A systematic review of the effectiveness and cost-effectiveness of palivizumab (Synagis®) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection.

A West Midlands Development and Evaluation Service Report

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Palivizumab (Synagis®) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection.

Question addressed by this review:

How effective and cost-effective is Palivizumab (Synagis®) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection?

Conclusion

Palivizumab appears to be an effective in preventing serious lower respiratory-tract infection caused by RSV requiring hospitalisation in high-risk infants. However, in our base-case cost-effectiveness model palivizumab was not good value for money if used in all children who meet the licensed indication. However, this is not how the drug is currently being used by clinicians in the UK who reserve it for those children at greatest risk. A sensitivity analysis varying the probability of hospitalisation in the absence of prophylaxis shows that palivizumab becomes increasingly cost effective as the probability of hospitalisation increases. When the probability is 31% or greater the ICER drops to below £30,000 per life year gained. The IMpact RSV published trial data does not permit an estimation of prognostic indicators.

EXPIRY DATE: 2003

West Midlands Health Technology Assessment Group

The West Midlands Health Technology Assessment Group (HTAG) 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.

About InterTASC

West Midlands HTAG is a member of InterTASC which is a national collaboration with three other units who do rapid reviews: the Trent Working Group on Acute Purchasing; the Wessex Institute for Health Research and Development; York Centre for Reviews and Dissemination. The aim of InterTASC is to share the work on reviewing the effectiveness and cost-effectiveness of health care interventions in order to avoid unnecessary duplication and improve the peer reviewing and quality control of reports.

Contribution of Authors

Sue Simpson undertook the collection and collation of evidence for this review, carried out an assessment of the effectiveness and cost effectiveness and wrote the report. Amanda Burls gave advice on the formulation of the question and overall process of the review, helped with of the writing and structuring of the report, carried out the cost effectiveness analysis and read and commented on the draft report.

Conflicts of Interest

This work has been undertaken by people funded by the NHS. The authors have received no funding from any sponsor in this work.

Palivizumab (Synagis®) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection.

West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the use of Palivizumab (Synagis®) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection 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.

Anticipated expiry date: 2003

- This report was completed in November 2001
- The searches were completed in January 2001
- There are no known clinical trials in progress of palivizumab in the general population for which the drug is indicated. However, there is a randomised controlled trial in progress evaluating the safety of palivizumab in children with a broad spectrum of congenital heart disease. A further trial of palivizumab in children with cystic fibrosis is also scheduled.

Palivizumab (Synagis®) in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection.

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Executive Summary

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection (LRTI) in infants and is subsequently responsible for hospitalisation in a number of patients particularly those who are born prematurely and those who have bronchopulmonary dysplasia (BPD). Hospitalization rates in at risk patients may be as high as 20% and a significant percentage of those hospitalised will require admission to an intensive care unit, with around a quarter requiring mechanical ventilation. Increased hospitalisation, morbidity and deaths amongst high risk individuals arise from complications of LRTI, the most serious being bronchiolitis (inflammation of the smaller airways of the lung) and pneumonia.

RSV is a seasonal disease, epidemics of which occur annually from October to March in the UK. This trend is reflected in hospital admission data, with an increased demand for paediatric beds particularly in December and January. In 1998, in the West Midlands information from Hospital Episode Statistics data indicate that there were 810 admissions for acute bronchiolitis caused by RSV resulting in 3149 bed days.

Treatment of patients with RSV LRTI consists primarily of supportive care and currently the only therapy for RSV infection is ribavirin. However, it has been concluded that trials of ribavirin for RSV lack sufficient power to provide reliable estimates of its effects and treatment requires hospitalisation, is costly and may result in allergic skin reactions, anaemia and other respiratory problems.

As current treatment options for RSV are limited the focus of therapy has shifted from treatment to prevention. Clinical trials evaluating vaccines have so far been unsuccessful but two products providing passive immunity against RSV have been developed successfully. These are: palivizumab (Synagis®), a humanised monoclonal antibody, and RSV intravenous immunoglobulin (RSV-IVIG, Respigam®).

RSV-IVIG is obtained from adult human plasma containing high titres of neutralising antibody to RSV. It is currently not licensed in the UK and has several disadvantages over palivizumab. These include risk of fluid overload, the requirement of intravenous cannulation and infusion over several hours, the possibility of transmission of infection from donors and disruption of the routine childhood vaccination schedule. In addition to this its availability can be unreliable if there are a shortage of donors.

