰ assessed the health-related quality of life (HRQoL) for preterm children at the age of 5 years using the

Health Utilities Index (HUI). The HUI describes a family of generic health status and HRQoL measures. Parents were sent the HUI2/3 and asked to complete the 15 questions to reflect their child's health over the previous 4 weeks. The HUI2 measures seven attributes of health status describing 24,000 unique health states, while HUI3 describes 972,000 unique health states. The HUI2 was originally developed for paediatric application and clinical evaluation studies, whereas HUI3 was developed for use in adults and population surveys. The median HUI2 multiattribute utility function was 0.88 (range 0.16–1.00) in the RSV-positive children, while the median HUI2 multiattribute utility function was 0.95 (range 0.03–1.00) in the non-RSV-positive children. The median HUI 3 multiattribute scores were 0.93 (range –0.05 to 1.00) for RSV-positive children and 0.97 (range –0.32 to 1.00) for non-RSV-positive children. These utility values are used in the model for preterm children with or without CLD and are listed in *Table 21*. As mentioned above, the utility estimate was made by asking parents (rather than children themselves) to complete the questions to reflect their child's health. This might introduce a bias in utility estimate. However, because the utility estimates for children hospitalised for RSV infection or not hospitalised for RSV infection were evaluated in the same way (i.e. parents completed the questionnaire) the effect of utility estimate made by parents for a child on the overall results is likely to be small and the conclusions unaltered.

Utility data for children and adults with CHD are lacking. The economic evaluation study by Yount *et al.*⁴⁶ extrapolated data from congestive heart failure to the CHD population and used a utility of 0.71 for children with CHD. We use the same utility values for children with CHD as those for preterm children with or without CLD (*Table 21*).

Assessment of cost-effectiveness using the base-case model

The results of cost-effectiveness are presented in three ways. Firstly, mean costs and QALYs for prophylaxis with palivizumab and no prophylaxis are presented and the incremental cost per QALY is calculated. For the base-case analysis, the incremental costs per LYG and per HAP are also presented. Secondly, cost-effectiveness–acceptability curves (CEACs) and scatterplots of incremental costs and outcomes generated from PSAs are presented. CEACs are used to illustrate uncertainty in results due to statistical variability around the parameter estimates. The curves demonstrate the likelihood that a strategy is cost-effective at different threshold values of willingness to pay for an additional QALY. The PSA is undertaken using appropriate distributions for all model variables. The model is run for 10,000 simulations. The results are summarised as the mean ICER for all simulations. Thirdly, the results of deterministic sensitivity analyses are presented for subgroups of the premature population and for specific RSV hospitalisation rates for children with CHD.

In order to consider the wider costs and benefits of prophylaxis with palivizumab to society, cost-effectiveness analyses are also undertaken from a societal perspective, taking into account the cost of parent work loss.

Assessment of cost-effectiveness using an extended model

It can be seen from the results of using realistic mortality rate estimates as parameters in the industry-sponsored model by Nuijten *et al.*²⁵ (which makes other assumptions favourable to palivizumab, such as the 100% occurrence of asthma in children admitted to hospital) that palivizumab does not meet conventional UK levels of cost-effectiveness in all children who meet the licensed indication.

TABLE 21 Estimated utilities

	Utility values		Source
	RSV hospitalisation	Not RSV hospitalisation	
Preterm with or without CLD	0.88	0.95	Greenough <i>et al.</i> , 2004; ⁷⁰ Nuijten <i>et al.</i> , 2007 ²⁵
Children with CHD	0.88	0.95	Greenough <i>et al.</i> , 2004; ⁷⁰ Nuijten <i>et al.</i> , 2007 ²⁵
CHD, congenital heart disease; CLD, chronic lung disease; RSV, respiratory syncytial virus.			

Nonetheless, if there were evidence that by preventing RSV hospitalisations we might reduce asthma morbidity, then this would improve the cost-effectiveness of palivizumab. Although there is no evidence to show a causal link between early RSV infection and atopic asthma, a recent cohort study showed that wheezing in early childhood is associated with an increased incidence of atopic asthma.⁵⁰ It is difficult to know whether children who are prone to asthma are more likely to become symptomatic when infected by RSV or whether RSV may increase the risk of asthma. We found five studies^{60,71–74} that reported asthma/wheezing rates for children who were admitted to hospital due to RSV infection and children who were not admitted to hospital due to RSV infection. The follow-up period varied from 2 to 15 years. The pooled sequelae rates were 0.23 for RSV hospitalisation and 0.12 for non-hospitalisation, giving a pooled odds ratio (OR) of 2.3 (95% CI 1.74–3.02). The studies suffered from various biases.

Because our clinical experts advised us that it was more likely that children prone to asthma were likely to get more symptomatic RSV infections rather than RSV infections causing asthma, we decided not to include asthma in our base-case model. Therefore, in order to model the possible effect of including increased asthma as a consequence of RSV infection, we undertook a separate analysis. To do this the BrumEE was

extended to take sequelae (asthma/wheezing) into account. The structure of the extended model is shown in *Figure 10*.

Sequelae-associated costs

The study by Greenough *et al.*⁶² compared the health care utilisation of children with CLD who had or had not been admitted to hospital with a proven RSV infection. A total of 235 children with a median gestational age of 27 weeks was included in this study. Forty-five of them had at least once been admitted to hospital for a proven RSV infection. The health care utilisation and the corresponding unit costs for children with proven RSV infection are shown in *Table 22*.

The sequelae-associated cost for those who were admitted to hospital due to RSV infection is estimated based on the health care utilisation of the children with a proven RSV infection and adjusted by subtracting the first-year RSV hospitalisation cost from the calculated 2-year costs.

Results of the BrumEE

Cost-effectiveness results using a deterministic model

The costs and outcomes for preterm infants without CLD, children with CLD and children with CHD are listed in *Tables 23, 24 and 25* respectively.

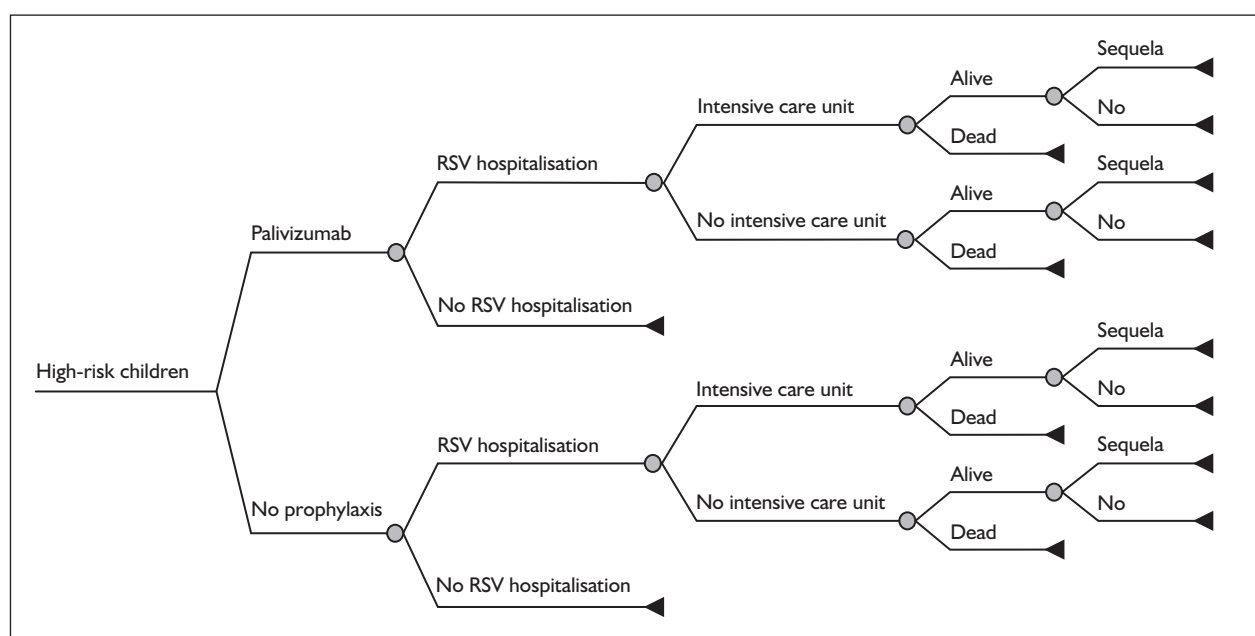


FIGURE 10 The extended decision tree model (taking sequelae into account).

TABLE 22 Resource use and costs of RSV hospitalisation (over 2 years)

	Resource use	Source	Unit cost	Source	Total
Days in hospital	39.8	Greenough et al., 2001 ⁶²	£237	Nuijten et al., 2007 ²⁵	£9433
Days in ICU	2.9	Greenough et al., 2001 ⁶²	£1723	Nuijten et al., 2007 ²⁵	£4997
Days in paediatric ward	30.7	Greenough et al., 2001 ⁶²	£492	Nuijten et al., 2007 ²⁵	£15104
Outpatients paediatric attendance	11.9	Greenough et al., 2001 ⁶²	£148	Nuijten et al., 2007 ²⁵	£1761
GP contacts	16.3	Greenough et al., 2001 ⁶²	£22	Curtis and Netten, 2006 ³¹	£352
Community care contacts	28.2	Greenough et al., 2001 ⁶²	£30	Nuijten et al., 2007 ²⁵	£846
Consultations with GP for respiratory illness	8.3	Greenough et al., 2001 ⁶²	£22	Curtis and Netten, 2006 ³¹	£179

ICU, intensive care unit; RSV, respiratory syncytial virus.

Table 26 presents the cost-effectiveness results of the deterministic analysis using the base-case model (with no sequelae). The ICERs between prophylaxis with palivizumab and no prophylaxis are £454,100/QALY for preterm infants without CLD, £63,800/QALY for children with CLD and £79,800/QALY for children with CHD from the NHS perspective.

In order to compare the results from the BrumEE with previous decision-analytical models, we also present the ICERs per LYG. These are, from an NHS perspective, £446,100/LYG for preterm infants without CLD, £62,600/LYG for children with CLD, and £78,400/LYG for children with CHD, as shown in Table 27.

TABLE 23 Average costs and outcomes for prophylaxis in preterm infants without CLD

Parameters	Palivizumab	No prophylaxis	Cost difference	Outcome difference
Costs				
Drug	£3437			
Drug administration (GP)	£21			
Drug administration (nurse)	£39			
Hospital	£67	£301		
Total cost (NHS)	£3564	£301	£3263	
Sequelae	£279	£1255		
Total cost (NHS), including sequelae	£3843	£1556	£2287	
Parent work loss	£226	£72		
Total cost (societal)	£3790	£373	£3417	
Total cost (societal), including sequelae	£4069	£1628	£2441	
Outcomes				
No discounting life-year lost	0.0059	0.0267		0.0208
No discounting QALYs	76.3141	76.2934		0.0207
Discounting life-year lost	0.0021	0.0094		0.0073
Discounting QALYs	26.5163	26.5092		0.0072

CLD, chronic lung disease; QALY, quality-adjusted life-year.

TABLE 24 Average costs and outcomes for prophylaxis in preterm children with CLD

Parameters	Palivizumab	No prophylaxis	Cost difference	Outcome difference
Costs				
Drug	£3437			
Drug administration (GP)	£21			
Drug administration (nurse)	£39			
Hospital	£293	£475		
<i>Total cost (NHS)</i>	<i>£3790</i>	<i>£475</i>	<i>£3315</i>	
Sequelae	£1180	£1912		
<i>Total cost (NHS), including sequelae</i>	<i>£4970</i>	<i>£2387</i>	<i>£2583</i>	
Parent work loss	£283	£120		
<i>Total cost (societal)</i>	<i>£4073</i>	<i>£595</i>	<i>£3478</i>	
<i>Total cost (societal), including sequelae</i>	<i>£5253</i>	<i>£2507</i>	<i>£2746</i>	
Outcomes				
No discounting life-year lost	0.2427	0.3932		0.1505
No discounting QALYs	76.0788	75.9292		0.1496
Discounting life-year lost	0.0853	0.1382		0.0529
Discounting QALYs	26.4346	26.3826		0.0520
CLD, chronic lung disease; QALY, quality-adjusted life-year.				

TABLE 25 Average costs and outcomes for prophylaxis in children with CHD

Parameters	Palivizumab	No prophylaxis	Cost difference	Outcome difference
Costs				
Drug	£3714			
Drug administration (GP)	£21			
Drug administration (nurse)	£39			
Hospital	£382	£697		
<i>Total cost (NHS)</i>	<i>£4155</i>	<i>£697</i>	<i>£3458</i>	
Sequelae	£799	£1461		
<i>Total cost (NHS), including sequelae</i>	<i>£4954</i>	<i>£2158</i>	<i>£2796</i>	
Parent work loss	£287	£140		
<i>Total cost (societal)</i>	<i>£4442</i>	<i>£837</i>	<i>£3605</i>	
<i>Total cost (societal), including sequelae</i>	<i>£5241</i>	<i>£2298</i>	<i>£2943</i>	
Outcomes				
No discounting life-year lost	0.1506	0.2752		0.1246
No discounting QALYs	75.4704	75.3466		0.1238
Discounting life-year lost	0.0533	0.0974		0.0441
Discounting QALYs	26.4156	26.3722		0.0434
CHD, congenital heart disease; QALY, quality-adjusted life-year.				

TABLE 26 Cost-effectiveness (£/QALY) results of the base-case model (NHS perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Preterm infants and children without CLD					
No prophylaxis	£301		26.5092		
Palivizumab	£3563	£3262	26.5163	0.0071	£454,100
Preterm infants and children with CLD					
No prophylaxis	£475		26.3826		
Palivizumab	£3789	£3314	26.4346	0.0520	£63,800
CHD children					
No prophylaxis	£697		26.3722		
Palivizumab	£4155	£3458	26.4156	0.0433	£79,800

CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

TABLE 27 Cost-effectiveness (£/LYG) results of the base-case model (NHS perspective)

Strategy	Cost	Cost difference	LYGs	LYG difference	ICER (£/LYG)
Preterm infants and children without CLD					
No prophylaxis	£301		0.0094		
Palivizumab	£3563	£3262	0.0021	0.0073	446,100
Preterm infants and children with CLD					
No prophylaxis	£475		0.1382		
Palivizumab	£3789	£3314	0.0853	0.0529	62,600
CHD children					
No prophylaxis	£697		0.0974		
Palivizumab	£4155	£3458	0.0533	0.0441	78,400

CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; LYG, life-year gained.

