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The clinical and cost-effectiveness of Immunoprophylaxis against respiratory syncytial virus with palivizumab in children

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The clinical and cost-effectiveness of of immunoprophylaxis against respiratory syncytial virus with palivizumab in children

A WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION REPORT

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS

Dechao Wang, Carole Cummins, Sue Bayliss, and Josie Sandercock undertook the research and production of the report, guided by Amanda Burls who commented on the content and presentation of the report.

CONFLICTS OF INTEREST

The authors all declare that they have no conflicts of interest.

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West Midlands Regional Evaluation Panel

Recommendation

Supported – for children with chronic lung disease or congenital heart disease born at less than 30 weeks gestation and who are less than 6 months old.

Borderline in other children who meet the licensed indication.

Anticipated expiry date:

2010

GLOSSARY/ABBREVIATIONS AND ACRONYMS

Abbreviation/ Acronym	Definition
AE	Adverse Event
BPD	Bronchopulmonary dysplasia
BrumEE	Birmingham Economic Evaluation
CEAC	Cost-Effectiveness Acceptibility Curve
CHD	Congenital Heart Disease
CLD	Chronic lung Disease
CRD	Centre for Review and Dissemination
DARE	Database of Abstracts of Reviews of Effects
EED	Economic Evaluation Database
GA	Gestational Age
HAP	Hospital Admission Prevented
HDS	Hospital Day Saved
HEED	Health Economic Evaluation Database
ICER	Incremental Cost-Effectiveness Ratio
ICU	Intensive Care Unit
IEA	Infection Episode Avoided
JCVI	Joint Committee on Vaccination and Immunisation
MTRAC	Midlands Therapeutic Review & Advisory Committee
NA	Not Applicable
NCCHTA	National Coordinating Centre for Health Technology Assessment
NHS	National Health Service
NIC	Net Ingredient Cost
LYG	Life Year Gained
NIHR	National Institute for Health Research
LRTI	Lower Respiratory Tract Infection
PICU	Paediatric Intensive Care Unit
PSA	Probabilistic Sensitivity Analysis
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RNA	Ribonucleic Acid
RSV	Respiratory Syncytial Virus
SD	Standard Deviation
UK	United Kingdom
US	United States

DEFINITIONS OF TERMS

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 four 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	It 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 one 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 which might affect their physical, mental and social well-being.
Quality-adjusted life-year (QALY)	An index of health gain where 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 don't 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.

EXECUTIVE SUMMARY

Background

Respiratory syncytial virus (RSV) 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). 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 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.

Objective

This review aims to systematically review the scientific evidence about the effectiveness and cost-effectiveness of palivizumab for the prevention RSV in children and see whether we can identify subgroups in whom palivizumab is cost-effective.

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 de novo decision analytic model (BrumEE) 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 was 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 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 palivizumab and 10.6% (53/500) in no prophylaxis groups (P= 0.0004).

Prophylaxis with palivizumab was associated with a 45% reduction in RSV-hospitalisation rate for children with CHD. RSV-hospitalisation rates were 5.3% (34/639) in the palivizumab group and 9.7% (63/648) in the no prophylaxis group (p=0.003). Both RCTs had a slightly higher mortality in the control group 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 eighteen 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 palivizumab may be not cost-effective when used 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 sixteen-fold for life-years gained (LYG), from £25,800/LYG to £404,900/LYG, and several hundred-fold for QALYs, from £3,200/QALY to £1,489,700/QALY for preterm infants without CLD or children with CLD. For children with CHD, the ICER varied from £5,300/LYG to £7,900/LYG and from £7,500/QALY to £68,700/QALY.

An analysis of what was leading to the discrepant ICERs showed 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 ICERs from a NHS perspective are £454,000/QALY for preterm infants without CLD, £64,000/QALY for children with CLD, and £80,000/QALY for children with CHD. These results confirm that palivizumab does not reach conventional levels of cost-effectiveness in any of the licensed indications if used for all eligible children.

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 £30k/QALY in a number of important subgroups of children with CLD. For children with CLD, the ICERs are between £12,000/QALY to £19,000/QALY for children with gestational age of less than 30 weeks, and birth age of less than 3 months, and between £19,000/QALY to £24,000/QALY for children with gestational age of less than 26 weeks and birth age of 3-6 months. For children with CLD and siblings in day-care groups, the ICERs are between £9,000/QALY to £25,000/QALY for children with gestational age of under 35 weeks, and birth age of less than 3 months, between £13,000/QALY to £24,000/QALY for children with gestational age of less than 30 weeks and birth age of 3-6 months, and between £19,000/QALY to £24,000/QALY for children with gestational age of less than 26 weeks and birth age of 6-9 months.

Conclusion

Prophylaxis with palivizumab is clinically effective for the reducing the risk of serious LRTI caused by RSV infection and requiring hospitalisation in high-risk children but does not represent good value for money if used indiscriminately in the licensed population. The BrumEE shows that prophylaxis with palivizumab may be cost-effective 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.

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1 AIM OF THE REVIEW

This review 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 look at prognostic factors for RSV infection with at view to the identification of subgroups of children for whom there may be important differences in cost-effectiveness.

2 BACKGROUND

2.1 Description of underlying health problem

RSV causes outbreaks of respiratory tract infection especially in the winter months in the UK. It can affect people of any age and is usually a mild, self limiting illness. It is most serious in infants and young children where 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 which 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 socio-economic status, exposure to tobacco smoke, and admission to hospital during the RSV season.

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% children less than 12 months of , of whom, 82.6% were re-infected in their second year, and 46% were re-infected 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% to 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 re-infection was inversely related to the level of neutralizing antibodies in the serum. Re-infection illnesses tended to be mild and risk of re-infection decreased to 33.3% during year four.[1] Other studies suggest that 40% of primary RSV infections leads to clinical bronchiolitis.[3]

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

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

Children from high-risk groups constitute 53% of all children hospitalized with RSV. Mortality is less than 1% in children without underlying illness. Mortality in those with heart and lung disease who are hospitalized is estimated to be around 3 to 5%.[4]

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 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 compared to unvaccinated controls and the trials resulted in the hospitalization of 80% of vaccines and two deaths.[5]

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

2.2 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 less than 6 months of age at the start of the RSV season
- <2 years of age and requiring treatment for bronchopulmonary dysplasia within the last 6 months
- <2 years of age and with haemodynamically significant congenital heart disease.