Palivizumab is a humanised murine monoclonal antibody licensed in the UK in 1999. Palivizumab's licensed indication is for the prevention of serious lower respiratory-tract infection, requiring hospitalisation, caused by RSV, in children born at 35 weeks of gestation or less and who are less than 6 months old at the onset of the RSV season, or in children less than 2 years old who have received treatment for bronchopulmonary dysplasia (BPD) within the proceeding 6 months. It is licensed for monthly use during the RSV season and is administered by intramuscular injection. It can be administered in the community without the need to refer patients to hospital. There is only one supplier, Abbott Laboratories (Berkshire, UK), who supply palivizumab under the trade name of Synagis®. It is sold in the form of a powder for reconstitution in single vial packs of 50mg and 100mg with water for injections. The net price for a 50-mg vial is currently £424.00 and for a 100-mg vial is £706.00.

Sales analysis of the 1999/2000 RSV season in the UK suggested that approximately 180 infants received palivizumab, equating to approximately one third of the usage of other major

European countries. A survey carried out by the Department of Public Health and Epidemiology at the University of Birmingham of pharmaceutical advisers in Great Britain found that the majority of health authorities did not at that time have a policy on the prescribing of palivizumab. Of those that did half allowed it for restricted use only and 39% did not allow it's use. There are currently no funds put aside for the provision of palivizumab.

This review considers the effectiveness and cost-effectiveness of palivizumab for the prevention of RSV infection in infants at high risk of infection.

One large randomised, double-blind, placebo-controlled, multi-centre trial was identified - the Impact-RSV study which formed the basis of our conclusions and the cost effectiveness analysis. A further phase I/II multicentre, randomized, double blind, placebo-controlled, dose escalation study was identified but the objective of this study was to describe the safety, tolerance, immunogenicity and pharmacokinetics of palivizumab and did not consider any of the primary or secondary outcomes listed in our study inclusion criteria.

The primary endpoint of the Impact-RSV study was hospitalisation for a respiratory illness with confirmed RSV infection. The results demonstrated a 55% reduction in the risk of hospitalisation attributable to RSV with palivizumab. Statistically significant decreases in hospitalisation were also seen in children with BPD (39% reduction) and premature infants without BPD (78% reduction).

There were no full economic evaluations identified that were applicable to the UK. A cost effectiveness analysis was carried based on the results from the IMpact-RSV study. Cost per hospital admission prevented and cost per life year gained (LYG) were calculated. The base case ICERs were found to be £43,000 per hospital admission prevented and £96,000 per LYG when used for all children who meet the licensed indication. A sensitivity analysis was carried out varying all parameters used in the base case. The results of the sensitivity analysis indicated that the ICERs are relatively insensitive to variations in all parameters apart from the probability of hospitalisation for RSV in the absence of prophylaxis. When this was varied it became apparent that the probability of hospitalisation would have to be 31% or above for palivizumab to be a cost-effective alternative to no prophylaxis.

We conclude that palivizumab appears to be effective prophylaxis for the prevention of serious lower respiratory-tract infection caused by RSV and requiring hospitalisation in high-risk infants. However, in our base case cost-effectiveness model palivizumab did not represent good value when used in all children who meet the licensed indication for palivizumab. However, this is not how the drug is currently being used by clinicians in the UK. A sensitivity analysis varying the probability of hospitalisation in the absence of prophylaxis shows that palivizumab becomes cost effective as the probability of hospitalisation increases. When the probability is 31% or greater the ICER drops to below £30,000 per life year gained. Reports[1] have indicated that the group at highest risk of hospitalisation are infants that have bronchopulmonary dysplasia who are supported by oxygen at home, however, the IMpact RSV published trial data does not permit an estimation of prognostic indicators.

The findings of this report are consistent with the current judicious use by clinicians. The current practice of providing palivizumab to infants at high risk of hospitalisation appears to be cost effective. As palivizumab is a new drug, if it is used the morbidity and mortality from RSV should be studied in those high-risk infants who do and do not receive prophylaxis.