TABLE 28 Cost-effectiveness (£/HAP) results of the base-case model (NHS perspective)

Strategy	Cost	Cost difference	HAPs	HAPs difference	ICER (£/HAP)
Preterm infants and children without CLD					
No prophylaxis	£301		0.081		
Palivizumab	£3563	£3262	0.018	0.0063	51,800
Preterm infants and children with CLD					
No prophylaxis	£475		0.128		
Palivizumab	£3789	£3314	0.079	0.049	67,600
CHD children					
No prophylaxis	£697		0.0972		
Palivizumab	£4155	£3458	0.0532	0.0440	78,600

CLD, chronic lung disease; HAP, hospital admission prevented; ICER, incremental cost-effectiveness ratio.

The ICERs for using palivizumab compared with no prophylaxis are £51,800/HAP for preterm infants without CLD, £67,600/HAP for children with CLD and £78,600/HAP for children with CHD (Table 28).

From a societal perspective, the ICERs for using palivizumab compared with no prophylaxis are £475,600/QALY for preterm infants without CLD, £66,900/QALY for children with CLD and £83,200/QALY for children with CHD, as shown in Table 29.

Deterministic sensitivity analysis of cost-effectiveness (NHS perspective)

For preterm infants without CLD, deterministic sensitivity analyses were carried out with different mortality rates of 0.0005, 0.0013, 0.0073 and 0.0811. The cost-effectiveness results are shown in Table 30. The results show that prophylaxis with palivizumab for preterm infants without CLD becomes more cost-effective as the RSV-related mortality rate increases. When the mortality rate of 8.11% (used in the study by Nuijten *et al.*²⁵) is applied, the ICER is £24,100/QALY, which is below the UK cost-effectiveness threshold (£30,000/QALY).

For children with CLD, deterministic sensitivity analyses were carried out with different mortality rates of 0.03 and 0.05. The cost-effectiveness results are shown in Table 31. The results show that prophylaxis with palivizumab for children with CLD becomes more cost-effective as the RSV-related mortality rate increases. However, none of the ICERs reaches the UK cost-effectiveness threshold (£30,000/QALY).

Table 32 shows the cost-effectiveness results for subpopulations of children with CHD. The ICER for prophylaxis with palivizumab versus no prophylaxis for children with cyanotic CHD is £159,400/QALY, which reflects the fact that the RSV hospitalisation rates are not significantly different between children with cyanotic CHD who do and those who do not receive prophylaxis with palivizumab. The ICER for prophylaxis with palivizumab compared with no prophylaxis for among with acyanotic CHD is £49,100/QALY, which is also above the conventional UK cost-effectiveness threshold.

Sensitivity analyses are carried out using the RSV hospitalisation rates of 0.5–2.5% reported in the cohort study by Duppenhaler *et al.*²⁶ for children with CHD. Figure 11 shows the sensitivity analysis results of cost-effectiveness as RSV hospital admission rate in the no prophylaxis group changes. The ICER is £123,300/QALY with a RSV hospital admission rate of 0.5% and £91,000/QALY with a RSV hospital admission rate of 2.5%.

Table 33 shows the cost-effectiveness for children with CHD at different birth ages. The RSV hospitalisation rates reported in the study by Boyce *et al.*⁷⁵ were used (shown in Table 33). The value of ICER is £63,300/QALY for children with CHD at aged 0–6 months, £126,000/QALY for children aged 6–12 months and £457,900/QALY for children aged 12–24 months.

Cost-effectiveness (extended model in NHS and societal perspective)

Table 34 shows the cost-effectiveness results for preterm infants and children with CHD using

TABLE 29 Cost-effectiveness (£/QALY) results of the base-case model (societal perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Preterm infants without CLD					
No prophylaxis	£372		26.5092		
Palivizumab	£3789	£3417	26.5163	0.0071	475,600
Children with CLD					
No prophylaxis	£596		26.3826		
Palivizumab	£4074	£3478	26.4346	0.0520	66,900
CHD children					
No prophylaxis	£838		26.3722		
Palivizumab	£4442	£3604	26.4156	0.0433	83,200

CHD, congenital heart disease; CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

TABLE 30 Cost-effectiveness with different mortality rates for preterm infants without CLD (the base-case model, NHS perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Mortality rate = 0.0005					
No prophylaxis	£301		26.5173		
Palivizumab	£3563	£3262	26.5182	0.0009	3,905,500
Mortality rate = 0.0013					
No prophylaxis	£301		26.5156		
Palivizumab	£3563	£3262	26.5178	0.0022	1,502,100
Mortality rate = 0.0043					
No prophylaxis	£301		26.5092		
Palivizumab	£3563	£3262	26.5163	0.0071	454,100
Mortality rate = 0.0073					
No prophylaxis	£301		26.5027		
Palivizumab	£3563	£3262	26.5149	0.0122	267,500
Mortality rate = 0.0811					
No prophylaxis	£301		26.3442		
Palivizumab	£3563	£3262	26.4797	0.1355	24,100
CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.					

TABLE 31 Cost-effectiveness with different mortality rates for children with CLD (the base-case model, NHS perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Mortality rate = 0.03					
No prophylaxis	£475		26.4166		
Palivizumab	£3789	£3314	26.4556	0.0390	85,000
Mortality rate = 0.04					
No prophylaxis	£475		26.3826		
Palivizumab	£3789	£3314	26.4346	0.0520	63,800
Mortality rate = 0.05					
No prophylaxis	£475		26.3487		
Palivizumab	£3789	£3314	26.4137	0.0650	51,000
CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.					

TABLE 32 Cost-effectiveness for subpopulations of children with CHD (the base-case model, NHS perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
CHD, cyanotic, hospitalisation rates = 0.056/0.079 (palivizumab/no prophylaxis)					
No prophylaxis	£567		26.3902		
Palivizumab	£4175	£3608	26.4128	0.0226	159,400
CHD, acyanotic, hospitalisation rates = 0.050/0.118 (palivizumab/no prophylaxis)					
No prophylaxis	£847		26.3518		
Palivizumab	£4132	£3285	26.4187	0.0669	49,100
CHD, congenital heart disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.					

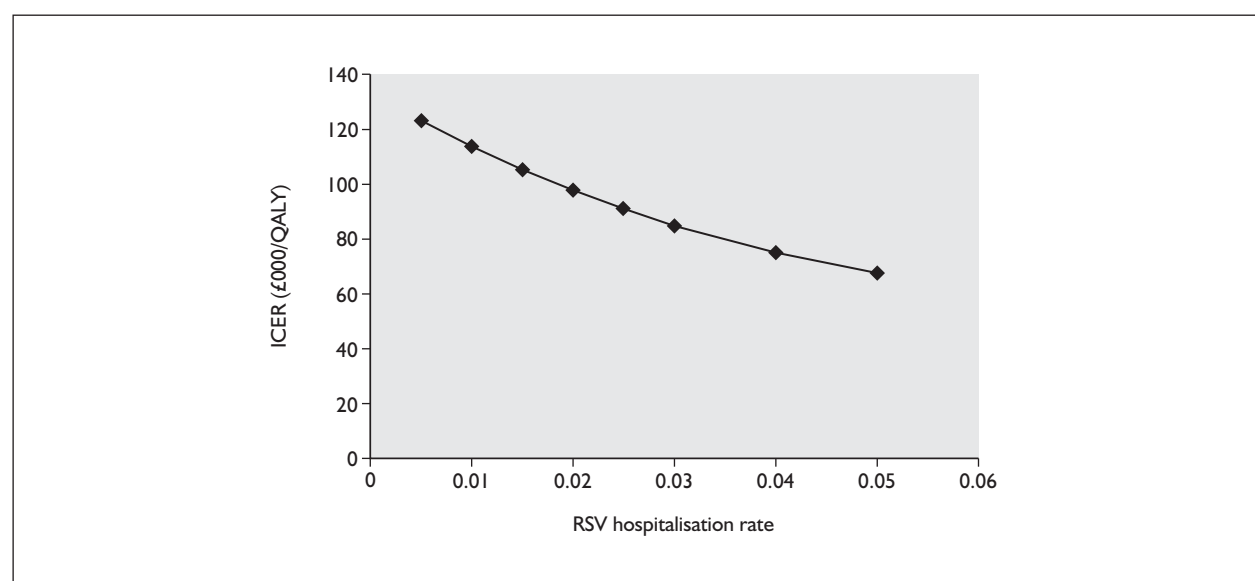


FIGURE 11 ICERs vary as RSV hospital admission rate changes.

TABLE 33 Cost-effectiveness with different mortality rates for children with CHD (the base-case model, NHS perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Age 0 to < 6 months, hospitalisation rate = 0.1208					
No prophylaxis	£861		26.3498		
Palivizumab	£4245	£3384	26.4033	0.0535	63,300
Age 6 to < 12 months, hospitalisation rate = 0.0635					
No prophylaxis	£456		26.4054		
Palivizumab	£4023	£3567	26.4337	0.0283	126,000
Age 12 to < 24 months, hospitalisation rate = 0.0182					
No prophylaxis	£131		26.4500		
Palivizumab	£3845	£3714	26.4581	0.0081	457,900
CHD, congenital heart disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.					

TABLE 34 Cost-effectiveness (£/QALY), taking sequelae into account (NHS perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Preterm infants without CLD					
No prophylaxis	£1556		26.5092		
Palivizumab	£3843	£2287	26.5163	0.0071	318,200
Children with CLD					
No prophylaxis	£2387		26.3826		
Palivizumab	£4970	£2583	26.4346	0.0520	49,700
Children with CHD					
No prophylaxis	£2158		26.3722		
Palivizumab	£4954	£2796	26.4156	0.0433	64,600
CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.					

the extended model (with consideration of sequelae) from the NHS perspective. The ICER for prophylaxis with palivizumab versus no prophylaxis for preterm infants without CLD is £318,200/QALY. The ICER for prophylaxis with palivizumab versus no prophylaxis for children with CLD is £49,700/QALY. The ICER for prophylaxis with palivizumab versus no prophylaxis for children with CHD is £64,600/QALY. These results demonstrate that prophylaxis with palivizumab for children with or without CLD tends to decrease ICER when sequelae are taken into account.

Table 35 shows the cost-effectiveness results for preterm infants and children with CHD using the extended model from societal perspective. The ICER for prophylaxis with palivizumab versus no prophylaxis for preterm infants without CLD is £339,700/QALY. The ICER for prophylaxis with palivizumab versus no prophylaxis for children with CLD is £52,800/QALY. The ICER for prophylaxis with palivizumab versus no prophylaxis for children with CHD is £67,900/QALY. These results demonstrate that prophylaxis with palivizumab for children with CHD tends to have a decreased ICER when potential sequelae are taken into account.

Cost-effectiveness results using a PSA (NHS perspective)

The incremental cost-effectiveness plane for prophylaxis with palivizumab compared with no prophylaxis for preterm infants without CLD is shown in Figure 12 (the parameter values and their distributions used in this analysis are given in Table 48 in Appendix 9). This shows that, although the

cost of palivizumab is always much higher than the cost of no prophylaxis, it always increases the QALY. The cost-effectiveness acceptability curve (CEAC) in Figure 13 shows that, compared with no prophylaxis, palivizumab has a probability of 50% of having an ICER below £460,000/QALY, a probability of 10% of having an ICER below £320,000/QALY and a probability of 90% of having an ICER below £690,000/QALY.

The incremental cost-effectiveness plane for prophylaxis with palivizumab compared with no prophylaxis for children with CLD is shown in Figure 14 (the parameter values and their distributions used in this analysis are shown in Table 49 in Appendix 9). This also shows that the cost of prophylaxis with palivizumab is always much higher than the cost of no prophylaxis and always increases the QALY. The CEAC in Figure 15 shows that, compared with no prophylaxis, palivizumab has a probability of 50% of having an ICER below £64,000/QALY, a probability of 10% of having an ICER below £48,000/QALY and a probability of 90% of having an ICER below £86,000/QALY.

The incremental cost-effectiveness plane for prophylaxis with palivizumab compared with no prophylaxis for children with CHD is shown in Figure 16 (the parameter values and their distributions used in this analysis are shown in Table 50). It demonstrates that the cost of prophylaxis with palivizumab is always much higher than the cost of no prophylaxis, and that in most cases prophylaxis with palivizumab increases the QALY. The CEAC in Figure 17 shows that, compared with no prophylaxis, palivizumab has a probability of

TABLE 38 Cost-effectiveness (£/QALY), taking sequelae into account (societal perspective)

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Preterm infants without CLD					
No prophylaxis	£1628		26.5092		
Palivizumab	£4069	£2441	26.5163	0.0071	339,700
Children with CLD					
No prophylaxis	£2507		26.3826		
Palivizumab	£5253	£2746	26.4346	0.0520	52,800
Children with CHD					
No prophylaxis	£2298		26.3722		
Palivizumab	£5241	£2943	26.4156	0.0433	67,900

CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

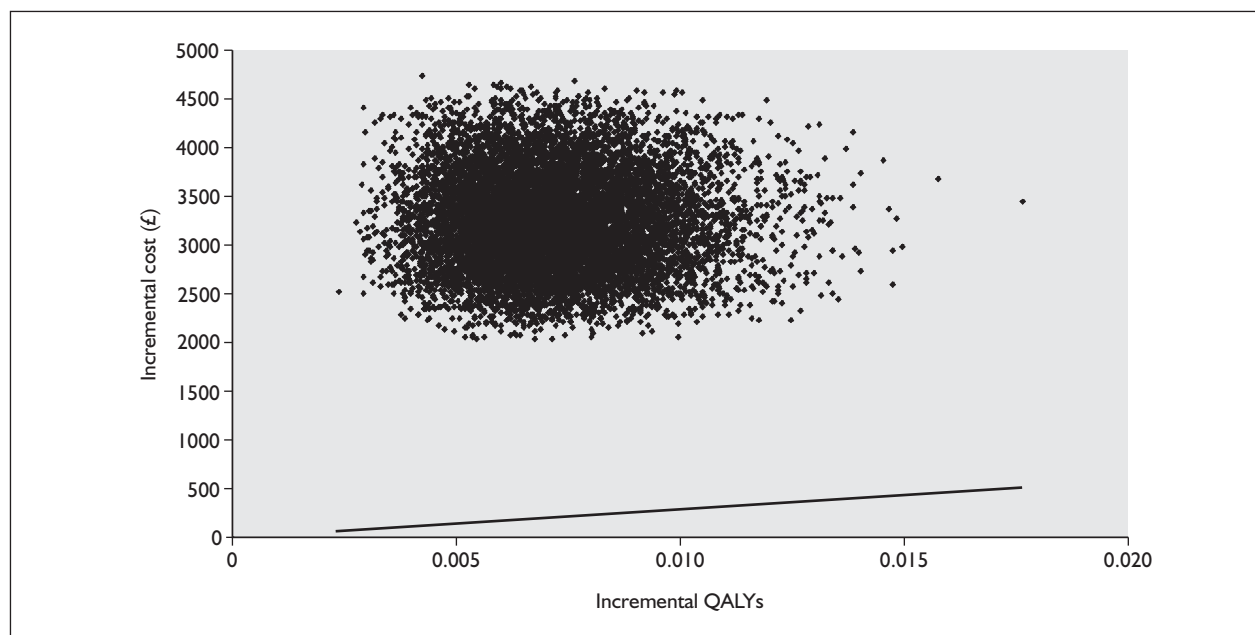


FIGURE 12 Incremental cost-effectiveness plane for prophylaxis with palivizumab compared with no prophylaxis for preterm infants without CLD. The line represents the £30,000/QALY willingness-to-pay threshold.