2.3 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.

2.3.1 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.[6] 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 be a specialist. It is then appropriate for general practitioners to prescribe and administer the course of intramuscular injections."*[7]

This advice is still current. The West Midlands Regional Advisory Panel's, (who advise healthcare commissioners about the appropriate use of technologies) recommendation 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."*[8]

The Scottish Intercollegiate Guidelines Network has produced a guideline on bronchiolitis that concludes palivizumab is effective but not cost-effective. It therefore recommends that it should not be used routinely. It may however be used on a case by case basis in infants under twelve 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.[9]

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, cardiomyopathy requiring treatment and 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 one year.[10] This is a different risk stratification to that used in the RCT of palivizumab in children with CHD.[11]

The Joint Committee on Vaccination and Immunisation (UK) recommend the use of palivizumab for: children under two years with CLD on home oxygen or with prolonged use of oxygen; infants under six months old with left to right shunt, or haemodynamically significant CHD, or pulmonary hypertension; children under two years with severe congenital immunodeficiency.[12] It should be noted that the latter recommendation is based on clinical judgment 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.

2.3.2 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 $1.2 billion in 2005.[13] 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. By starting a child on palivizumab and having a general practitioner prescribe and

administer the subsequent four doses, it is possible for secondary and tertiary care physicians to shift much of the prescribing cost of palivizumab away from their own budgets. Therefore we sought data on prescribing in primary care. Data for both the West Midlands and for England was provided to us by colleagues at the Department of Medicines Management at Keele University and are presented graphically in Figure 1 and Figure 2. Primary care prescribing shows a predictable seasonal pattern and highly restricted use. The total cost (NIC) of palivizumab prescribed in primary care in England in 2005 was £39,000 and £44,000 in the first 10 months of 2006.[13] 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.

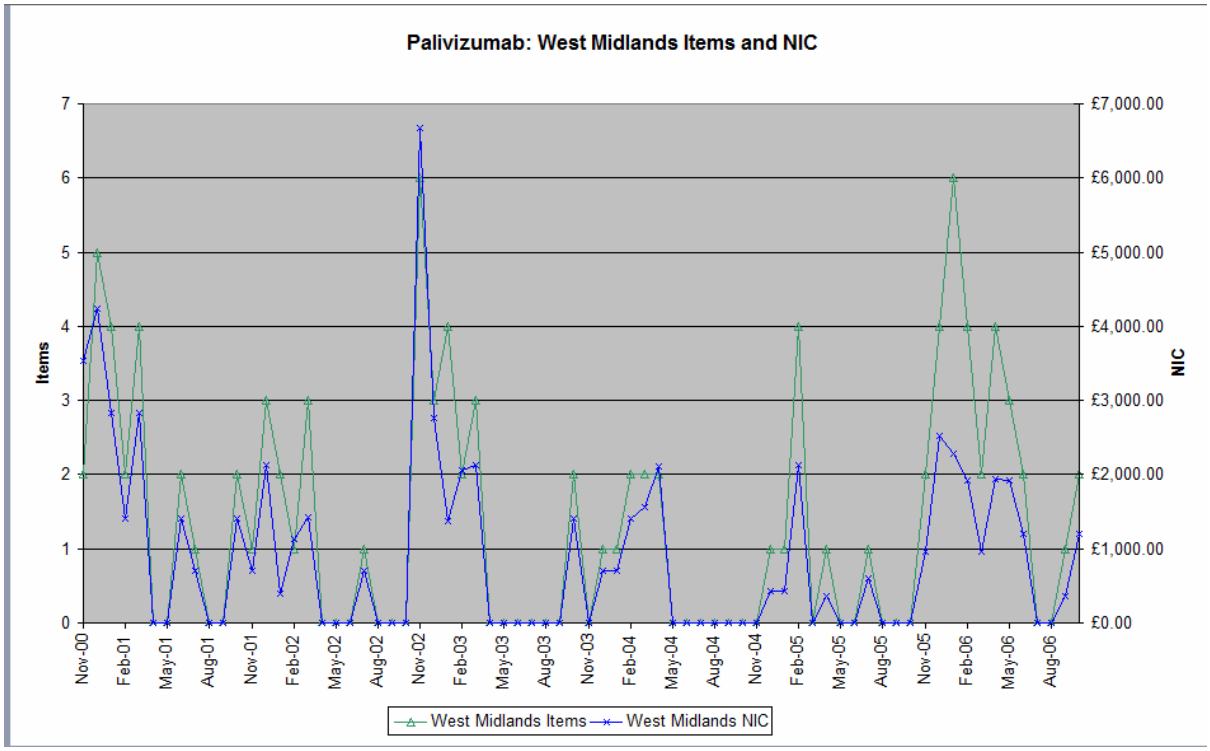


Figure 1 Palivizumab prescribing by item and net ingredient cost (NIC) in West Midlands