1 Introduction

1.1 The technology evaluated

Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection in infants and is subsequently responsible for hospitalisation in a number of patients particularly those who are born prematurely and those who have bronchopulmonary dysplasia.

Palivizumab (Synagis®) is a humanised murine monoclonal antibody, produced by recombinant technology licensed for the prevention of serious lower respiratory-tract infection, requiring hospitalisation, caused by RSV, in children born at 35 weeks of gestation or less and who are less than 6 months old at onset of RSV, or in children less than 2 years old who have received treatment for bronchopulmonary dysplasia (BPD) within the proceeding 6 months. Palivizumab was licensed in the USA in June 1998 and was licensed across Europe in 1999.

1.2 Objective of this report

This report looks at the effectiveness, safety and cost-effectiveness of palivizumab for the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection compared to placebo or alternative prophylaxis.

2 Background

2.1 Respiratory Syncytial Virus (RSV)

RSV is the leading cause of lower respiratory tract infections (LRTIs) in infants and young children [2-4] and is increasingly recognised as an important cause of respiratory infection in adults, the elderly and immunocompromised individuals.[5] RSV is an ubiquitous virus which is not restricted by geographical, cultural or economic factors.[6] It infects nearly all children by the time they are 2 years old[3] (by 1 year 25-50% will have been infected and by 5 years 95%.[7]) Most infants develop a natural immunity to the virus but this is incomplete, short-lived and reinfection is the norm.[8] Reinfections are generally progressively milder[9] so in the absence of immunodeficiency, infections in adults and older children usually present with mild symptoms similar to the common cold. An infants first RSV infection is said to be the most severe.[3; 10]

Peak rates of RSV occur in infants aged 6 weeks to 6 months.[4; 11] Infection rates in Houston, USA, were 68.8 per 100 child-years in infancy, and 82.6 per 100 child-years in the second year of life.[12] In Sweden, antibodies to RSV develop in 87% of children by age 18 months and virtually all children by age 3 years.[13]

The most common infection caused by RSV is of the upper respiratory tract. After an average 3 to 5 days incubation period RSV typically begins as a simple upper respiratory tract infection with nasal secretions, a mild cough and low-grade fever. Approximately 40% of infants infected with RSV have lower respiratory tract involvement.[14] Within a few days of upper respiratory tract symptoms those infants with a LRTI develop a more severe cough,

often associated with wheezing, subcostal and intercostal retraction and tachypnoea at rest. Such infants may have increased respiratory distress when attempting to feed resulting in dehydration.[3]

For most infants, infection of the lower respiratory tract with RSV is a self-limiting condition. The large majority of patients can be treated at home with careful attention to adequate hydration, maintenance of feeding, monitoring of behaviour and observation of deterioration of respiratory effort.[14] However, a minority of patients, between 0.5 and 2% will require hospitalisation.[11] As everyone at some stage becomes infected with RSV, the risk factors of interest are severe sequelae of RSV infection rather than absolute risk of infection.[9] The younger the infant the greater the likelihood that severe lower respiratory tract disease requiring hospitalisation will occur.[15] RSV is a major cause of morbidity and mortality after the neonatal period particularly for premature infants and infants with bronchopulmonary dysplasia (BPD) (more recently known as chronic lung disease (CLD)), congenital heart disease, cystic fibrosis or immune deficiency.[4]

Prematurity is associated with a greater risk for RSV infection of any severity. Premature infants, particularly those born at less than 32 weeks gestation are at increased risk for severe RSV infections as they are born before the transfer of maternal anti-bodies occurred.[16] However, there is little information regarding the relative risk associated with different degrees of prematurity.[17] These and other risk factors associated with severe RSV disease are displayed in Table 1. Hospitalization rates in these at risk patients may be as high as 20%.[18] In addition, data from Canada suggest that 25% to 36% of hospitalised infants with RSV and underlying prematurity, heart disease, or lung disease will require admission to an intensive care unit (ICU), and 18% to 25% of these will require mechanical ventilation.[19] In the UK, it is generally the case that if the infant does not require mechanical ventilation they will not be admitted to an ICU.