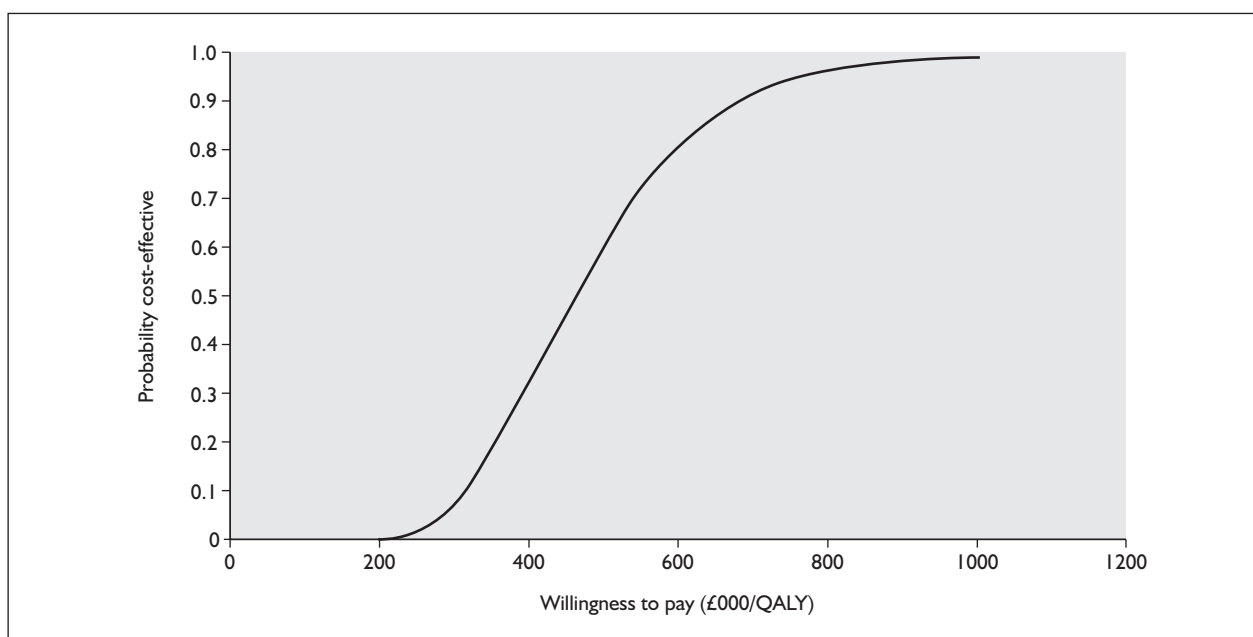


FIGURE 13 Cost-effectiveness-acceptability curve for prophylaxis with palivizumab compared with no prophylaxis for preterm infants without CLD.

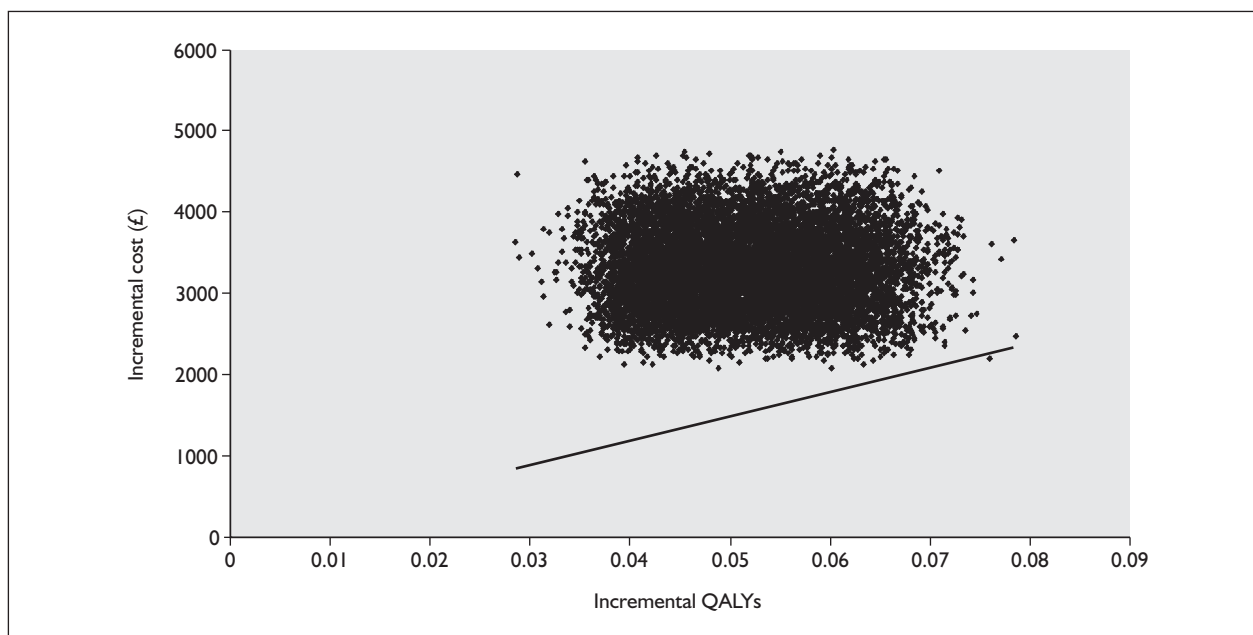


FIGURE 14 Incremental cost-effectiveness plane for prophylaxis with palivizumab compared with no prophylaxis for children with CLD. The line represents the £30,000/QALY willingness-to-pay threshold.

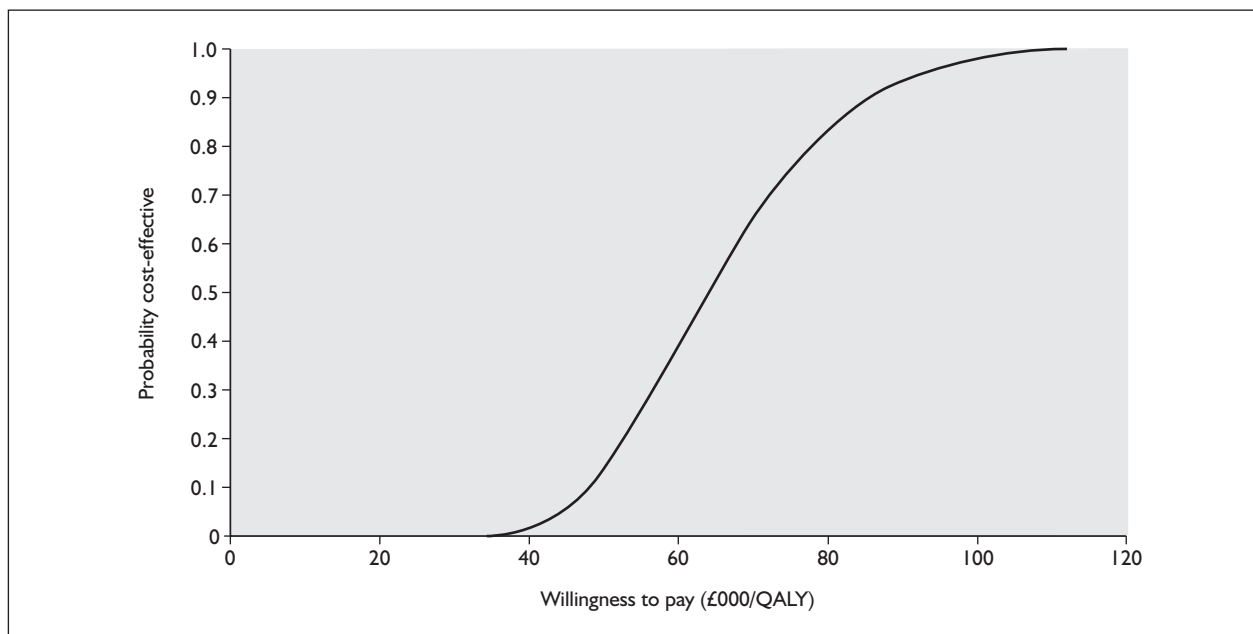


FIGURE 15 Cost-effectiveness-acceptability curve for prophylaxis with palivizumab compared with no prophylaxis for children with CLD.

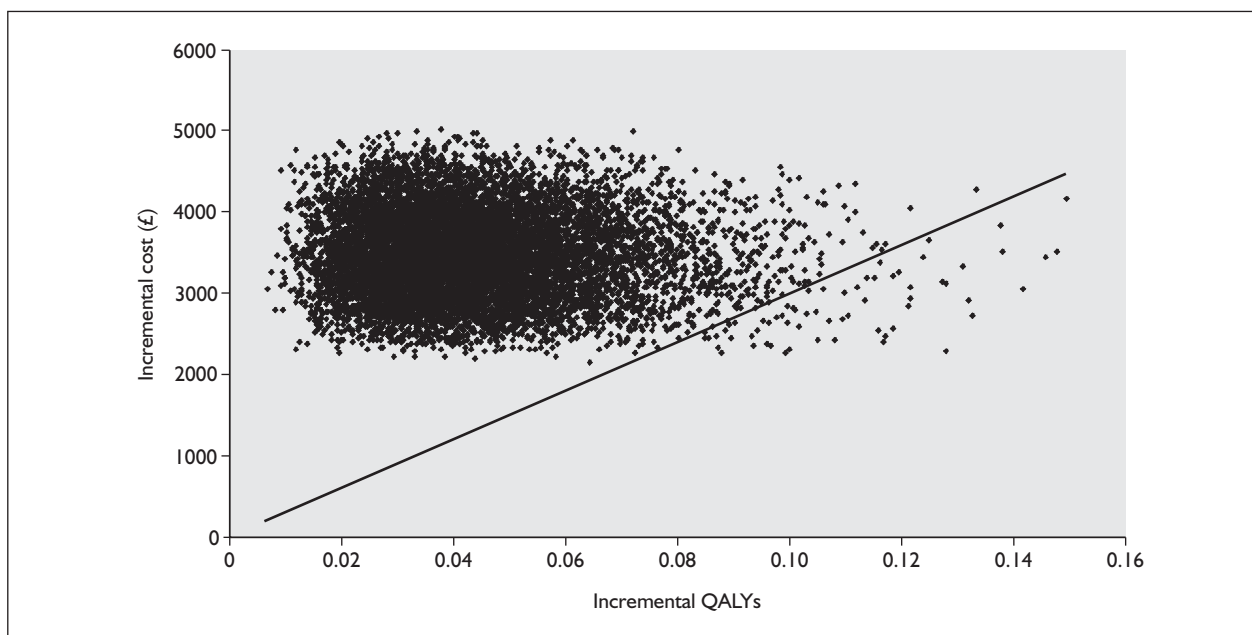


FIGURE 16 Incremental cost-effectiveness plane for prophylaxis with palivizumab compared with no prophylaxis for children with CHD. The line represents £30K/QALY willingness to pay threshold.

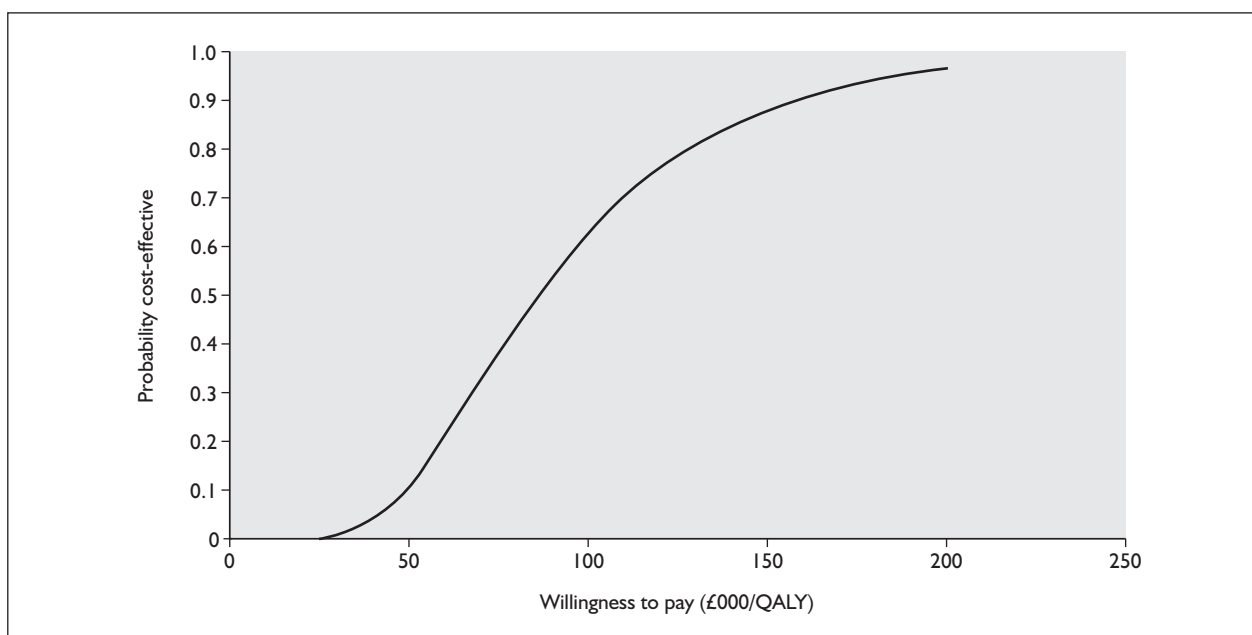


FIGURE 17 Cost-effectiveness acceptability curve for prophylaxis with palivizumab compared with no prophylaxis for children with CHD.