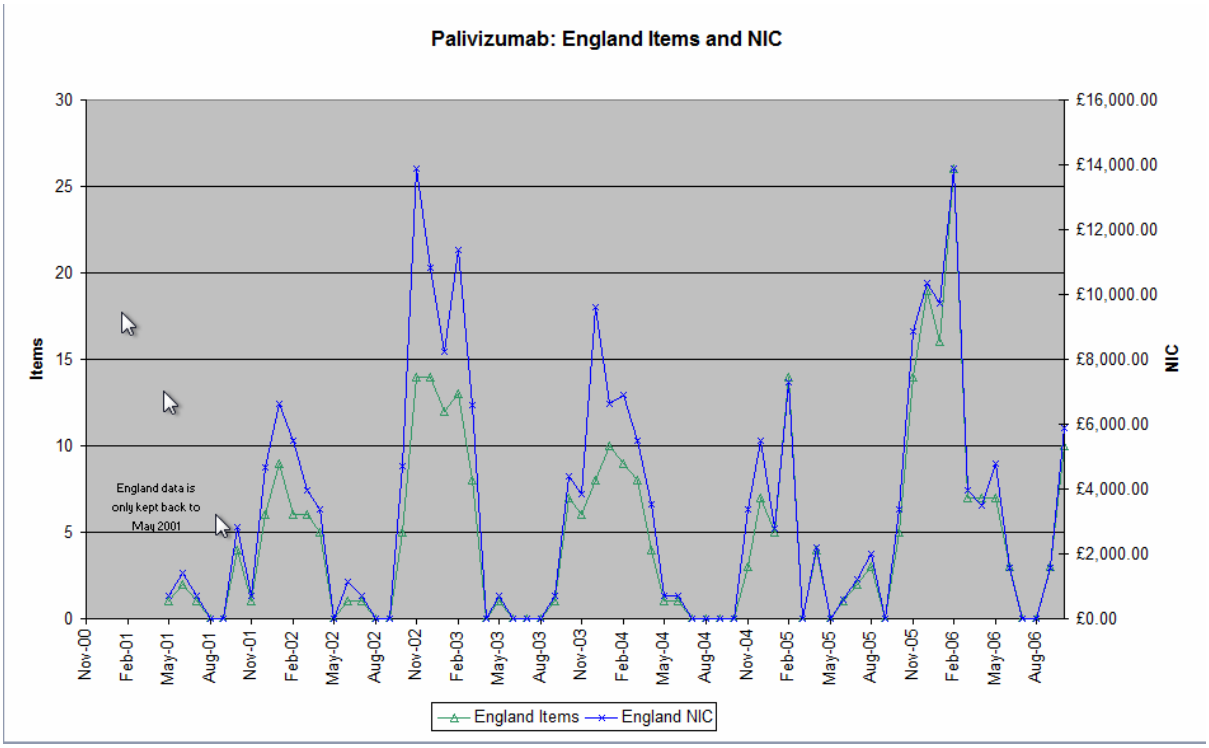
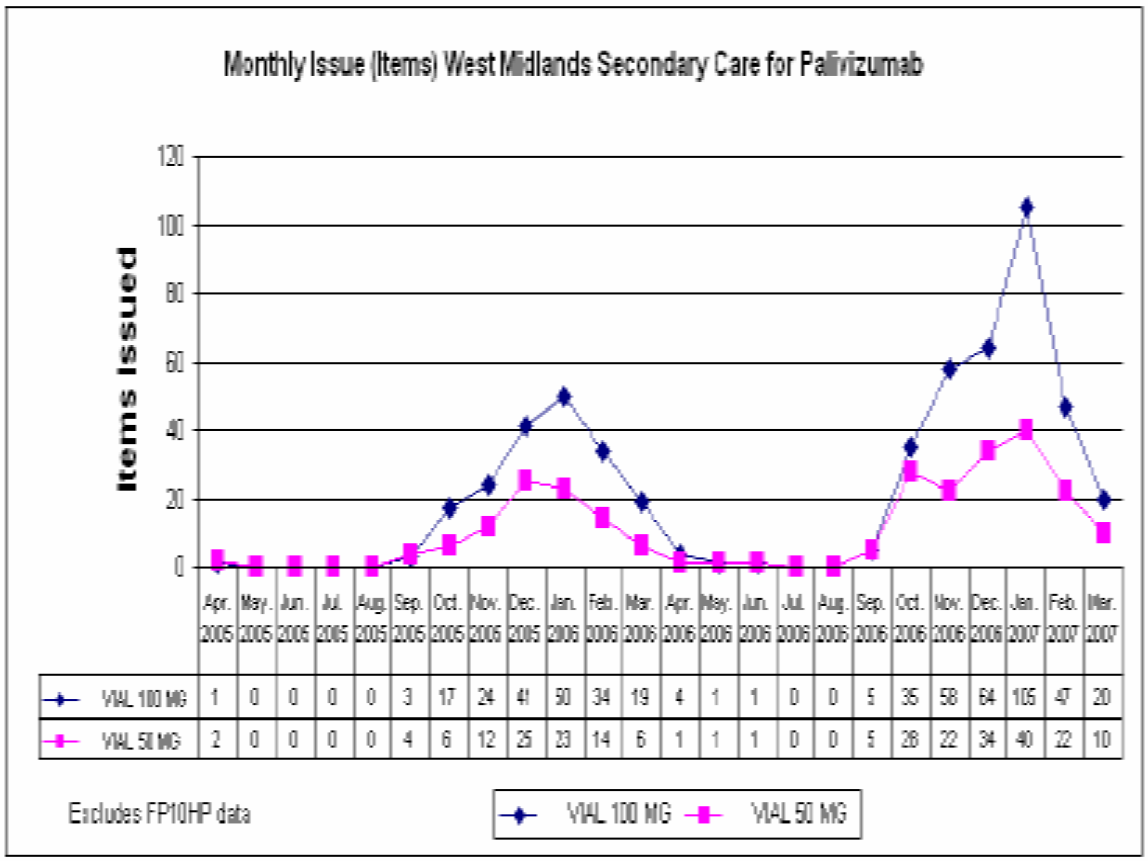


Figure 2 Palivizumab prescribing by item and net ingredient cost (NIC) in England



	Apr. 2005	May. 2005	Jun. 2005	Jul. 2005	Aug. 2005	Sep. 2005	Oct. 2005	Nov. 2005	Dec. 2005	Jan. 2006	Feb. 2006	Mar. 2006	Apr. 2006	May. 2006	Jun. 2006	Jul. 2006	Aug. 2006	Sep. 2006	Oct. 2006	Nov. 2006	Dec. 2006	Jan. 2007	Feb. 2007	Mar. 2007
VIAL 100 MG	1	0	0	0	0	3	17	24	41	50	34	19	4	1	1	0	0	5	35	58	64	105	47	20
VIAL 50 MG	2	0	0	0	0	4	6	12	25	23	14	6	1	1	1	0	0	5	28	22	34	40	22	10

Figure 3 Palivizumab secondary care prescribing by item, West Midlands

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.

3 METHOD

3.1 Review of clinical effectiveness

3.1.1 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 *meta*Register and Clinical Trials.gov
- Reference lists of relevant studies
- Relevant internet sources

No date limits or language restrictions were applied.