Table 1 - Risk factors associated with severe RSV disease

Patient factors	Medical risk factors	Environmental risk factors
• Male gender • Young age:<1year, especially <6 months	• Prematurity • Lung disease (e.g. BPD, cystic fibrosis) • Congenital heart disease • Other congenital abnormalities • Immunosuppression (e.g., chemotherapy, congenital immunodeficiencies, and transplant patients) • Hypoxia, apnea, respiratory arrest during acute illness • Pulmonary consolidation on chest x-ray	• Crowded living environment • Increased number of siblings • Day care attendance • Exposure to passive smoking • Hospitalization during the RSV season

Source: Sandritter & Kraus (1997)[16] using data from Hall (1993)[10], Hall & McCarthy (1995)[20] and Wang et al (1995)[19]

Increased hospitalisation, morbidity and deaths amongst high-risk individuals arises from complications of LRTI, the most serious being bronchiolitis (inflammation of the smaller airways of the lung) and pneumonia. RSV has been identified as the causative agent in 5-40% of pneumonias in young children and 50-90% of the cases of bronchiolitis.[7] The fatality rate

in infants with heart or lung disease who are hospitalized with RSV infection ranges from 0.5 to 4%.[19; 21]

RSV infection in children less than 4 weeks of age is uncommon due to transplacental transfer of maternal antibodies.[22] More than 50% of infants hospitalised are between 1 and 3 months of age and studies have shown that male infants are 1.3 to 1.4 times more likely to be hospitalised than female infants.[2]

2.1.1 Long term complications

Investigations of the long term prognosis of patients with RSV disease in infancy have shown measurable respiratory abnormalities immediately or several years following infection.[23] The rates of recurrent lower respiratory symptoms in infants who were hospitalised with their initial RSV infection range as high as 82% at 2 years after infection.[24] There is evidence that early RSV infection predisposes children to recurrent wheezing during their early childhood but that airway morbidity is transient and subsides during school age.[25] Studies have found in a rat model that RSV potentiates neurogenic-mediated airway inflammation, which persists after the virus is cleared.[26] Other possible complications include pulmonary function deficits and airway hyper-reactivity as many as ten years following severe RSV disease in infancy.[23] Severe RSV pneumonia or bronchiolitis in infancy has been identified as a possible risk factor for childhood asthma in genetically predisposed children.[27; 28]

2.1.2 Seasonality of RSV

RSV is a seasonal disease, epidemics of which occur annually from October to March in the UK. Peak numbers are reported in December and January with the size of the peak varying from winter to winter. In the winter of 1998/99 the number of cases reported by laboratories in England and Wales to the PHLS Communicable Disease Surveillance Centre peaked over the Christmas period (20^{th} –26^{th} December 1998) with 1193 cases.[29] This seasonal trend is mirrored in hospital admission data (see Figure 1) and leads to increased demand for paediatric beds.

2.1.3 Morbidity and Mortality from RSV Infection

RSV is the commonest cause of hospital admissions due to acute respiratory illness in young children.[29] The risk of being admitted to hospital in the first year of life with RSV infection for an infant living in an urban area was estimated at 1 in 50 in one study in north-east England[8].

A recent study in the UK published data from one regional neonatal unit on the morbidity and mortality from RSV infection in 82 pre-term infants born in 1995.[1] In particular the study looked at readmission rates to paediatric wards and intensive care units. The results of the study, showing the hospitalisation rates and some relevant resource use rates, are displayed in Table 3. No infant died during any of the admissions. All 82 infants encountered 2 RSV seasons before they reached age 2 years (corrected for prematurity). 40 of the 82 encountered a third RSV season. For each season the infants were categorised into four groups. The overall hospitalisation rate for RSV-positive and RSV-unknown respiratory tract infections in the first season the infants encountered was 8%, the majority of these infants being in the "infants with CLD who had stopped oxygen in the prior six months" group. The study suggested that the first RSV season encountered accounts for the most morbidity. This finding

is similar to that of Wang et al who found a decrease in frequency of hospitalisation with increasing age, with the greatest drop in those over 1 year.[19]

A study by Clarke et al[30], assessed the rate of RSV hospitalisation in 2 cohorts of high risk infants in Liverpool over two RSV seasons (1998/99 and 1999/2000). The population in one of the cohorts was defined as infants who, at the beginning of the seasons studied, were under 24 months of age and discharged home with supplemental oxygen i.e., infants with BPD (n=137). The mean rate of hospitalisation for bronchiolitis in this cohort of infants was 24.1% over the two seasons. A major omission in this study was the fact that less than 50% of infants who were hospitalised with bronchiolitis from both cohorts were tested for RSV (33/68). However, 27 (82%) of those tested were RSV positive. Assuming that 82% of all bronchiolitis admissions were RSV positive, the average RSV hospitalisation rate over the two seasons would be 19.7% in the BPD infants.