50% of having an ICER below £85,000/QALY, a probability of 10% of having an ICER below £50,000/QALY and a probability of 90% of having an ICER below £158,000/QALY.

As can be seen above, the deterministic model gives similar but slightly lower estimates for the ICERs for palivizumab compared with no prophylaxis than the median willingness-to-pay threshold of the PSA. The best summary estimate for policy-makers from the latter type of analysis (which incorporates more of the uncertainty than does a deterministic model with sensitivity analyses) is currently considered to be the average ICER from the PSA. These are summarised in the *Table 36* and again are very similar. A comparison of the estimates from the different methods is given in *Table 37*.

Results for PSA for subgroups with different risk factors

Gestational and birth ages

The cost-effectiveness for children with different risk factors was analysed. The most important risk factors for hospitalisation are gestational age, chronological age at the start of the RSV season and the presence of CLD or CHD. We therefore used the BrumEE to produce four economic evaluations – one for infants under 6 months old who are premature; one for children up to the age of 2 who have CLD; one for children up to the age of 2 who have siblings in day-care groups; and one for children up to the age of 2 who have CLD and siblings in day-care groups – stratifying by the risk factors of chronological age and gestational age.

The incremental cost/QALY for children with only gestational age (less than 24 up to 34 weeks) and low birth age as risk factors is relatively high (shown in *Table 38*) – it is greater than £60,000/QALY in all subgroups.

However the incremental cost/QALY fell when the additional risk factor of having CLD was added. *Table 39* shows the cost-effectiveness spectrum for children with CLD. The ICERs are less than or equal to £30,000/QALY for infants under 6 months and with a gestational age of less than 26 weeks and for infants under 3 months and with a gestational age of less than 30 weeks. The values of ICER lie between £30,000/QALY and £40,000/QALY for infants under 3 months of age with a gestational age of less than 30 weeks, for infants aged 3–6 months with a gestational age less than 28 weeks and for infants up to 9 months old with a gestational age of less than 24 weeks.

Table 40 gives the cost-effectiveness spectrum for children who only have the added risk factor of having a sibling in a day-care unit or school. The value of the ICERs never falls below £50,000/QALY in any subgroup.

Table 41 shows the cost-effectiveness spectrum for children with both CLD and siblings in a day-care unit or at school. The values of ICERs were less than or equal to £30,000/QALY for infants under 3 months and with a gestational age of less than 35 weeks, for infants aged 3–6 months and with a gestational age of less than 30 weeks and for infants aged 6–9 months old and with a gestational age of less than 26 weeks.

TABLE 36 Average ICER from PSA

Strategy	Cost	Cost difference	QALYs	QALY difference	ICER (£/QALY)
Preterm infants without CLD					
No prophylaxis	£299		26.3239		
Palivizumab	£3555	£3256	26.3310	0.0072	454,100
Children with CLD					
No prophylaxis	£477		26.2079		
Palivizumab	£3789	£3312	26.2595	0.0517	64,100
Children with CHD					
No prophylaxis	£693		26.1997		
Palivizumab	£4166	£3473	26.2423	0.0427	81,400

CHD, chronic heart disease; CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

TABLE 37 Comparative ICERs from different methods of BrumEE

Strategy	Incremental cost/QALY (£)				
	Deterministic analysis	10% probability of effectiveness from PSA	50% probability of effectiveness from PSA	90% probability of effectiveness from PSA	Average from PSA
Preterm infants without CLD	454,000	320,000	460,000	690,000	454,000
Children with CLD	64,000	48,000	64,000	86,000	64,000
Children with CHD	80,000	50,000	85,000	158,000	81,000

CHD, chronic heart disease; CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.

TABLE 38 Average incremental cost/QALY from PSA in infants without CLD

Birth age (months)	Gestational age (weeks)					
	≤ 24	24–26	26–28	28–30	30–32	32–34
< 3	102,000	136,000	196,000	270,000	361,000	530,000
3–6	197,000	270,000	357,000	529,000	753,000	954,000
6–9	360,000	526,000	751,000	954,000	1283,000	1922,000

CLD, chronic lung disease; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.
ICER cost/QALY coding: all £60,000 and over.

TABLE 39 Average incremental cost/QALY from PSA in children with CLD

Birth age (months)	Gestational age (weeks)					
	≤ 24	24–26	26–28	28–30	30–32	32–34
<3	12,000 ^a	15,000 ^a	19,000 ^a	23,000 ^a	31,000 ^b	40,000 ^b
3–6	19,000 ^a	24,000 ^a	31,000 ^b	42,000 ^c	54,000 ^d	75,000 ^e
6–9	31,000 ^b	42,000 ^c	54,000 ^d	75,000 ^e	105,000 ^e	141,000 ^e
9–12	59,000 ^d	75,000 ^e	105,000 ^e	142,000 ^e	213,000 ^e	284,000 ^e
12–15	105,000 ^e	140,000 ^e	213,000 ^e	285,000 ^e	430,000 ^e	429,000 ^e
15–18	211,000 ^e	286,000 ^e	432,000 ^e	431,000 ^e	862,000 ^e	867,000 ^e
18–21	429,000 ^e	428,000 ^e	862,000 ^e	867,000 ^e	859,000 ^e	∞
21–24	864,000 ^e	865,000 ^e	864,000 ^e	∞	∞	∞

CLD, chronic lung disease; PSA, probabilistic sensitivity analysis; QALY, quality-adjusted life-year.
ICER cost/QALY coding:
a < £30,000
b £30,000 to < £39,999
c £40,000 to < £49,999
d £50,000 to < £59,999
e £60,000 and over.

TABLE 40 Average ICER from PSA: children with siblings in day-care groups

Birth age (months)	Gestational age (weeks)					
	≤ 24	24–26	26–28	28–30	30–32	32–34
< 3	59,000 ^a	80,000	108,000	145,000	198,000	267,000
3–6	108,000	146,000	198,000	269,000	404,000	531,000
6–9	212,000	294,000	403,000	525,000	751,000	958,000
9–12	402,000	527,000	752,000	947,000	1,280,000	1,925,000
12–15	752,000	947,000	1,284,000	1,934,000	3,890,000	3,893,000
15–18	1,275,000	1,931,000	3,897,000	3,939,000	3,886,000	3,868,000
18–21	3,882,000	3,915,000	3,896,000	3,883,000	∞	∞
21–24	3,874,000	∞	∞	∞	∞	∞

ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.
 ICER cost/QALY coding:
 a £50,000 to < £59,999; all others £60,000 and over.

Other risk factors

Although the patient population included in the licensed indication is clearly defined, it is clinically heterogeneous and includes children with very different risks of hospitalisation following RSV and the tables above show estimates of the probability of hospitalisation for birth, gestational age and having a sibling at school or day care.

However, there are other risk factors that further increase the probability that an infant will be

hospitalised for RSV and which will reduce the incremental cost/QALY. Information on risk factors was taken from pragmatically selected high-quality studies. Only studies that included risk factors adjusted for gestational age or which included only patients within a narrow gestational age band were included. The additional factors are tabulated in *Table 42*, with information about the study from which the estimates are taken. It should be remembered that residual confounding is likely to influence the estimate of risk in these

TABLE 41 Average ICER from PSA: for children with CLD and siblings in day care

Birth age (months)	Gestational age (weeks)					
	≤ 24	24–26	26–28	28–30	30–32	32–34
< 3	9,000 ^a	10,000 ^a	12,000 ^a	15,000 ^a	19,000 ^a	25,000 ^a
3–6	13,000 ^a	15,000 ^a	19,000 ^a	24,000 ^a	33,000 ^b	42,000 ^c
6–9	19,000 ^a	24,000 ^a	33,000 ^b	42,000 ^c	59,000 ^d	75,000 ^e
9–12	33,000 ^b	45,000 ^c	58,000 ^d	76,000 ^e	105,000 ^e	141,000 ^e
12–15	59,000 ^d	83,000 ^e	105,000 ^e	140,000 ^e	212,000 ^e	284,000 ^e
15–18	105,000 ^e	141,000 ^e	214,000 ^e	286,000 ^e	430,000 ^e	430,000 ^e
18–21	213,000 ^e	285,000 ^e	428,000 ^e	429,000 ^e	863,000 ^e	866,000 ^e
21–24	430,000 ^e	431,000 ^e	867,000 ^e	870,000 ^e	859,000 ^e	∞

CLD, chronic lung disease; ICER, incremental cost-effectiveness ratio; PSA, probabilistic sensitivity analysis.
 ICER cost/QALY coding:
 a < £30,000
 b £30,000 to < £39,999
 c £40,000 to < £49,999
 d £50,000 to < £59,999
 e £60,000 and over.

TABLE 42 Risk factors for RSV hospitalisation other than chronological age and adjusted/controlled for gestational age

Study	Description	Risk factor	Estimate ^a (95% CI)
Rietvald <i>et al.</i> , 2006 ⁵³	Retrospective population-based cohort study, the Netherlands, 2469 hospitalised out of 140,661 children born 1996–1998	Male	1.4 (1.3–1.5)
		Birth weight: ≤ 2500 g	1.7 (1.5–2.0)
		Birth weight: 2501–3000 g	1.3 (1.1–1.4)
Boyce <i>et al.</i> , 2000 ⁷⁵	Retrospective cohort, July 1989 to June 1993, Tennessee, USA. RSV season defined as November to April. Children less than 3 years enrolled from birth. Used Medicaid data files in incidence density study with child years denominator, excess rate in influenza season subtracted	Condition other than BPD or CHD	2.3 (2.1–2.6)
		≥ 1 sibling	1.4 (1.3–1.5)
		Male	1.3 (1.2–1.4)
		White race (Tennessee, USA)	1.3 (1.2–1.4)
		Rural residence (Tennessee, USA)	1.3 (1.2–1.4)
		Maternal smoking	1.3 (1.2–1.4)
		Maternal education ≤ 12 years	1.2 (1.1–1.3)
Figueras-Aloy, 2004 ⁷⁶	Prospective case–control study, 50 Spanish hospitals, October 2002 to April 2003, cases 33–35 gestational age at birth hospitalised for RSV (186), controls born at same time, 33–35 gestational age	History of wheezing in family	1.90 (1.19–3.01)
		School-age siblings (≥ 1)	2.85 (1.88–4.33)
		≥ 4 residents and visitors (excluding school-age siblings and subject)	1.91 (1.19–3.07)
		Breast feeding ≤ 2 months	3.26 (1.96–5.42)
		Smoking, day care not significant	
Law, 2004 ⁷⁷	Prospective cohort (PICNIC), 16 Canadian regions, November 2000 to June 2001, November 2001 to June 2002, following children born November to April at 33–35 weeks GA, no RSV prophylaxis. 1862 children	Born in November, December or January	4.88 (2.57–9.29)
		Male	1.91 (1.10–3.31)
		Small for gestational age	2.19 (1.14–4.22)
		Subject attending day care	12.32 (2.56–59.34)
		Any preschool-age siblings	2.76 (1.51–5.03)
		≥ 2 smokers in the household [OR 1.71 (95% CI 0.97–3.00)], > 5 individuals in the home (including subject), eczema in first-degree relative not significant	
		School-age siblings	1.64 (1.05–2.55)
		Tobacco smoke exposure	1.63 (1.05–2.56)
Carbonell-Estrany, 2001 ⁷⁸	Cohort of 1206 children born at ≤ 32 weeks from April 1999 to April 2000.		

BPD, bronchopulmonary dysplasia; CHD, chronic heart disease; CI, confidence interval. GA, gestational age; OR, odds ratio; RSV, respiratory syncytial virus.

a Odds ratio from multiple logistic regression except Boyce (Poisson regression, incidence rate ratio).

observational studies. Where potential risk factors are associated with each other, the choice of factors entered into the model will influence the factors included in the final model. Further risk factors for RSV hospitalisation identified consistently in the included studies were male gender and intrauterine growth retardation/lower birth weight (as lower birth weight is a risk factor independent of gestational age, it is an indicator of relatively poor intrauterine growth). There were inconsistent results for maternal smoking. Other risk factors

appeared only in one study, for example breast feeding for 2 months or less and November, December or January birthday: this reflects the different selection of variables for inclusion in multivariate models in the studies. It should be remembered that factors identified as important in one society will not necessarily have the same impact in other settings; for example, the impact of race and rural residence may be different in northern Europe and the southern USA.

These risk factors have not been formally included in the BrumEE as, without further work to identify relevant studies systematically, review their quality, extract data, consider whether pooling of estimates would be appropriate and to evaluate further risk stratification, there is the risk of reducing the accuracy and precision of the model estimates to an unacceptable degree. However, the presence of additional risk factors may be important in making the clinical decision as to whether to offer palivizumab prophylaxis to a particular baby as they increase the risk of hospitalisation. We think that it may not be inappropriate for a clinician to treat a child who has two or more of these *additional* risk factors as falling into a band of cost-effectiveness that is one level more cost-effective than shown in *Table 38* and, possibly, a child who has most or all of these risk factors as falling in a band that is two levels more cost-effective.

Summary

- The assessment group developed a decision tree with Monte Carlo simulation model to assess the cost-effectiveness of prophylaxis with palivizumab, compared with no prophylaxis. The model has been designed to estimate costs, from a UK NHS perspective and a societal perspective, and outcomes in terms of QALYs, for a lifetime time horizon.
- According to this model, prophylaxis with palivizumab is not a cost-effective strategy for preterm infants and children with CHD compared with no prophylaxis from both an NHS perspective and societal perspective. These findings are robust to probabilistic and other sensitivity analyses.
- Prophylaxis with palivizumab is also not a cost-effective strategy for preterm infants or infants with CLD who have no other risk factors.
- Subgroup analyses showed that prophylaxis with palivizumab for children with CLD may be cost-effective, at a willingness-to-pay threshold of £30,000/QALY, in
 - infants under 3 months old at the start of the RSV season who were born at 30 weeks gestational age or less
 - infants under 6 months old at the start of the RSV season who were born at 26 weeks gestational age or less.
- Further analyses showed that prophylaxis with palivizumab for children with CLD, and who also have a sibling in day care or school, may be cost-effective, at a willingness to pay threshold of £30,000/QALY, in
 - infants under 3 months old at the start of the RSV season who were born at 35 weeks gestational age or less
 - infants under 6 months old at the start of the RSV season who born at 30 weeks gestational age or less
 - infants under 9 months old at the start of the RSV season who born at 26 weeks gestational age or less.