3.1.2 Inclusion and exclusion criteria

Studies have been included if they meet the following criteria:

Randomised controlled trials (RCTs) *or* systematic reviews of RCTs with:

- Inclusion of at least some high risk children
- Use of palivizumab in a preventive setting with dose and frequency comparable to that described in the licence

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

3.1.3 Data extraction strategy

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

3.1.4 Quality assessment strategy

The quality of included studies has been assessed according to guidelines proposed in NHS CRD Report No.4[14] by one reviewer, and independently checked for

agreement by a second reviewer. Disagreements were resolved by discussion.

3.2 Review of cost effectiveness

3.2.1 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 EED and DARE) 2006 Issue 4 Office of Health Economics HEED database January 2007 issue
- Internet sites
- Searches were not limited by date and there were no language restrictions.

3.2.2 Inclusion and exclusion criteria

Inclusion and exclusion 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.

3.2.3 Data extraction 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.[15] A modified version of the Oxman & Guyatt[16] assessment

tool and scale was used to assess the quality of reviews. Disagreements were resolved by discussion.

3.2.4 Analysis

In order to make different ICERs comparable, they were converted from their respective currencies to pounds sterling (£) using an online currency converter.[14] 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.[15] 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.

3.3 The Birmingham economic evaluation

Given the disparity of results of existing economic evaluations and the fact that none of the models were suitable to address the questions posed in this review, we decided to construct a *de novo* model, the Birmingham Economic Evaluation (BrumEE).

3.3.1 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 to 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 R programming language.[17] All costs are presented in 2006 UK pounds sterling (£). Both costs and benefits are discounted at 3.5%.

3.3.2 Structure of the model

The model structure is shown in Figure 4. The model follows high-risk children for their first RSV season. The high-risk children are divided into two groups: those with

palivizumab prophylaxis and those with no 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. 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.[11,18]

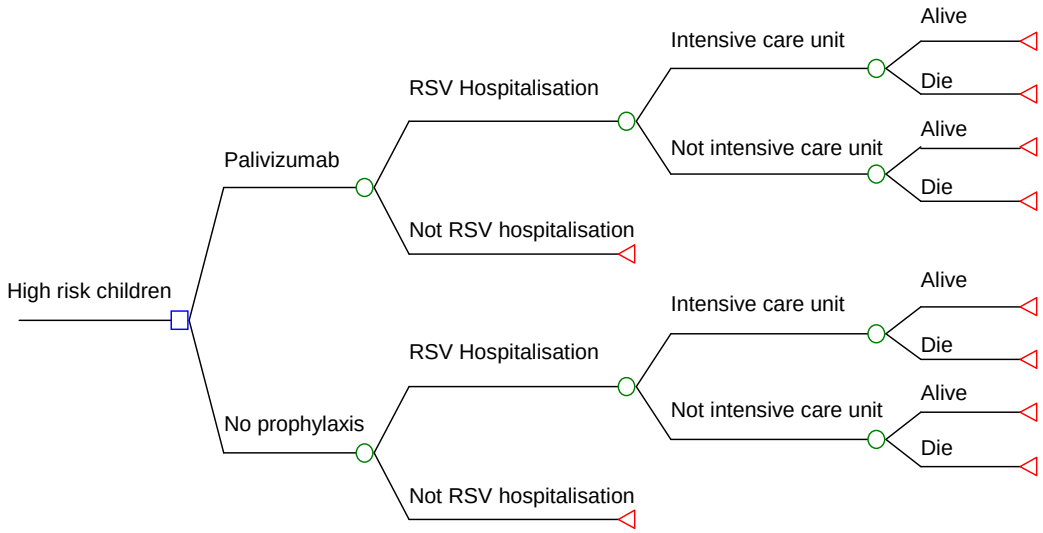


Figure 4 A decision analytic model

3.3.3 Estimation of model parameters

RSV hospitalisation rates, probability of ICU admission, mortality rates were obtained from the two RCTs[11,18] or synthesised from cohort studies[4,19-25]. The costs were identified, measured, and valued in both NHS and societal perspectives[11,18,20,26-31], which include medical costs, administration costs, hospitalisation costs, and parent work loss costs. The life expectancy for children at risk of RSV infection was 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 estimated from National statistics (1997 – 2001).[32] The utilities for children with or without RSV hospitalisation were obtained

from the study by Greenough.[33] The detailed estimates of these parameters were described in a NCCHTA report (This project was funded by the NIHR HTA Programme as project number 06/29/01, and a peer reviewed version will be published in full in Health Technology Assessment in middle 2008).

3.3.3.1 Prognostic factor studies in RSV

The limited RCT data does not distinguish adequately between subgroups of risk within the "high risk" groups (e.g. groups defined by different gestational ages or age at 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.

In order to seek the best available information, we looked for prognostic studies identified during the search for the systematic review and undertook a further specific systematic search for prognostic studies. Based on scrutiny of title and abstract we selected those that were of most relevance to the current UK context and of highest quality.[34-36] The risk of hospitalisation due to RSV was estimated for different subgroups, cross-tabulated by gestational age and birth age. The detailed estimate of hospitalisation risk was described in the NCCHTA report.

4 RESULTS

4.1 Review of clinical effectiveness

4.1.1 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. Of these 17 papers, 14 were excluded on reading the paper. Two RCTs of palivizumab (IMpact[18] and Feltes[11]) and one systematic review[37], that met the inclusion criteria, were identified from the clinical effectiveness searches. Additional five systematic reviews were identified in the economic searches. None of these systematic reviews, however, included any trials other than those identified in the searches.

4.1.2 Primary outcomes of the 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 very good follow-up of trial patients. The primary outcomes of the RCTs are summarised in Table 1.

Table 1 Results of RCTs

Study	**RSV hospitalisation**		
	Palivizumab	**No prophylaxis**	**Reduction in RSV hospitalisation (Palivizumab vs. no prophylaxis)**
Study Group[18] 1998	4.8% (N=1002)	10.6% (N=500)	55% (95% CI 38-72%), p=.0004)
	7.9% (with CLD, N=496)	12.8% (with CLD, N=266)	39% (95% CI 20-58), p=.038
	1.8% (no CLD, N=506)	8.1% (no CLD, N=234)	78% (95% CI 66-90), p<.001
Feltes[11] 2003	5.3% (N=639)	9.7% (N=648)	45% (95% CI 23-67), p=0.003
	5.6% (cyanotic, N=339)	5.6% (cyanotic, N=343)	29% p=0.285
	5.0% (acyanotic, N=330)	11.0% (acyanotic, N=305)	58% p=0.003

4.1.3 Overall adverse events

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.