A further UK study looking at hospitalisation for RSV included all infants, not only those born pre-term, and found a national admission rate of 3%.[31]

Table 2 - RSV hospitalisation rates and resource use rates in a cohort of 82 pre-term infants born in 1995.

Infant category	Season	Total babies studied	Admitted with LRTI: RSV positive	Admitted with LRTI: RSV unknown	Total ward days	Total PICU days	Total vent days	Total CPAP days	Total Oxygen days
Infants with CLD on home oxygen	1	7	1 (14%)	0	18	20	18	0	14
	2	1	0	0	-	-	-	-	-
	3	0	0	0	-	-	-	-	-
Infants with CLD who had stopped oxygen in prior 6 months	1	27	2 (7%)	2(7%)	16	6	4	1	11
	2	4	0	0	-	-	-	-	-
	3	0	0	0	-	-	-	-	-
Infants not in groups 1 or 2 <29 weeks gestation	1	7	0	0	-	-	-	-	-
	2	33	0	1	1	0	0	0	0
	3	15	0	0	-	-	-	-	-
Infants not in groups 1 or 2, 29-32 weeks gestation	1	41	0	1	1	0	0	0	0
	2	44	0	0	-	-	-	-	-
	3	25	0	0	-	-	-	-	-

Source: Thomas et al.[1]

Other studies from America have found the incidence of hospitalisation for RSV among pre-term infants to be between 2.8% and 37%.[32-35] The higher rates come from studies either looking only at pre-term infants with underlying pulmonary or cardiac problems or from the control arms of RCTs for RSV IG. The population based study from Northern Calfornia[32] showed similar overall hospitalisation rates (3.2%) to the study by Thomas et al[1] and showed a higher rate of hospitalisation in infants who were oxygen dependent at 28 days of life (14.2% P≤0.01%).

A study in Spain[36], conducted in 14 neonatal units throughout the country, including children born at ≤32 weeks gestation, found that of 584 evaluable patients, 118 (20.2%) were hospitalised for respiratory illness. In 89 of these pathogen identification was attempted and RSV was the causative agent in 59 (10.1%) of these cases. Of the 59 hospitalisations for RSV 15 (25%) required ICU admission and 3 (5%) required mechanical ventilation.

2.1.4 Hospital Admissions in England due to RSV

In England, in 1998-99, there were 8162 hospital admissions in the total population for lower respiratory diseases (viral pneumonia, acute bronchitis, and acute bronchiolitis) caused by RSV infection resulting in a total of 31056 bed days. The average number of bed days per admission being 3.8 days. The majority of these admissions were in the 0-14 age group with the mean age of admission being 5-years for viral pneumonia, 1-year for acute bronchitis and 0-years for acute bronchiolitis. The information for the West Midlands collected for patients less than 3 years old is displayed in Table 3. What HES data does not tell us is the severity of the illness and the type of care provided during hospitalisation (i.e., intensive care or general care). In addition as RSV testing is not routinely carried out in all LRTI admissions these figures may underestimate the incidence of LRTI admissions.

Figure 1 – Number of hospital admissions in children under 3 for acute bronchiolitis due to RSV (ICD10 –J21.0). West Midlands region 1995 (week 13) to 1999 (week 13).