Chapter 5

Discussion

Clinical effectiveness

Two good-quality trials provide evidence of the effectiveness of palivizumab in reducing the rate of RSV hospitalisation and RSV hospitalisation days in premature (≤ 35 weeks) infants and children with CLD and in children aged up to 2 years with CHD. Palivizumab appears to be safe and well tolerated.

Subgroup analysis suggested that palivizumab may be more effective in premature babies than in children with CLD. The reduction in RSV hospitalisation was greater in children with non-cyanotic rather than cyanotic CHD, but in this case there was no convincing evidence from subgroup analysis that the effect sizes were different.

Three systematic reviews^{9,17,20} assessed the clinical effectiveness of palivizumab based on the two RCTs. They gave the same conclusion: palivizumab is effective for the prevention of RSV infection in infants and children who are at high risk.

Cost-effectiveness

We have identified three systematic reviews and 18 primary studies for economic evaluations of prophylaxis with palivizumab.

The three systematic reviews on cost-effectiveness analysis came to similar conclusions. The study by Dunfield and Mierzwinski-Urban¹⁷ stated that the results of the included economic evaluation studies were variable due to different cost data sources, and that palivizumab was not cost-effective when used in all for whom it is recommended. Dunfield and Mierzwinski-Urban¹⁷ concluded that only children with a very high risk of RSV should be administered palivizumab owing to the high cost of palivizumab. The study by Embleton *et al.*²⁰ reported that none of the identified studies was a comprehensive economic analysis and that the costs of prophylaxis were far in excess of any likely savings achieved by decreasing hospital admission rates and concluded that continued use of palivizumab for high-risk infants, such as those with CLD, may appear justified in the absence of a comprehensive economic assessment. The study by

Kamal *et al.*³² reported that divergent results may be explained by differences in the study methods, assumptions and the poor quality of some economic evaluations and that the potential cost of palivizumab prophylaxis far exceeded the actual cost of hospitalisation; therefore, policy-makers, or providers, or payers need to critically appraise and judiciously interpret studies reporting the cost-effectiveness of palivizumab.

Four primary studies^{9,25,41,45} reported cost-effectiveness in terms of cost/LYG for preterm children with or without CLD. To make comparisons, we converted all ICERs into the UK pounds sterling at equivalent 2006 prices.

The ICERs varied from £25,800/LYG to £404,900/LYG:

- Two studies^{25,37} reported cost-effectiveness in terms of cost per LYG for children with CHD, with ICERs varying from £5300/LYG to £7900/LYG.
- Three studies^{25,40,47} reported cost-effectiveness in terms of cost per QALY for preterm children with or without CLD, with ICERs varying from £3200/QALY to £1,489,700/QALY.
- Two studies^{16,46} reported cost-effectiveness in terms of cost per QALY for children with CHD, with ICER varying from £7500/QALY to £68,700/QALY.

Other studies assessed cost-effectiveness in terms of cost/HAP for preterm children with or without CLD. The ICER varied from £5300/HAP to £69,200/HAP.

We have developed a decision-analytical model, the BrumEE, to assess the cost-effectiveness of prophylaxis with palivizumab.

The BrumEE shows that the ICERs for prophylaxis with palivizumab compared with no prophylaxis are £454,100/QALY for preterm infants without CLD, £63,800/QALY for children with CLD and £79,800/QALY for children with CHD, from an NHS perspective. The base-case model also shows that the ICERs between prophylaxis with palivizumab and no prophylaxis are £446,100/LYG for preterm

infants without CLD, £62,600/LYG for children with CLD and £78,400/LYG for children with CHD from an NHS perspective, and that the ICERs between prophylaxis with palivizumab and no prophylaxis are £51,800/HAP for preterm infants without CLD, £67,600/HAP for children with CLD and £78,600/HAP for children with CHD from an NHS perspective. The similar cost-effectiveness results have been obtained from a societal perspective (£475,600/QALY for preterm infants without CLD, £66,900/QALY for children with CLD and £83,200/QALY for children with CHD). The probabilistic sensitivity analyses have shown that, compared with no prophylaxis, prophylaxis with palivizumab for preterm infants without CLD has a probability of 50% of having an ICER below £460,000/QALY, that prophylaxis with palivizumab for children with CLD has a probability of 50% of having an ICER below £64,000/QALY, and that prophylaxis with palivizumab for children with CHD has a probability of 50% of having an ICER below £85,000/QALY.

Strengths and limitations

The strengths of the assessment group economic model include the following aspects.

- Firstly, the cost-effectiveness of prophylaxis with palivizumab has been assessed in the time horizon of lifetime and expressed in terms of cost per LYG and cost per QALY (rather than in a 1-year time horizon and expressed only in cost per HAP, as in most previous models).

- Secondly, the mortality rates for those who admit to hospital due to RSV infection have been synthesised from meta-analysis of the available published evidence.
- Thirdly, analysis was conducted from both an NHS and a societal perspective.
- Finally, in addition to the base-case model, an extended model was used to assess the cost-effectiveness of prophylaxis with palivizumab when sequelae are taken into account.

The assessment group model has the following limitations.

- There is limited availability of good-quality scientific evidence to inform some of the parameters and some studies have quite a varied range of estimates.
- Evidence to inform the parameters of the model were sought and selected pragmatically rather than through a systematic review.
- The cost of sequelae was derived from only one study. It was estimated by subtracting the first-year cost due to RSV hospital admission from the total 2-year costs from a cohort study. The extended model was built with an assumption that the yearly sequelae costs are the same over several years.
- The utility values for children with CHD were assumed to be the same as those for preterm infants without CLD or children with CLD.
- Only one RSV season was considered in the models.
- The premature infants or children with CLD/CHD were assumed to have a normal full life expectancy.

Chapter 6

Conclusions

Implications for decision and policy-making

Prophylaxis with palivizumab is clinically effective for the prevention of serious LRTI caused by RSV infection and requiring hospitalisation in high-risk children. This conclusion is based on two RCTs: the IMpact-RSV study¹⁶ found a 55% of reduction in RSV hospitalisation among preterm infants without CLD or children with CLD; and the Feltes *et al.*¹² study found a 45% reduction in RSV hospitalisation for children with CHD. There is some evidence that prophylaxis may be particularly effective in premature infants.

In terms of cost-effectiveness, prophylaxis with palivizumab does not represent good value based on any willingness-to pay-threshold below £60,000/QALY (the current UK ICER threshold is about £30,000/QALY) when used unselectively in preterm infants without CLD or children with CLD or CHD. This conclusion is in consistent with most previous economic evaluation studies, especially when only a short-term effect of RSV infection is considered (e.g. ICER is expressed as cost per HAP). However, our base-case model does show that prophylaxis with palivizumab may be cost-effective for some subgroups, such as young preterm infants with CLD.

The cost-effectiveness of prophylaxis with palivizumab is affected by the cost of palivizumab, and the length of stay and sequelae that RSV infection might have, in addition to the hospitalisation and mortality rates of RSV infection.

Suggested research priorities

Future research should be directed towards the following.

The body of evidence of the cost-effectiveness of prophylaxis with palivizumab is conditional on the quality of clinical evidence. Future research should focus on the major uncertainties in cost-effectiveness identified by the BrumEE, particularly in RSV-related mortality rate, and the length of

effect of RSV infection on morbidity and mortality in the UK settings. Further large observational studies are desirable for the estimate of the mortality rate for children with CLD or preterm infants without CLD and who are admitted to hospital because of RSV infection. The health-related quality of life for RSV-infected children was assessed in the previous studies by measuring seven attributes of health status describing 24,000 unique health states for preterm children at the age of 5 years. Long-follow-up (> 5 years) observational studies will be useful for the estimate of the health-related quality of life and the period for which RSV infection has an effect on morbidity and mortality. In the first instance, a systematic review would more clearly identify gaps in knowledge and would inform the design of observational studies. A systematic review of the prognostic factors for hospital admission should be undertaken to permit the development of clinical guidelines to enable clinicians to identify the most appropriate children to be treated with palivizumab. Questions that could usefully be addressed in such research include:

- What are the prognostic factors for hospital admission due to RSV infection?
- What are the risks of these prognostic factors for hospital admission due to RSV infection?

Questions that could usefully be addressed in the systematic review and further observational research if the review confirmed that this was needed include:

- What is the mortality rate for children with CLD or preterm infants without CLD who are admitted to hospital due to RSV infection?
- What is the health-related quality of life for children with CLD or preterm infants without CLD who are admitted to hospital due to RSV infection?
- What is the health-related quality of life for children with CLD or preterm infants without CLD who are not admitted to hospital due to RSV infection?
- What is the health-related quality of life for children with CHD who are admitted to hospital due to RSV infection?

- What is the health-related quality of life for children with CHD who are not admitted to hospital due to RSV infection?
- For how long does RSV infection have an effect on morbidity and mortality in children with or without CLD or CHD?

The BrumEE models suggest that prophylaxis with palivizumab may be cost-effective for some subgroups, such as preterm infants with CLD. However, the hospital admission rates for these patient subgroups were obtained from subgroup analyses, and the mortality rates for these patient subgroups were assumed to be the same as those for the group considered as a whole. Future research should focus on the major uncertainties

for patient subgroups, including preterm infants with different gestational ages. Further RCTs may be useful in estimating hospitalisation rates for children with CLD and/or who have a sibling in day care or at school, are under 6 months old at the start of the RSV season and who were born at 30 weeks gestational age or less. Questions that could usefully be addressed in such research include:

- What is the effect size of prophylaxis with palivizumab in terms of hospitalisation rates for children with CLD and/or who have a sibling in day care or at school, and who are under 6 months old at the start of the RSV season and who were born at 30 weeks gestational age or less?



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Contributions of authors

Dechao Wang reviewed the economic evaluation studies, developed the decision-analytical model, and contributed to the drafting of the economic analysis, discussion and conclusion sections.

Carole Cummins applied the inclusion and exclusion criteria, extracted data, and contributed to the drafting of the clinical effectiveness section.

Sue Bayliss was information specialist to the team and devised and ran the search strategies.

Josie Sandercock contributed to the protocol development, selection of prognostic studies and modelling of risks for prognostic subgroups.

Dr Amanda Burls was the senior reviewer on this report. She contributed to the protocol development and design of the model and

undertook data extraction for the systematic review of the effectiveness studies and the economic evaluations. She wrote the first draft of the report, read and commented on the final draft of the report and is guarantor.

About 'home unit'

The West Midlands Health Technology Assessment Collaboration (WMHTAC) is an organisation involving several universities and academic groups who collaboratively undertake research synthesis to produce health technology assessments. Most of our members are based in the Department of Public Health and Epidemiology, University of Birmingham; however, other members are drawn from a wide field of expertise including economists and mathematical modellers from the Health Economics Facility, University of Birmingham, Leeds University and pharmacists and methodologists from the Department of Medicines Management, Keele University.

WMHTAC produces systematic reviews, health technology assessments and economic evaluations for NHS R&D HTA programme (NCCHTA), the National Institute for Health and Clinical Excellence (NICE), and for the health service in the West Midlands. WMHTAC also undertakes methodological research on research synthesis, and provides training in systematic reviews and health technology assessment.



References

- Glezen PW, Taber LH, Frank AL, Kasel JA. Risk of primary infection and re-infection with respiratory syncytial virus. *Am J Dis Child* 1986;**140**:543–6.
- Ottolini MG, Hemming VG. Prevention and treatment recommendations for respiratory syncytial virus infection. *Drugs* 2007;**1997**:867–84.
- Simoes EAF. Respiratory syncytial virus infection. *Lancet* 1999;**354**:847–52.
- www.advisorybodies.doh.gov.uk/jcvi/mins220605.htm (accessed July 2007).
- Stensballe LG, Devasundaram JK, Simoes EA. Respiratory syncytial virus epidemics: the ups and downs of a seasonal virus. *Pediatr Infect Dis J* 2003;**22**(2 Suppl.):S21–32.
- www.who.int/vaccine_research/diseases/ari/en/index3.html (accessed May 2007).
- <http://bnfc.org/bnfc/bnfc/current/129087.htm> (accessed 19 July 2007).
- MTRAC. Palivizumab (Synagis®) for the prevention of hospitalisation due to RSV (BNF: 5.3). VS00–21. 2000. Keele University, Staffordshire, MTRAC at the Department of Medicine Management. Ref Type: Generic.
- Simpson S, Burls A. A systematic review of the effectiveness and cost-effectiveness of palivizumab (Synagis(R)) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection (www.publichealth.bham.ac.uk/wmhtac/2001).
- www.sign.ac.uk/pdf/sign91.pdf (accessed 19 July 2007).
- Tulloh RM, Feltes TF, Tulloh RMR, Feltes TF. The European Forum for Clinical Management: prophylaxis against the respiratory syncytial virus in infants and young children with congenital cardiac disease. *Cardiol Young* 2005;**15**:274–8.
- Feltes TF, Cabalka AK, Meissner HC, Piazza FM, Carlin DA, Top FH, *et al.* Palivizumab Prophylaxis reduces hospitalisation due to respiratory syncytial virus in young children with hemodynamically significant congenital heart disease. *J Pediatr* 2003;**143**:540.
- www.advisorybodies.doh.gov.uk/jcvi/mins111104rvi.htm.
- Jo Lockett, Department of Medicines Management, Keele University, personal communication, 14 February 2007.
- Centre for Review and Dissemination (CRD). *Guidance for those carrying out or commissioning reviews. Undertaking systematic reviews of research on effectiveness*. CRD Report 4, 2nd edn, 2001.
- American Academy of Pediatrics. 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;**102**:531–7.
- Dunfield L, Mierzwinski-Urban M. Palivizumab prophylaxis against respiratory syncytial virus. *Canad Agency Drugs Technol Health* 2007;**80**:1–9.
- Raya OL, Marquez CS, Navarro Caballero JA, Portero R. Cost-effectiveness of palivizumab in the prevention of hospital admissions for syncytial respiratory virus in pre-term babies born at 32 to 35 weeks (www.juntadeandalucia.es/salud/aetsa/2006).
- Viswanathan M, King VJ, Bordley C, Honeycutt AA, Wittenborn J, Jackman AM, *et al.* Management of bronchiolitis in infants and children. *Evidence Report: Technology Assessment (Summary)* 2003;**69**:1–5.
- Embleton ND, Harkensee C, Mckean MC. Palivizumab for preterm infants. Is it worth it? (Brief record). *Arch Dis Child* 2005; **90**:F286–9.
- Subramanian KN, Weisman LE, Rhodes T, Ariagno R, Sanchez PJ, Steichen J, *et al.* Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. *Pediatr Infect Dis J* 1998;**17**:110–115.
- Saez-Llorens X, Castano E, Null D, Steichen J, Sanchez PJ, Ramilo O, *et al.* Safety and pharmacokinetics of an intramuscular humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. The MEDI-493 Study Group. *Pediatr Infect Dis J* 1998;**17**:787–791.