4.1.4 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, 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.

4.2 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. Twenty-one studies reached the final stage of our review and were considered for data extraction. Three of the included studies are systematic reviews of economic evaluations and the remaining eighteen are primary economic evaluation studies.

The quality of the systematic reviews was moderate: none assessed the quality of the included primary economic evaluation studies. All the reviews qualitatively

summarised the results of the included economic evaluations and did not develop decision analytic 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 may be not cost-effective when used in all children for whom it is licensed, and that continued use of palivizumab for very high risk children may be justified.

The quality of the included primary economic evaluation studies was assessed. They were 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. Less than half of the studies used a lifetime time horizon. Others did not specify the time horizon or used a time horizon of one year. Half of the studies did not report the price year.

Most studies performed cost-effectiveness or cost-utility analyses, the remaining studies performed cost benefit analysis. Most reported the ICER in terms of cost per hospital admission prevented (HAP), some studies reported the incremental cost per life-year gained (LYG), and others reported the incremental cost 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 2. The results of the included economic evaluation studies show that the ICERs vary from £5,307/HAP to £69,240/HAP with mean of £33,190/HAP (SD £17,807/HAP), from £5,288/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).

4.3 An analysis of existing economic evaluations

In order to find what is driving the differences between the ICERs of the existing economic evaluation studies, we looked at the characteristics of the previous economic evaluations and found the following discrepancies among these studies. (1) Doses of palivizumab used in the economic evaluations were different, varying from four to six, while two studies did not specify dose. (2) These studies used different perspectives, half of the studies estimated ICERs from societal perspective and others from provider or hospital perspective. (3) The time horizons were different, most varying from 1 year to 2 years, two of the studies did not specify time horizon. (4) The populations were different. For example, different studies reported cost-effectiveness for different sub-populations with different risk factors, such as having a sibling in day-care groups, preterm children with CLD and born at different gestational ages. (5) The outcomes were different. Some studies reported ICERs in terms of cost per HAP, some in cost per LYG, and others in cost per QALY. (6) Discounting was different. Some studies applied different discounting rates (1.5% to 5%), while others did not apply discounting. (7) Mortality rates were different, varying from 1% to 8.11%. Compared to other studies, the study by Nuijten[26] assumed a higher mortality rate (8.11%). This is probably the main reason that the study by Nuijten[26] reported a very low value of ICER.

Table 2 Summary of results of economic evaluations

Author	Country	Study Year	Price Year	Dose	Discount rate (%)	Hospitalisation rates (%)		Population	Main findings	
						Palivizumab	No prophylaxis		Reported in price year	Converted to £ (sterling) 2006
Farina[38]	Argentina	2002	2000	4	Not specified	10.71	23.8	Born at ≤35 weeks GA (≤6 months), or at ≤28weeks GA (≤12 months), or CLD ≤2 years	$15,358/HAP	£8,000/HAP
Numa[39]	Australia	2000	Not specified	5	Not specified	4.8	10.6	Born at ≤35 weeks GA (≤6 months), or CLD ≤2 years, weight <6.7kg	A$27,786/HDS	£14,400/HDS*
								Born at ≤35 weeks GA (≤6 months), or CLD ≤2 years, weight ≥ 6.7kg	A$55,572/HDS	£28,900/HDS*
Reeve[40]	Australia	2006	Not specified	5	Not specified	2.0	4.0	Children hospitalised with RSV positive either born at ≤33 weeks GA	A$98,818/HAP	£42,000/HAP*
						2.3	4.4	Birth weight <2500g	A$88,547/HAP	£37,700/HAP*
						2.2	5.0	Indigenous and birth weight <2500g	A$73,294/HAP	£31,200/HAP*
						1.8	4.8	Birth weight <2500g and siblings	A$69,861/HAP	£29,700/HAP*
						2.3	5.1	E-NICU	A$79,619/HAP	£33,900/HAP*
Roeckl-Wiedmann[41]	Germany	2003	2000	5	No discounting	24	54	Born at ≤35 weeks GA with CLD, siblings in day-care groups, and discharge between Oct &Dec	€6,639/HAP	£5,300/HAP
						10	23	Born at ≤35 weeks GA with siblings in day-care groups, and discharge between Oct &Dec	€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 Oct &Dec	€204,684HAP	£162,800/HAP
Chiroli[42]	Italy	2005	2004	5	No discounting	5.3	9.7	CHD ≤2 years	€7,186/LYG	£4,300/LYG
Vogel[43]	New Zealand	2002	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[44]	Spain	2003	Unclear	Unclear up to 50mg, full 5 dose in total	N/A	Unclear		Born at ≤30 weeks GA	€12,915/HAP	£9,500/HAP
								Born at ≤32 weeks GA	€20,900/HAP	£15,400/HAP Appears to be data driven, states with 35 weeks GA, then treats only ≤32 weeks GA

Lázaro de Mercado[45]	Spain	2006	2006	15mg/kg mean of 3.88 doses	3%	1.8	8,1	Born at 32-35 weeks GA	€4,605/QALY for (societal) €13,849/QALY for (provider)	£3,200/QALY (societal) £9,500/QALY (provider)
Ortega[46]	Spain	2006	2005	3.8 doses (mean), sharing vials	N/A	2.7	6.6	Born at 32-35 weeks GA	€42,761/HAP to €68,104/HAP	£29,400/HAP to £46,800/HAP
Simpson[8]	UK	2001	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[26]	UK	2007	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
						5.3	9.7	CHD ≤2 years	£6,664/QALY £7,002/LYG	£7,500/QALY £7,900/LYG
Joffe[47]	US	1999	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 Sept-Nov	$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 Dec-Aug	$110,000/LYG	£101,200/LYG
						3.6	8	Born at 23-32 weeks GA, length of oxygen <28 days, month of NICU discharge Sept-Nov	$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 Dec-Aug	$440,000/LYG	£404,900/LYG
						5.0	11	Born at 33-36 weeks GA, length of oxygen ≥28 days, month of NICU discharge Sept-Nov	$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 Dec-Aug	$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 Sept-Nov	$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 Dec-Aug	$1,200,000/LYG	£110,4001/LYG
Lofland[48]	US	2000	Not specified	5	Not specified	5[†]	10[†]	Born at ≤35 weeks GA (≤6 months)	$39,591/IEA if palivizumab therapy cost $2,500	£31,300/ IEA* if palivizumab therapy cost $2,500