23. Sampalis JS, Sampalis JS. Morbidity and mortality after RSV-associated hospitalizations among premature Canadian infants. *J Pediatr* 2003; **143**(5 Suppl.):S150–6.
24. Wang EL, Law BJ, Stephens D. Pediatric Investigators Collaborative Network on Infections in Canada (PICNIC) prospective study of risk factors and outcomes in patients hospitalized with respiratory syncytial viral lower respiratory tract infection. *J Pediatr* 1995; **126**:212–19.
25. Nuijten MJ, Wittenberg W, Lebmeier M. Cost effectiveness of palivizumab for respiratory syncytial virus prophylaxis in high-risk children: a UK analysis. *Pharmacoeconomics* 2007; **25**:55–71.
26. Duppenhaler A, Ammann RA, Gorgievski-Hrisoho M, Pfammatter J, Aebi C. Low incidence of respiratory syncytial virus hospitalisations in haemodynamically significant congenital heart disease. *Arch Dis Child*;2004; **89**:961–965.
27. Null D, Pollara B, Dennehy PH, Steichen J, Sanchez PJ, Givner LB, *et al.* Safety and immunogenicity of palivizumab (Synagis) administered for two seasons. *Pediatr Infect Dis J* 2005; **24**:1021–3.
28. www.nlm.nih.gov/nichsr/edu/healthecon/drummond_list.html (accessed March 2007).
29. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol* 1991; **44**:1271–8.
30. www.ameinfo.com/currency (accessed March 2007).
31. Curtis L, Netten A. Unit Costs of Health and Social Care 2006 (www.pssru.ac.uk/pdf/uc/uc2006/uc2006.pdf, pp. 1–217).
32. Kamal BS, Doshi J, Campbell J. Economic analyses of respiratory syncytial virus immunoprophylaxis in high-risk infants – A systematic review (Brief record). *Archiv Pediatr Adolesc Med* 2002; **156**:1034–41.
33. Farina D, Rodriguez SP, Bauer G, Novali L, Bouzas L, Gonzalez H, *et al.* Respiratory syncytial virus prophylaxis: cost-effective analysis in Argentina. *Pediatr Infect Dis J* 2002; **21**:287–91.
34. Numa A. Outcome of respiratory syncytial virus infection and a cost–benefit analysis of prophylaxis. *J Paediatr Child Health* 2000; **36**:422–7.
35. Reeve CA, Whitehall JS, Buettner PG, Norton R, Reeve DM, Francis F, *et al.* Cost-effectiveness of respiratory syncytial virus prophylaxis with palivizumab. *J Paediatr Child Health* 2006; **42**:253–8.
36. Roeckl-Wiedmann I, Liese JG, Grill E, Fischer B, Carr D, Belohradsky BH, *et al.* Economic evaluation of possible prevention of RSV-related hospitalizations in premature infants in Germany. *Eur J Paediatr* 2003; **162**:237–44.
37. Chiroli S M. Cost-efficacy analysis of palivizumab in the prevention of respiratory syncytial virus infections in young children with hemodynamically significant congenital heart disease. *Ital J Pediatr* 2005; **31**:188–94.
38. 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**:352–7.
39. De Armentia SLL. Potential impact and cost-efficacy of bronchiolitis prophylaxis with palivizumab in preterm infants with a gestational age of less than 33 weeks. *Annales de Pediatria* 2003; **59**:328–33.
40. Lazaro YDM, Figueras AJ, Domenech ME, Echaniz U, I, Closa MR, Wood MA, *et al.* The efficiency (cost-effectiveness) of palivizumab as prophylaxis against respiratory syncytial virus infection in premature infants with a gestational age of 32–35 weeks in Spain [in Spanish]. *Anales de Pediatria* 2006; **65**:316–24.
41. Joffe S R. Cost-effectiveness of respiratory syncytial virus prophylaxis among preterm infants. *Pediatrics* 1999; **104**:419–27.
42. 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**:1357–69.
43. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM, Stevens TP, *et al.* Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. *Arch Pediatr Adolesc Med* 2000; **154**:55–61.
44. Shireman TI, Braman KS. Impact and cost-effectiveness of respiratory syncytial virus prophylaxis for Kansas Medicaid's high-risk children. *Arch Paediatr Adolesc Med* 2002; **156**:1251–25.
45. Strutton DR, Stang PE. Prophylaxis against respiratory syncytial virus (RSV), varicella, and pneumococcal infections: economic-based decision-making. *J Pediatr* 2003; **143**(5 Suppl. S):S157–62.
46. Yount LE, Mahle WT, Yount LE, Mahle WT. Economic analysis of palivizumab in infants with congenital heart disease. *Pediatrics* 2004; **114**:1606–11.

47. ElHassan NO, Sorbero ME, Hall CB, Stevens TP, Dick AW, ElHassan NO, *et al.* Cost-effectiveness analysis of palivizumab in premature infants without chronic lung disease. *Arch Pediatr Adolesc Med* 2006;**160**:1070–6.
48. Moler FW, Khan AS, Meliones JN, Custer JR, Palmisano J, Shope TC, *et al.* Respiratory syncytial virus morbidity and mortality estimates in congenital heart disease patients: a recent experience. *Crit Care Med* 1992;**20**:1406–13.
49. Navas L, Wang E, de C, V, Robinson J. Improved outcome of respiratory syncytial virus infection in a high-risk hospitalized population of Canadian children. Pediatric Investigators Collaborative Network on Infections in Canada. *J Pediatr* 1992;**121**:348–54.
50. Everard ML. The relationship between respiratory syncytial virus infections and the development of wheezing and asthma in children. *Curr Opin Allerg Clin Immunol* 2006;**6**:56–61.
51. Carbonell-Estrany X, Quero J, Bustos G, Coter A, Domenech E, Figueras-Aloy J, *et al.* Rehospitalization because of respiratory syncytial virus infection in premature infants younger than 33 weeks of gestation: a prospective study. IRIS Study Group. *Pediatr Infect Dis J* 2000;**19**:592–7.
52. Carbonell-Estrany X, Figueras-Aloy J, Law BJ. Identifying risk factors for severe respiratory syncytial virus among infants born after 33 through 35 completed weeks of gestation: different methodologies yield consistent findings. *Pediatr Infect Dis J* 2004;**23**(11 Suppl.):S193–S201.
53. Rietveld E, Vergouwe Y, Steyerberg EW, Huysman MW, de GR, Moll HA, *et al.* Hospitalization for respiratory syncytial virus infection in young children: development of a clinical prediction rule. *Pediatr Infect Dis J* 2006;**25**:201–7.
54. Iwane MK, Edwards KM, Szilagyi PG, Walker FJ, Griffin MR, Weinberg GA, *et al.* Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. *Pediatrics* 2004;**113**:1758–64.
55. Deshpande SA, Northern V, Deshpande SA, Northern V. The clinical and health economic burden of respiratory syncytial virus disease among children under 2 years of age in a defined geographical area. *Arch Dis Child* 2003;**88**:1065–9.
56. Arnold SR, Wang EE, Law BJ, Boucher FD, Stephens D, Robinson JL, *et al.* Variable morbidity of respiratory syncytial virus infection in patients with underlying lung disease: a review of the PICNIC RSV database. Pediatric Investigators Collaborative Network on Infections in Canada. *Pediatr Infect Dis J* 1999;**18**:866–9.
57. Clark SJ, Beresford MW, Subhedar NV, Shaw NJ, Clark SJ, Beresford MW, *et al.* Respiratory syncytial virus infection in high risk infants and the potential impact of prophylaxis in a United Kingdom cohort. *Arch Dis Child* 2000;**83**:313–16.
58. Grimaldi M, Cornet B, Milou C, Gouyon JB, Grimaldi M, Cornet B, *et al.* Prospective regional study of an epidemic of respiratory syncytial virus (RSV) bronchiolitis. *Archives de Pediatrie* 2002;**9**:572–80.
59. Holberg CJ, Wright AL, Martinez FD, Ray CG, Taussig LM, Lebowitz MD, *et al.* Risk factors for respiratory syncytial virus-associated lower respiratory illnesses in the first year of life. *Am J Epidemiol* 1991;**133**:1135–51.
60. Kneyber MCJ, Steyerberg EW, de GR, Moll HA, Kneyber MCJ, Steyerberg EW, *et al.* Long-term effects of respiratory syncytial virus (RSV) bronchiolitis in infants and young children: a quantitative review. *Acta Paediatr* 2000;**89**:654–60.
61. Chater T, Davey N, Draper E, Jones S, McKinney P, *et al.* National Report of the Paediatric Intensive Care Audit Network 2004–2005. University of Leeds: Paediatric Intensive Care Audit Network (PICANet) 2006.
62. Greenough A, Cox S, Alexander J, Lenney W, Turnbull F, Burgess S, *et al.* Health care utilisation of infants with chronic lung disease, related to hospitalisation for RSV infection. *Arch Dis Child* 2001;**85**:463–8.
63. Broughton S, Roberts A, Fox G, Pollina E, Zuckerman M, Chaudhry S, *et al.* Prospective study of healthcare utilisation and respiratory morbidity due to RSV infection in prematurely born infants. *Thorax* 2005;**60**:1039–44.
64. <http://bnf.org/bnf/bnf/current/82142.htm> (accessed May 2007).
65. Thomas M, Bedford-Russell A, Sharland M. Hospitalisation for RSV infection in ex-preterm infants-implications for use of RSV immune globulin. *Arch Dis Child* 2000;**83**:122–7.
66. www.statistics.gov.uk/articles/labour_market_trends/Working_time_patterns.pdf (accessed May 2007).
67. www.esrcsocietytoday.ac.uk/ESRCInfoCentre/facts/UK/index41.aspx?ComponentId=12619&SourcePageId=18129 (accessed May 2007).
68. National Statistics. Trends in life expectancy by social class 1972 – 2001. www.statistics.gov.uk/

- statbase/product.asp?vlink=8460&More=N 2005 (accessed May 2007).
69. Wren C, O'Sullivan JJ. Survival with congenital heart disease and need for follow up in adult life. *Heart* 2001;**85**:438–43.
70. Greenough A, Alexander J, Burgess S, Bytham J, Chetcuti PA, Hagan J, *et al.* Health care utilisation of prematurely born, preschool children related to hospitalisation for RSV infection. *Arch Dis Child* 2004;**89**:673–8.
71. Henderson J, Hilliard TN, Sherriff A, Stalker D, Al SN, Thomas HM, *et al.* Hospitalization for RSV bronchiolitis before 12 months of age and subsequent asthma, atopy and wheeze: a longitudinal birth cohort study. *Pediatr Allergy Immunol* 2005;**16**:386–92.
72. Noble V, Murray M, Webb MS, Alexander J, Swarbrick AS, Milner AD, *et al.* Respiratory status and allergy nine to 10 years after acute bronchiolitis. *Arch Dis Child* 1997;**76**:315–19.
73. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, *et al.* Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;**171**:137–41.
74. Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Korppi MO, Hyvarinen MK, *et al.* Teenage asthma after severe early childhood wheezing: an 11-year prospective follow-up. *Pediatr Pulmonol* 2005;**40**:316–23.
75. Boyce TG, Mellen BG, Mitchel EF, Jr., Wright PF, Griffin MR, Boyce TG, *et al.* Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. *J Pediatr* 2000;**137**:865–70.
76. Figueras-Aloy J, Carbonell-Estrany X, Quero J, IRIS Study Group., Figueras-Aloy J, Carbonell-Estrany X, *et al.* Case-control study of the risk factors linked to respiratory syncytial virus infection requiring hospitalization in premature infants born at a gestational age of 33–35 weeks in Spain.[see comment]. *Pediatr Infect Dis J* 2004;**23**:815–820.
77. Law BJ, Langley JM, Allen U, Paes B, Lee DS, Mitchell I, *et al.* The Pediatric Investigators Collaborative Network on Infections in Canada study of predictors of hospitalization for respiratory syncytial virus infection for infants born at 33 through 35 completed weeks of gestation [see comment]. *Pediatr Infect Dis J* 2004;**23**:806–814.
78. Carbonell-Estrany X, Quero J, IRIS Study Group., Carbonell-Estrany X, Quero J, and the IRIS Study Group. Hospitalization rates for respiratory syncytial virus infection in premature infants born during two consecutive seasons. *Pediatr Infect Dis J* 2001;**20**:874–879.
79. Lenney W, Connor E. Humanised monoclonal antibody to respiratory syncytial virus (MEDI-493) significantly reduces the incidence of RSV hospitalisation in at-risk infants [abstract]. *Eur Respir J* 1998;**12**(Suppl. 28):270S.

Appendix I

Search strategies – effectiveness

Database: Ovid MEDLINE(R), 1950 to March, Week 2, 2007

Search strategy

1. exp Respiratory Syncytial Virus, Human/or rsv.
mp.
2. respiratory syncytial virus.mp.
3. bronchiolitis.mp. or exp Bronchiolitis, Viral/
4. or/1–3
5. palivizumab.mp.
6. monoclonal antibod\$.mp.
7. exp Antibodies, Monoclonal/
8. synagis.mp.
9. exp Immunotherapy/or immunoprophylaxis.
mp.
10. or/5–9
11. 4 and 10
12. (systematic adj review\$).tw.
13. (data adj synthesis).tw.
14. (published adj studies).ab.
15. (data adj extraction).ab.
16. meta-analysis/
17. meta-analysis.ti.
18. comment.pt.
19. letter.pt.
20. editorial.pt.
21. animal/
22. human/
23. 21 not (21 and 22)
24. 11 not (18 or 19 or 20 or 23)
25. or/12–17
26. 24 and 25

Database: EMBASE(Ovid), 1980 to 2007, week 12

1. exp Respiratory Syncytial Pneumovirus/or rsv.
mp. or exp Bronchiolitis/
2. bronchiolitis.mp.
3. respiratory syncytial virus.mp.
4. or/1–3
5. palivizumab.mp. or exp PALIVIZUMAB/
6. exp Monoclonal Antibody/or monoclonal
antibod\$.mp.
7. synagis.mp.
8. immunoprophylaxis.mp. or exp
IMMUNOPROPHYLAXIS/
9. or/5–8
10. 4 and 9
11. 'meta-analysis'

12. metaanalys\$.ti,ab.
13. meta-analys\$.ti,ab.
14. meta analys\$.ti,ab.
15. cochrane.ti,ab,de.
16. (review\$or overview\$).ti,ab.
17. (synthes\$adj3 (literature\$or research\$or study
or studies or data)).mp.
18. pooled analy\$.ti,ab.
19. (systematic\$adj2 review\$).ti,ab.
20. or/11–19
21. 10 and 20
22. 19 or 11
23. 10 and 22

Cochrane Library (Wiley internet version), 2007, Issue 1

Search strategy

- #1 respiratory next syncytial
- #2 rsv
- #3 bronchiolitis
- #4 MeSH descriptor Bronchiolitis, Viral, this
term only
- #5 MeSH descriptor Respiratory Syncytial Virus,
Human, this term only
- #6 (#1 OR #2 OR #3 OR #4 OR #5)
- #7 immunoprophylaxis
- #8 monoclonal next antibod*
- #9 MeSH descriptor Antibodies, Monoclonal
explode all trees
- #10 palivizumab
- #11 (#7 OR #8 OR #9 OR #10)
- #12 (#6 AND #11)

Database: Ovid MEDLINE(R) in- process and other non-indexed citations, 26 March 2007

Search strategy

1. respiratory syncytial virus.mp.
2. bronchiolitis.mp. or exp Bronchiolitis, Viral/
3. palivizumab.mp.
4. monoclonal antibod\$.mp.
5. synagis.mp.
6. xp Immunotherapy/or immunoprophylaxis.
mp.
7. or/1–2
8. or/3–6
9. 7 and 8

Database: Ovid MEDLINE(R), 1950 to March, Week 2, 2007

Search strategy

1. exp Respiratory Syncytial Virus, Human/or rsv.
mp.
2. respiratory syncytial virus.mp.
3. bronchiolitis.mp. or exp Bronchiolitis, Viral/
4. or/1-3
5. palivizumab.mp.
6. monoclonal antibod\$.mp.
7. exp Antibodies, Monoclonal/
8. synagis.mp.
9. exp Immunotherapy/or immunoprophylaxis.
mp.
10. or/5-9
11. 11. 4 and 10
12. randomised controlled trial.pt.
13. controlled clinical trial.pt.
14. 14. randomised controlled trials.sh.
15. random allocation.sh.
16. double-blind method.sh.
17. single-blind method.sh.
18. or/12-17
19. (animals not human).sh.
20. 18 not 19
21. clinical trial.pt.
22. exp clinical trials/
23. (clin\$adj25 trial\$.ti,ab.
24. ((singl\$or doubl\$or trebl\$or tripl\$) adj25
(blind\$or mask\$)).ti,ab.
25. placebos.sh.
26. placebo\$.ti,ab.
27. random\$.ti,ab.
28. research design.sh.
29. or/21-28
30. 29 not 19
31. 30 not 20
32. comparative study.sh.
33. exp evaluation studies/
34. follow up studies.sh.
35. prospective studies.sh.
36. (control\$or prospectiv\$or volunteer\$).ti,ab.
37. or/32-36
38. 37 not 19
39. 38 not (20 or 31)
40. 20 or 31 or 39
41. 11 and 40
42. from 41 keep 1-280

Database: EMBASE (Ovid), 1980 to 2007, week 12

Search strategy

1. exp Respiratory Syncytial Pneumovirus/or rsv.
mp. or exp Bronchiolitis/

2. bronchiolitis.mp.
3. respiratory syncytial virus.mp.
4. or/1-3
5. palivizumab.mp. or exp PALIVIZUMAB/
6. exp Monoclonal Antibody/or monoclonal
antibod\$.mp.
7. synagis.mp.
8. immunoprophylaxis.mp. or exp
IMMUNOPROPHYLAXIS/
9. or/5-8
10. 4 and 9
11. randomised controlled trial/
12. exp clinical trial/
13. exp controlled study/
14. or/11-12
15. 10 and 14

Database: CINAHL (Cumulative Index to Nursing & Allied Health Literature), 1982 to March 2007

Search strategy

1. exp Respiratory Syncytial Viruses/or rsv.mp. or
exp Bronchiolitis/
2. respiratory syncytial virus.mp.
3. bronchiolitis.mp.
4. or/1-3
5. palivizumab.mp. or exp PALIVIZUMAB/
6. monoclonal antibod\$.mp.
7. exp Antibodies, Monoclonal/
8. synagis.mp.
9. immunoprophylaxis.mp.
10. immunotherapy.mp. or exp
IMMUNOTHERAPY/
11. or/5-10
12. 4 and 11
13. exp CLINICAL TRIALS/
14. 12 and 13
15. from 12 keep 1-112

SCI (Web of Knowledge), 1900 to 27 March 2007

Search terms

RSV or respiratory syncytial virus or bronchiolitis

palivizumab or synagis or immunoprophylaxis or
monoclonal antibod*

random* or trial*

Appendix 2

Search strategies – cost-effectiveness

Database: Ovid MEDLINE(R), 1950 to January, week 3, 2007

Search strategy

1. exp Respiratory Syncytial Virus, Human/or rsv.
mp.
2. respiratory syncytial virus.mp.
3. bronchiolitis.mp. or exp Bronchiolitis, Viral/
or/1–3
5. palivizumab.mp.
6. monoclonal antibod\$.mp.
7. exp Antibodies, Monoclonal/
synagis.mp.
9. exp Immunotherapy/or immunoprophylaxis.
mp.
10. or/5–9
11. 4 and 10
12. economics/
13. exp 'costs and cost analysis'/
14. cost of illness/
15. exp health care costs/
16. economic value of life/
17. exp economics medical/
18. exp economics hospital/
19. economics pharmaceutical/
20. exp 'fees and charges'/
21. (econom\$or cost or costs or costly or costing or
price or pricing or pharmacoeconomic\$).tw.
22. (expenditure\$not energy).tw.
23. (value adj1 money).tw.
24. budget\$.tw.
25. or/12–24
26. 11 and 25

Database: Ovid MEDLINE(R), 1950 to January, week 3, 2007

Search strategy

1. exp Respiratory Syncytial Virus, Human/or rsv.
mp.
2. respiratory syncytial virus.mp.
3. bronchiolitis.mp. or exp Bronchiolitis, Viral/
or/1–3
5. palivizumab.mp.
6. monoclonal antibod\$.mp.
7. exp Antibodies, Monoclonal/
synagis.mp.
9. exp Immunotherapy/or immunoprophylaxis.
mp.
10. or/5–9
11. 4 and 10

12. decision support techniques/
13. markov.mp.
14. exp models economic/
15. decision analysis.mp.
16. cost benefit analysis/
17. or/12–16
18. 11 and 17
19. 4 and 17
20. 18 or 19

Database: Ovid MEDLINE(R), 1950 to January, week 3, 2007

Search strategy

1. exp Respiratory Syncytial Virus, Human/or rsv.
mp.
2. respiratory syncytial virus.mp.
3. bronchiolitis.mp. or exp Bronchiolitis, Viral/
or/1–3
5. palivizumab.mp.
6. monoclonal antibod\$.mp.
7. exp Antibodies, Monoclonal/
synagis.mp.
9. exp Immunotherapy/or immunoprophylaxis.
mp.
10. or/5–9
11. 4 and 10
12. quality of life/
13. life style/
14. health status/
15. health status indicators/
16. or/12–15
17. 4 and 16

Database: EMBASE, 1980 to 2007, week 03

Search strategy

1. exp Respiratory Syncytial Pneumovirus/or rsv.
mp. or exp Bronchiolitis/
2. bronchiolitis.mp.
3. respiratory syncytial virus.mp.
4. or/1–3
5. palivizumab.mp. or exp PALIVIZUMAB/
6. exp Monoclonal Antibody/or monoclonal
antibod\$.mp.
7. synagis.mp.
8. immunoprophylaxis.mp. or exp
IMMUNOPROPHYLAXIS/
9. or/5–8
10. 4 and 9

11. cost benefit analysis/
12. cost-effectiveness analysis/
13. cost minimization analysis/
14. cost utility analysis/
15. economic evaluation/
16. (cost or costs or costed or costly or costing).tw.
17. (economic\$or pharmacoeconomic\$or price\$or pricing).tw.
18. (technology adj assessment\$).tw.
19. or/11–18
20. 10 and 19

**Database: EMBASE, 1980
to 2007, week 03**

Search strategy

1. exp Respiratory Syncytial Pneumovirus/or rsv.
mp. or exp Bronchiolitis/
2. bronchiolitis.mp.
3. respiratory syncytial virus.mp.
4. or/1–3
5. quality of life.mp. or exp 'Quality of Life'/
6. health status.mp. or exp Health Status/
7. or/5–6
8. 4 and 7
9. lung transplant\$.mp.
10. 8 not 9

**Cochrane Library (Wiley
internet version), 2007, Issue 1**

Search terms

- #1 respiratory next syncytial
- #2 rsv
- #3 bronchiolitis
- #4 MeSH descriptor Bronchiolitis, Viral, this
term only
- #5 MeSH descriptor Respiratory Syncytial Virus,
Human, this term only
- #6 (#1 OR #2 OR #3 OR #4 OR #5)
- #7 immunoprophylaxis
- #8 monoclonal next antibod*
- #9 MeSH descriptor Antibodies, Monoclonal
explode all trees
- #10 palivizumab
- #11 (#7 OR #8 OR #9 OR #10)
- #12 (#6 AND #11)

**Office of Health Economics
HEED database, January 2006**

Search terms

RSV or respiratory syncytial virus or bronchiolitis

palivizumab or synagis or immunoprophylaxis or
monoclonal antibod*

Appendix 3

Search strategies – prognosis

**Database: Ovid MEDLINE(R),
1950 to January, week 2, 2007**

Search strategy

- | | |
|--|---|
| <ol style="list-style-type: none">1. exp Respiratory Syncytial Virus, Human/or rsv.
mp.2. respiratory syncytial virus.mp.3. bronchiolitis.mp. or exp Bronchiolitis, Viral/
or/1–35. prognosis.mp. or exp Prognosis/ | <ol style="list-style-type: none">6. outcome\$.mp.7. risk\$.mp. or exp Risk Factors/
hospitali?ation.mp.9. exp Follow-Up Studies/or follow-up.mp.10. complication\$.mp.11. exp Cohort Studies/or cohort\$.mp.12. or/5–1013. 11 and 13 |
|--|---|

Appendix 4

Search strategies – RSV hospitalisation

**Database: Ovid MEDLINE(R),
1950 to January, week 2, 2007**

Search strategy

- | | |
|---|---|
| <ol style="list-style-type: none">1. exp Respiratory Syncytial Virus, Human/or rsv.
mp.2. respiratory syncytial virus.mp.3. bronchiolitis.mp. or exp Bronchiolitis, Viral/4. or/1–35. prognosis.mp. or exp Prognosis/ | <ol style="list-style-type: none">6. outcome\$.mp.7. risk\$.mp. or exp Risk Factors/8. hospitali?ation.mp.9. exp Follow-Up Studies/or follow-up.mp.10. complication\$.mp.11. exp Cohort Studies/or cohort\$.mp.12. or/5–1013. 4 and 1214. 11 and 13 |
|---|---|

Appendix 5

Characteristics of excluded studies

TABLE 43 Excluded clinical effectiveness studies

Reference	Reason for exclusion
Duppenthaler A, Ammann RA, Gorgievski-Hrisoho M, Pfammatter J, Aebi C. Low incidence of respiratory syncytial virus hospitalisations in haemodynamically significant congenital heart disease. <i>Arch Dis Child</i> 2004; 89 :961–5	Cohort study (neither RCT nor systematic review)
Fenton C, Scott LI, Plosker GL. Palivizumab: a review of its use as prophylaxis for serious respiratory syncytial virus infection. <i>Pediatr Drugs</i> 2004; 6 :177–97	Narrative review
Groothuis JR, Groothuis JR. Safety and tolerance of palivizumab administration in a large Northern Hemisphere trial. Northern Hemisphere Expanded Access Study Group. <i>Pediatr Infect Dis J</i> 2001; 20 :628–30	Open label palivizumab study (neither RCT nor systematic review)
Groothuis JR, Nishida H. Prevention of respiratory syncytial virus infections in high-risk infants by monoclonal antibody (palivizumab). <i>Pediatr Int</i> 2002; 44 :235–41	Narrative review
Groothuis JR, Groothuis JR. Safety of palivizumab in preterm infants 29 to 32 weeks' gestational age without chronic lung disease to prevent serious respiratory syncytial virus infection. <i>Eur J Clin Microbiol Infect Dis</i> 2003; 22 :414–17	Open label palivizumab study (neither RCT nor systematic review)
Health Care Insurance Board. <i>Passive immunization against RSV-infections in too early born children – primary research</i> . Diemen: Health Care Insurance Board / College voor zorgverzekeringen (CVZ); 2005	Cost-effectiveness study
Johnson S, Griego SD, Pfarr DS, Doyle ML, Woods R, Carlin D, et al. A direct comparison of the activities of two humanized respiratory syncytial virus monoclonal antibodies: MEDI-493 and RSHZ19. <i>J Infect Dis</i> 1999; 180 :35–40	Animal study
Korbal P, Mikolajczak A, Szymaski W, Korbal P, Mikolajczak A, Szymaski W. [Effectiveness of passive immunisation against respiratory syncytium virus in a group of premature infants with birth weight below 1000 grams]. [in Polish]. <i>Ginek Pol</i> 2003; 74 :1154–9	Neither RCT nor systematic review
Lenney W, Connor E. Humanised monoclonal antibody to respiratory syncytial virus (MEDI-493) significantly reduces the incidence of RSV hospitalisation in at-risk infants [abstract]. <i>Eur Respir J Suppl</i> 1998; 12 (Suppl 28):270S	Abstract duplicating information in IMpact-RSV Study Group 1998
Null D Jr, Pollara B, Dennehy PH, Steichen J, Sanchez PJ, Givner LB, et al. Safety and immunogenicity of palivizumab (Synagis) administered for two seasons. <i>Pediatr Infect Dis J</i> 2005; 24 :1021–3	55/86 participants in IMpact-RSV Study Group 1998 received palivizumab in second season.
Saez-Llorens X, Moreno MT, Ramilo O, Sanchez PJ, Top FH, Jr., Connor EM, et al. Safety and pharmacokinetics of palivizumab therapy in children hospitalized with respiratory syncytial virus infection. <i>Pediatr Infect Dis J</i> 2004; 23 :707–12	Phase I/II placebo controlled RCT in children hospitalised with RSV
Subramanian KN, Weisman LE, Rhodes T, Ariagno R, Sanchez PJ, Steichen J, et al. Safety, tolerance and pharmacokinetics of a humanized monoclonal antibody to respiratory syncytial virus in premature infants and infants with bronchopulmonary dysplasia. MEDI-493 Study Group. <i>Pediatr Infect Dis J</i> 1998; 17 :110–15	Phase I/II multicentre double-blind randomised trial, but drug was administered intravenously not via intramuscular injections.
Wu SY, Bonaparte J, Pyati S, Wu SY, Bonaparte J, Pyati S. Palivizumab use in very premature infants in the neonatal intensive care unit. [see comment] <i>Pediatrics</i> 2004; 114 :e554–e556	Not RCT