						5	10		$79,706/ IEA* if palivizumab therapy cost $4,500	£63,000/IEA* if palivizumab therapy cost $4,500
Stevens[49]	US	2000	Not specified	5	Not specified	9.3	20.6	Born at ≤26 weeks GA	$18,183/HAP	£14,400/HAP*
						6.6	14.6	Born at 27-28 weeks GA	$24,113/HAP	£19,100/HAP*
						5.1	11.3	Born at 29-30 weeks GA	$36,878/HAP	£29,200/HAP*
						2.9	6.4	Born at 31-32 weeks GA	$72,712/HAP	£57,500/HAP*
Shireman[50]	US	2002	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 £3,746*, hospitalisation cost decreased by £559*
Strutton[51]	US	2003	2002	Not specified	5% for both cost and benefit	Not specified	Not specified	Born at ≤35 weeks GA	$66,200/LYG (societal)	£53,200/LYG (societal)
						Not specified	Not specified		$66,400/LYG (payer)	£53,300/LYG (payer)
Yount[29]	US	2004	2002	5	3 for both cost and benefit	5.3	9.7	CHD ≤2 years	$114337/QALY	£91,800/QALY
ElHassan[52]	US	2006	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

* cost year was not clearly defined, assumed to be the same as study year
† Incidence of RSV infection

In order to evaluate the effect of the high mortality rate on the cost-effectiveness, we re-constructed the model described in the study by Nuijten[26] and ran it using different mortality rates (from 8% to 1%). The results showed that the ICER becomes £38,000/QALY when a mortality rate of 1% is applied. Note that the best estimate of mortality for premature children without CLD that we could find is smaller than 1% and therefore the probable ICER will be in excess of £38,000/QALY. 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.

4.4 Results of BrumEE

4.4.1 Cost-effectiveness results using the deterministic model

The costs and outcomes for preterm infants without CLD, children with CLD and children with CHD are listed in Table 11, Table 12, and Table 13 in Appendix, respectively.

Table 3 below presents the cost-effectiveness results of the deterministic analysis using the base case model. 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.

Table 3 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

From a societal perspective the ICERs for using palivizumab compared to 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 4, below.

Table 4 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

4.4.2 Probabilistic sensitivity analysis of cost-effectiveness (NHS perspective)

The cost-effectiveness acceptability curve (CEAC) for prophylaxis with palivizumab compared to no prophylaxis for preterm infants without CLD is shown in Figure 5. 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.

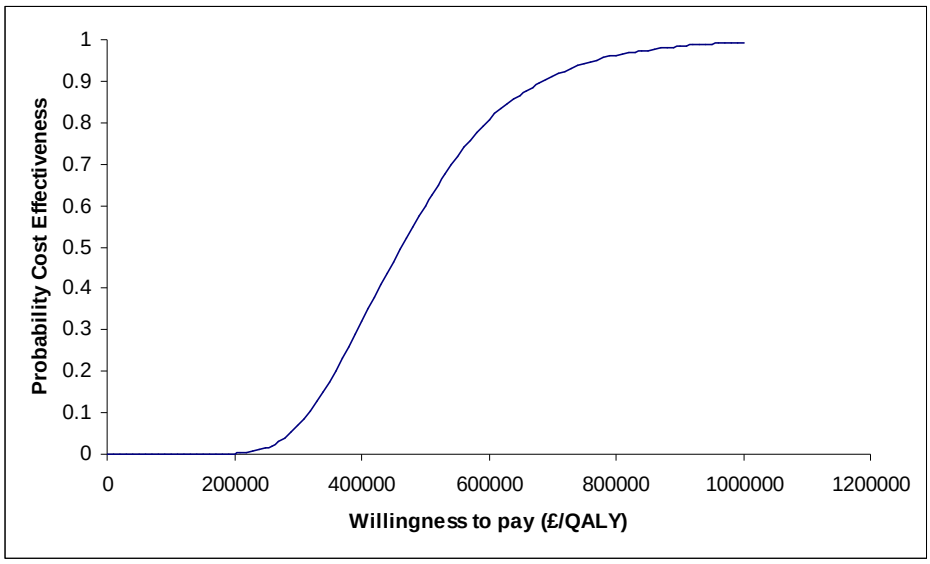


Figure 5 Cost-effectiveness acceptability curve for prophylaxis with palivizumab compared with no prophylaxis for preterm infants without CLD.

The CEAC for prophylaxis with palivizumab compared with no prophylaxis for children with CLD is shown in Figure 6. Compared with no prophylaxis, palivizumab has a probability of 50% with an ICER below £64,000/QALY, a probability of 10% with an ICER below £48,000/QALY, and a probability of 90% with an ICER below £86,000/QALY.

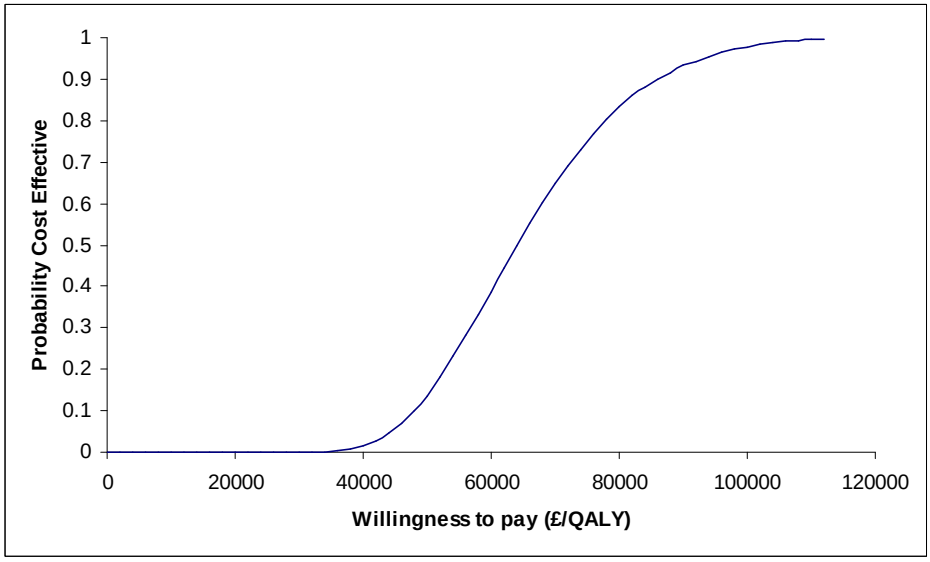


Figure 6 Cost-effectiveness acceptability curve for prophylaxis with palivizumab compared with no prophylaxis for children with CLD.

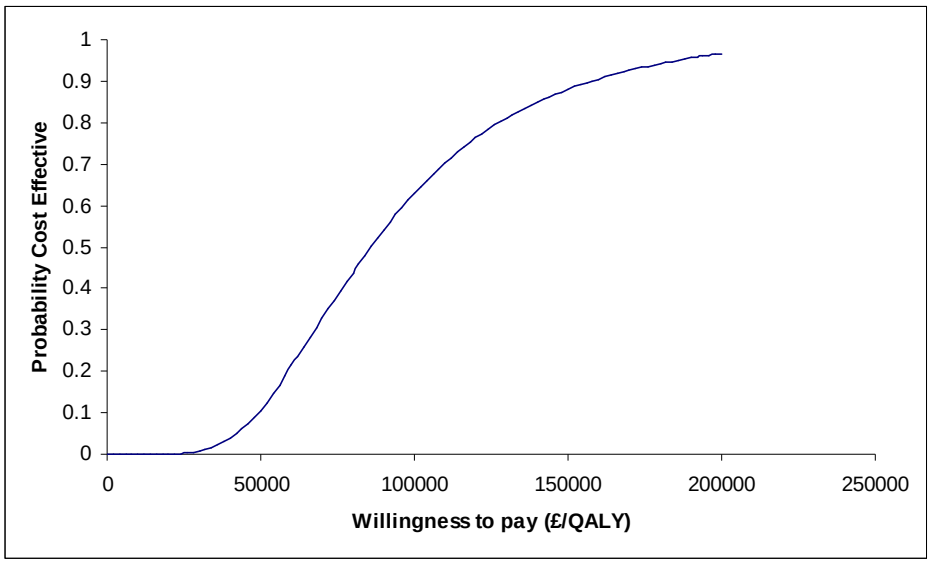


Figure 7 Cost-effectiveness acceptability curve for prophylaxis with palivizumab compared with no prophylaxis for children with CHD.

The CEAC for prophylaxis with palivizumab compared with no prophylaxis for children with CHD is shown in Figure 7. Compared with no prophylaxis, palivizumab has a probability of 50% with an ICER below £85,000/QALY, a probability of 10% with an ICER below £50,000/QALY, and a probability of 90% with an ICER below £158,000/QALY.

As can be seen above, the base case model gives similar but slightly lower estimates of the ICERs for palivizumab compared to no prophylaxis than the median willingness to pay threshold of the probabilistic sensitivity analysis. The best summary estimate for policy makers from latter type of analysis (which incorporates more of the uncertainty than a deterministic model with sensitivity analyses) is currently considered to be the average ICER from the PSA. These are summarised in the Table 5 below and again are very similar. A comparison of the estimates from the different methods is given in Table 6.

Table 5 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

Table 6 Comparative ICERs from different methods of BrumEE

	Incremental Cost/QALY				
Strategy	**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	454k	320k	460k	690k	454k
Children with CLD	64k	48k	64k	86k	64k
Children with CHD	80k	50k	85k	158k	81k

4.4.3 Identification of subgroups with different risk factors

The cost-effectiveness for children with different risk factors was analysed. The most important risk factors for hospitalisation are gestational age, chronological age at start of the RSV season, and presence of chronic lung disease or congenital heart disease. Because none of relevant data was found for children with CHD, we therefore used the BrumEE to produced two economic evaluations: one for infants under six months old who are premature; and one for children up to the age of two who have CLD, 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 7) – it is greater than £60,000/QALY in all subgroups.

Table 7 Average Incremental Cost/QALY from PSA in infants without CLD

	Gestational age (weeks)					
Birth age (months)	**≤24**	**24-26**	**26-28**	**28-30**	**30-32**	**32-34**
<3	**102K**	**136K**	**196K**	**270K**	**361K**	**530K**
3-6	**197K**	**270K**	**357K**	**529K**	**753K**	**954K**
6-9	**360K**	**526K**	**751K**	**954K**	**1283K**	**1922K**
ICER Cost/QALY Coding:<£30K; £30 to <40K;£40 to <50K; £50 to <60K; £60K and over						

However the incremental cost/QALY fell when the additional risk factor of having CLD was added. Table 8 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, or infants under 3 months and with a gestational age of less than 30 weeks. The values of ICER lies between £30,000/QALY and £40,000/QALY for infants under 3 months of age with a gestational age of less than 30 weeks, or 3 to 6 months old with a gestational age less than 28 weeks, or up to 9 months old with a gestational age of less than 24 weeks.

Table 8 Average Incremental Cost/QALY from PSA in children with CLD

	Gestational age (weeks)					
Birth age (months)	≤24	24-26	26-28	28-30	30-32	32-34
<3	12K	15K	19K	23K	31K	40K
3-6	19K	24K	31K	42K	54K	75K
6-9	31K	42K	54K	75K	105K	141K
9-12	59K	75K	105K	142K	213K	284K
12-15	105K	140K	213K	285K	430K	429K
15-18	211K	286K	432K	431K	862K	867K
18-21	429K	428K	862K	867K	859K	∞K
21-24	864K	865K	864K	∞K	∞K	∞K
ICER Cost/QALY Coding:<£30K; £30 to <40K;£40 to <50K; £50 to <60K; £60K and over						

Table 9 page 39 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 values of ICERs never fall below £50k/QALY in any subgroup.