TABLE 44 Excluded cost-effectiveness studies

Reference	Reasons for exclusion
Glanville AR, Scott AI, Morton JM, Aboyoun CL, Plit ML, Carter IW, et al. Intravenous ribavirin is a safe and cost-effective treatment for respiratory syncytial virus infection after lung transplantation. <i>J Heart Lung Transplant</i> 2005; 24 :2114–19	Not for comparing palivizumab and no prophylaxis
Harkensee C, Brodrie M, Embleton ND, McKean M. Passive immunisation of preterm infants with palivizumab against RSV infection. <i>J Infect</i> 2006; 52 :2–8	No relevant data
Hashmi NA, Cosgrove JF, MacMahon P, Hashmi NA, Cosgrove JF, MacMahon P. Prophylaxis in RSV infection (Palivizumab) – is it worthwhile? <i>Irish Med J</i> 2000; 93 :284	No relevant data
Klassen TP, Klassen TP. Economic evaluations of immunoprophylaxis in infants at high risk for respiratory syncytial virus: shedding light or creating confusion? [comment] <i>Arch Pediatr Adolesc Med</i> 2002; 156 :1180–1	No relevant data
Macartney KK, Gorelick MH, Manning ML, Hodinka RL, Bell LM, Macartney KK, et al. Nosocomial respiratory syncytial virus infections: the cost-effectiveness and cost-benefit of infection control. <i>Pediatrics</i> 2000; 106 :520–6	Not for comparing palivizumab and no prophylaxis
Marchetti A, Lau H, Magar R, Wang L, Devercelli G, Marchetti A, et al. Impact of palivizumab on expected costs of respiratory syncytial virus infection in preterm infants: potential for savings. <i>Clin Ther</i> 1999; 21 :752–66	Neither CEA nor CUA nor CBA
Schrand LM, Elliott JM, Ross MB, Bell EF, Mutnick AH, Schrand LM, et al. A cost-benefit analysis of RSV prophylaxis in high-risk infants. [see comment] <i>Ann Pharmacother</i> 2001; 35 :1186–93	Not for comparing palivizumab and no prophylaxis
Storch GA. Humanized monoclonal antibody for prevention of respiratory syncytial virus infection. <i>Pediatrics</i> 1998; 102 :648–51	No relevant data
Sze LL, Etches P, Robinson JL. Net cost of palivizumab for respiratory syncytial virus prophylaxis during the 1998/99 season in northern Alberta. <i>Paediatr Child Hlth</i> 2001; 6 :525–32	No relevant data
Thomas M, Bedford-Russell A, Sharland M. Hospitalisation for RSV infection in ex-preterm infants: implications for use of RSV immunoglobulin. <i>Arch Dis Child</i> 2000; 83 :122–7	Neither CEA nor CUA nor CBA
Wegner S, Vann JJ, Liu G, Byrns P, Cypra C, Campbell W, et al. Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program. <i>Pediatrics</i> 2004; 114 :1612–19	Neither CEA nor CUA nor CBA
Wills S, Simpson JH, Coutts J. Cost minimisation of RSV prevention with palivizumab. <i>Arch Dis Child</i> 2006; 91 :717	No relevant data
CEA, cost-effectiveness analysis; CBA, cost-benefit analysis; CUA, cost-utility analysis.	

Appendix 6

Quality assessment of systematic reviews

TABLE 45 Quality assessment of systematic reviews of cost-effectiveness

Author	Country	Search method reported?	Comprehensive search?	Inclusion criteria reported?	Selection bias avoided?	Validity criteria reported?	Validity for each study assessed appropriately?	Combining method reported?	Findings combined appropriately?	Conclusion supported by data?
Dunfield and Mierzwinski-Urban, 2007 ¹⁷	Canada	Yes	Yes	Partially	Cannot tell	Partially	No	No	Partially	Yes
Embleton et al., 2005 ²⁰	UK	Yes	Yes	Yes	Yes	No	No	No	Partially	Yes
Kamal et al., 2002 ³²	USA	Yes	Partially	Yes	Partially	No	No	No	Partially	Yes

Appendix 7

Quality assessment of included RCTs for clinical effectiveness

TABLE 46 Quality assessment of included RCTs for clinical effectiveness

Study	Randomised?	Concealment of randomisation	Blinded	Intention-to-treat analysis	Loss to follow-up reported?	Jadad score
The IMpact-RSV Study Group, 1998 ^{a16}	Yes	Yes, central interactive voice system	Yes	Yes	Yes, 99% in each arm completed follow-up	5
Feltes <i>et al.</i> , 2003 ¹²	Yes	Yes, central interactive voice system	Yes	Yes	Yes, 95.6% of palivizumab and 95.5% of placebo group completed the study	5
a Also reported in Lenney, 1998 ⁷⁷						

Appendix 8

Quality assessment of included primary studies for cost-effectiveness

TABLE 47 Quality assessment of included primary studies for cost-effectiveness

Author	Country	Well-defined question?	Description of competing alternatives given?	Effectiveness established?	Relevant costs and consequences identified?	Costs and consequences measured accurately?	Costs and consequences valued credibly?	Costs and consequences adjusted for differential timing?	Incremental analysis of cost and consequences performed?	Uncertainty of costs and consequences considered?	Results clearly presented and discussed?
Farina et al., 2002 ³³	Argentina	Yes	Partially	Yes	Yes	Partially	Partially	Cannot tell	Yes	Partially	Partially
Numa, 2000 ³⁴	Australia	Yes	No	Yes	No	Yes	No	Cannot tell	Yes	Partially	Partially
Reeve et al., 2006 ³⁵	Australia	Yes	Partially	Yes	No	Cannot tell	Partially	Cannot tell	Yes	No	Partially
Roekl-Wiedmann et al., 2003 ³⁶	Germany	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Partially	Yes
Chiroli, 2005 ³⁷	Italy	Yes	Yes	Yes	Yes	No	Partially	Yes	Yes	Partially	Yes
Vogel et al., 2002 ³⁸	New Zealand	Yes	Yes	Yes	Yes	Yes	Yes	Cannot tell	Yes	Partially	
De Armentia, 2003 ³⁹	Spain	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	No	Yes
Lázaro et al., 2006 ⁴⁰	Spain	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Raya et al., 2006 ¹⁸	Spain	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes

Author	Country	Well-defined question?	Description of competing alternatives given?	Effectiveness established?	Relevant costs and consequences identified?	Costs and consequences measured accurately?	Costs and consequences valued credibly?	Costs and consequences adjusted for differential timing?	Incremental analysis of cost and consequences performed?	Uncertainty of costs and consequences considered?	Results clearly presented and discussed?
Simpson and Burls, 2001 ⁹	UK	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially	Partially
Nuijten et al., 2007 ²⁵	UK	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Partially
Joffe, 1999 ⁴¹	USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially	Yes
Lofland et al., 2000 ⁴²	USA	Yes	Yes	Yes	Partially	Partially	Partially	Cannot tell	Yes	Partially	Partially
Stevens et al., 2000 ⁴³	USA	Yes	Partially	Yes	Partially	Yes	Partially	Cannot tell	Yes	Partially	Partially
Shireman and Braman, 2002 ⁴⁴	USA	Yes	Yes	Yes	Partially	Yes	Cannot tell	Cannot tell	No	No	Yes
Strutton and Stang, 2003 ⁴⁵	USA	Yes	Partially	Partially	Yes	Cannot tell	Cannot tell	Yes	Yes	No	Partially
Yount et al., 2004 ⁴⁶	USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially	Yes
ElHassan et al., 2006 ⁴⁷	USA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partially	Partially

Appendix 9

Parameter values and their distributions used in the probabilistic sensitivity analysis

TABLE 48 Parameter distributions for preterm infants without CLD

Beta distributions

Parameter	Expected value	α	β
Probability of RSV hospitalisation (no prophylaxis)	0.081	344.384	3934.08
Mortality rate of RSV hospitalisation	0.0043	17.221	3982.226
Utility of RSV hospitalisation	0.88	702.101	95.770
Utility of non-RSV hospitalisation	0.95	976.417	51.397
Probability of ICU stay	0.107	26.270	219.218

Uniform distributions

Parameter	Expected value	a	b
Dose of palivizumab	5	4	6
Period of morbidity due to RSV	5	2	8

Normal distributions

Parameter	Mean	SD
Log relative risk of RSV hospitalisation	-1.5404	0.0771
Length of ICU stay	1.370	0.259
Length of general ward stay	6.470	0.644
Life expectancy	77.80	11.83

CLD, chronic lung disease; ICU, intensive care unit; RSV, respiratory syncytial virus; SD, standard deviation.

TABLE 49 Parameter distributions for preterm infants with CLD**Beta distributions**

Parameter	Expected value	α	β
Probability of RSV hospitalisation (no prophylaxis)	0.128	573.974	3900.294
Utility of RSV hospitalisation	0.88	702.101	95.770
Utility of non-RSV hospitalisation	0.95	976.417	51.397
Probability of ICU sstay	0.107	26.270	219.218

Uniform distributions

Parameter	Expected value	a	b
Dose of palivizumab	5	4	6
Period of morbidity due to RSV	5	2	8
Mortality rate of RSV hospitalisation	0.04	0.03	0.05

Normal distributions

Parameter	Mean	SD
Log relative risk of RSV hospitalisation	-0.4826	0.0253
Length of ICU stay	1.370	0.259
Length of general ward stay	6.470	0.644
Life expectancy	77.80	11.83
CLD, chronic lung disease; ICU, intensive care unit; RSV, respiratory syncytial virus; SD, standard deviation.		

TABLE 50 Parameter distributions for CHD**Beta distributions**

Parameter	Expected value	α	β
Probability of RSV hospitalisation (no prophylaxis)	0.097	21.895	203.830
Mortality rate of RSV hospitalisation	0.0372	8.012	207.920
Utility of RSV hospitalisation	0.88	702.101	95.770
Utility of non-RSV hospitalisation	0.95	976.417	51.397
Probability of ICU stay	0.387	123.685	195.916

Uniform distributions

Parameter	Expected value	a	b
Dose of palivizumab	5	4	6
Period of morbidity due to RSV	5	2	8

Normal distributions

Parameter	Mean	SD
Log relative risk of RSV hospitalisation	-0.603	0.042
Length of ICU stay	6.14	1.009
Length of general ward stay	6.25	0.635
Life expectancy	77.11	11.83

CLD, chronic lung disease; ICU, intensive care unit; RSV, respiratory syncytial virus; SD, standard deviation.

Appendix 10

Probability of hospitalisation for RSV infection of no prophylaxis in children with or without CLD or CHD

TABLE 51 Probability of hospitalisation for RSV infection of no prophylaxis in children without CLD

Birth age (months)	Gestational age (weeks)					
	≤24	24–26	26–28	28–30	30–32	32–34
<3	0.29	0.23	0.17	0.13	0.10	0.07
3–6	0.17	0.13	0.10	0.07	0.05	0.04
6–9	0.10	0.07	0.05	0.04	0.03	0.02
9–12	0.05	0.04	0.03	0.02	0.01	0.01
12–15	0.03	0.02	0.01	0.01	0.01	0.01
15–18	0.01	0.01	0.01	0.01	0.00	0.00
18–21	0.01	0.01	0.00	0.00	0.00	0.00
21–24	0.00	0.00	0.00	0.00	0.00	0.00

CLD, chronic lung disease; RSV, respiratory syncytial virus.

TABLE 52 Probability of hospitalisation for RSV infection of no prophylaxis in children with CLD

Birth age (months)	Gestational age (weeks)					
	≤24	24–26	26–28	28–30	30–32	32–34
<3	0.55	0.47	0.39	0.32	0.25	0.20
3–6	0.39	0.32	0.25	0.19	0.15	0.11
6–9	0.25	0.19	0.15	0.11	0.08	0.06
9–12	0.14	0.11	0.08	0.06	0.04	0.03
12–15	0.08	0.06	0.04	0.03	0.02	0.02
15–18	0.04	0.03	0.02	0.02	0.01	0.01
18–21	0.02	0.02	0.01	0.01	0.01	0.00
21–24	0.01	0.01	0.01	0.00	0.00	0.00

CLD, chronic lung disease; RSV, respiratory syncytial virus.

TABLE 53 Probability of hospitalisation for RSV infection of no prophylaxis in children with siblings in day-care groups

Birth age (months)	Gestational age (weeks)					
	≤24	24–26	26–28	28–30	30–32	32–34
<3	0.43	0.35	0.28	0.22	0.17	0.13
3–6	0.28	0.22	0.17	0.13	0.09	0.07
6–9	0.16	0.12	0.09	0.07	0.05	0.04
9–12	0.09	0.07	0.05	0.04	0.03	0.02
12–15	0.05	0.04	0.03	0.02	0.01	0.01
15–18	0.03	0.02	0.01	0.01	0.01	0.01
18–21	0.01	0.01	0.01	0.01	0.00	0.00
21–24	0.01	0.00	0.00	0.00	0.00	0.00

RSV, respiratory syncytial virus.

TABLE 54 Probability of hospitalisation for RSV infection of no prophylaxis in children with CLD and with siblings in day-care groups

Birth age (months)	Gestational age (weeks)					
	≤24	24–26	26–28	28–30	30–32	32–34
<3	0.70	0.62	0.55	0.47	0.39	0.31
3–6	0.54	0.46	0.38	0.31	0.24	0.19
6–9	0.38	0.31	0.24	0.19	0.14	0.11
9–12	0.24	0.18	0.14	0.11	0.08	0.06
12–15	0.14	0.10	0.08	0.06	0.04	0.03
15–18	0.08	0.06	0.04	0.03	0.02	0.02
18–21	0.04	0.03	0.02	0.02	0.01	0.01
21–24	0.02	0.02	0.01	0.01	0.01	0.00

CLD, chronic lung disease; RSV, respiratory syncytial virus.

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We look forward to hearing from you.