Table 9 Average ICER from PSA: Children with siblings in day-care groups

	Gestational age (weeks)					
Birth age (months)	≤24	24-26	26-28	28-30	30-32	32-34
<3	59K	80K	108K	145K	198K	267K
3-6	108K	146K	198K	269K	404K	531K
6-9	212K	294K	403K	525K	751K	958K
9-12	402K	527K	752K	947K	1280K	1925K
12-15	752K	947K	1284K	1934K	3890K	3893K
15-18	1275K	1931K	3897K	3939K	3886K	3868K
18-21	3882K	3915K	3896K	3883K	∞K	∞K
21-24	3874K	∞K	∞K	∞K	∞K	∞K
ICER Cost/QALY Coding:<£30K; £30 to <40K;£40 to <50K; £50 to <60K; £60K and over						

Table 10 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, or 3 to 6 months old and with a gestational age of less than 30 weeks, or 6 to 9 months old and with a gestational age of less than 26 weeks.

Table 10 Average ICER from PSA: for children with CLD and siblings in day-care group

	Gestational age (weeks)					
Birth age (months)	≤24	24-26	26-28	28-30	30-32	32-34
<3	9K	10K	12K	15K	19K	25K
3-6	13K	15K	19K	24K	33K	42K
6-9	19K	24K	33K	42K	59K	75K
9-12	33K	45K	58K	76K	105K	141K
12-15	59K	83K	105K	140K	212K	284K
15-18	105K	141K	214K	286K	430K	430K
18-21	213K	285K	428K	429K	863K	866K
21-24	430K	431K	867K	870K	859K	∞K
ICER Cost/QALY Coding:<£30K; £30 to <40K;£40 to <50K; £50 to <60K; £60K and over						

4.4.4 Summary

- The assessment group developed a decision tree with Monte Carlo simulation model to assess the cost-effectiveness of prophylaxis with palivizumab, compared to no prophylaxis. The model has been designed to estimate costs,

from the perspective of the UK NHS perspective and 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 to no prophylaxis from both 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 £30k/QALY, in
    - infants under three months old at the start of the RSV season who were born at 30 weeks gestational age or less
    - infants under six 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, who also have a sibling in day care or school, may be cost-effective, at a willingness to pay threshold of £30k/QALY, in
    - infants under three months old at the start of the RSV season who were born at 35 weeks gestational age or less
    - infants under six months old at the start of the RSV season who born at 30 weeks gestational age or less
    - infants under nine months old at the start of the RSV season who born at 26 weeks gestational age or less

5 DISCUSSION

5.1 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 <= two years with congenital heart disease. Palivizumab appears 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 congenital heart disease but in this case there was no convincing evidence from subgroup analysis that the effect sizes were different.

The systematic reviews 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.

5.2 Cost-effectiveness

We have identified three systematic reviews and eighteen 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[37] 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 colleagues concluded that only children with a very high risk of RSV should be administered palivizumab due to the high cost of palivizumab. The study by Embleton[53] reported that none of the identified studies were comprehensive economic analyses 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 CLD, may appear justified in the absence of a comprehensive economic assessment. The study by Kamal-Bahl[54] 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, policymakers, or providers, or payers need to critically appraise and judiciously interpret studies reporting the cost-effectiveness of palivizumab.

Four primary studies[8,26,47,51] 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 2006 prices equivalents. The ICERs varied from £25,800/LYG to £404,900/LYG. Two studies[26,42] reported cost-effectiveness in terms of cost per LYG for children with CHD, with ICERs varying from £5,300/LYG to £7,900/LYG. Three studies[26,45,52] reported cost-effectiveness in terms of cost per QALY for preterm children with or without CLD, with ICER varying from £3,200/QALY to £1,489,700/QALY. Two studies[26,29] reported cost-effectiveness in terms of cost per QALY for children with CHD, with ICER varying from £7,500/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 £5,300/HAP to £69,200/HAP.

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

The BrumEE shows that the ICERs for prophylaxis with palivizumab compared to 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 NHS perspective. The similar cost-effectiveness results have been obtained from 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% with an ICER below £460,000/QALY, that prophylaxis with palivizumab for children with CLD has a probability of 50% with an ICER below £64,000/QALY, and that prophylaxis with palivizumab for children with CHD has a probability of 50% with an ICER below £85,000/QALY.

5.3 Strengths and limitations

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

- Cost-effectiveness of prophylaxis with palivizumab has been assessed in the time horizon of lifetime and expressed in terms of and cost per QALY (rather than in one year time horizon and expressed only in cost per HAP like most previous models).
- The mortality rates for those who admit to hospital due to RSV infection have been synthesised from meta-analysis of the available published evidence.
- Analysis was conducted from both an NHS and a societal perspective.

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 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 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.

6 CONCLUSIONS

6.1 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 study[18] showed a 55% of reduction of RSV hospitalisation for preterm infants without CLD or children with CLD; and the Feltes study[11] indicated a 45% of reduction of 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 a good value when used unselectively in preterm infants without CLD or children with CLD or CHD. This conclusion is in consistence with most of the 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 pre-term 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.

6.2 Suggested research priorities

Future research should be directed toward 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 BrumeEE, particularly in mortality, hospital admission rates, ICU utilisation, and the length of effect of RSV infection on morbidity and mortality in the UK settings. This should be undertaken by systematic review in the first instance.
- 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 when they considered as a whole. Future research should focus on the major uncertainties for patient subgroups, including preterm infants with different gestational ages.
- 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.

- The economic models need to be updated on the availability of such future data.
- It might be necessary to carry out further research regarding the public's willingness to pay for this type of patient group.

7 APPENDIX

Table 11 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**	
Parent work loss	£226	£72		
Total cost (Societal)	**£3790**	**£373**	**£3417**	
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**

Table 12 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		
Total cost (NHS)	**£3790**	**£475**	**£3315**	
Parent work loss	£283	£120		
Total cost (Societal)	**£4073**	**£595**	**£3478**	
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**

Table 13 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		
Total cost (NHS)	**£4155**	**£697**	**£3458**	
Parent work loss	£287	£140		
Total cost (Societal)	**£4442**	**£837**	**£3605**	
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**

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