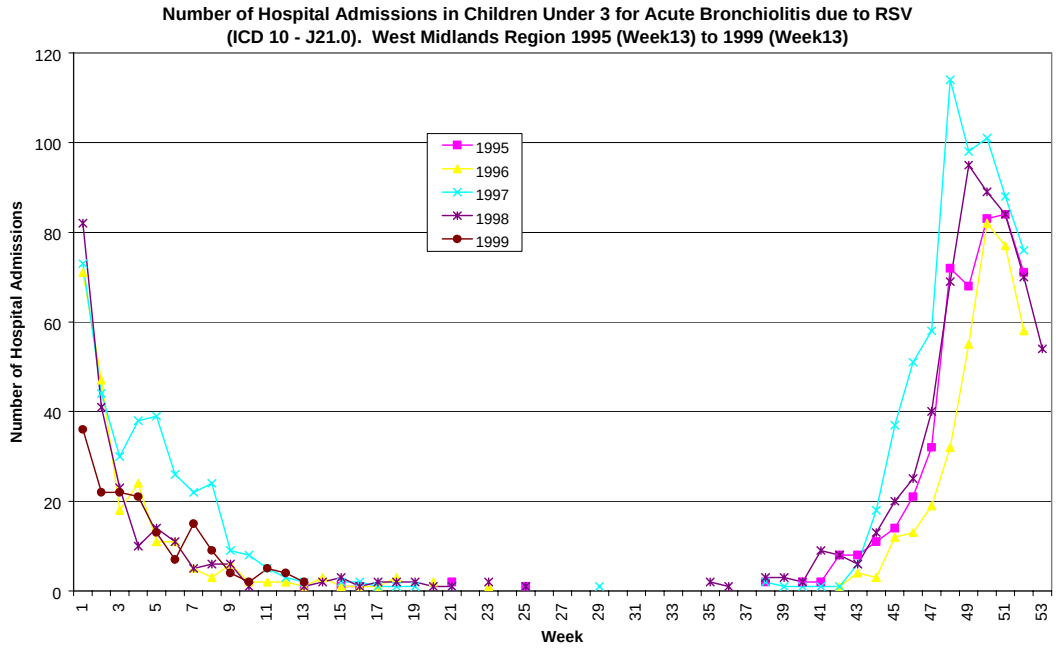


Table 3 - HES Data West Midlands Region 1995 (wk 13) to 1999 (wk 13) ICD 10 J21.0 (Acute Bronchiolitis due to Respiratory Syncitial Virus
Infants < 3 years

	1995	**1996**	**1997**	**1998**	**1999***
Total no. of admissions	484	571	986	810	162
Total no. of bed days	1850	2306	3743	3149	675
No of bed days per admission	3.8	4.0	3.8	3.9	4.2

* Data for 13 weeks only

2.1.5 Intensive Care

The majority of infants requiring intensive care are those with BPD, congenital heart disease and or those who were born prematurely[22]. Nasal continuous positive airways pressure is effective for some infants but most require intermittent positive pressure ventilation.

3 Current Service Provision

3.1 Treatment for RSV

The treatment of patients with RSV LRTI consists primarily of supportive care, including respiratory support and provision of intravenous fluids and low concentrations of supplemental oxygen.[16] Bronchodilators have also been used when wheezing is part of the clinical presentation although their benefit has been debated. Corticosteroids have not been shown to have a beneficial effect in RSV disease and are not routinely indicated. [23; 37]

Currently the only therapy for RSV infection is ribavirin. This is given by aerosol inhalation from a nebulizer via a specialised small particle aerosol generator unit daily for up to 18 hours.[38] Its use has been shown to improve the severity score of infections, LRTI symptoms and oxygen saturation and to decrease the number of days of mechanical ventilation, oxygen therapy and hospitalisation in infants with RSV pulmonary infections. However, it has been concluded that trials of ribavirin for RSV lack sufficient power to provide reliable estimates of its effects.[39] Treatment requires hospitalisation, is costly and may result in allergic skin reactions, anaemia and other respiratory problems.

3.2 Prevention of RSV

As current treatment options for RSV are limited the focus of therapy has shifted from treatment to prevention. RSV infection is transmitted by the hands after direct contact with contaminated surfaces (fomites) or by secretions from infected patients (large droplet aerosols).[16] RSV in patient secretions has been found to survive for up to 7 hours on countertops, on gloves, paper tissues and cloth, and for half an hour on skin.[40] It is highly contagious demonstrated by the high rates of infection in larger families and day care centres. RSV infection within the hospital environment is particularly high. Hospital infection control measures and the application of universal precautions including hand washing and gloving can reduce transmission rates.[9]

Prevention of the occurrence of RSV disease in industrial countries has been identified by the World Health Organization as a priority of the Global programme for vaccines.[9]

Immunisation is a potential way to prevent RSV, however, despite over 25 years of research, clinical trials evaluating vaccines have so far been unsuccessful. A major obstacle to vaccine development is safety. This lack of success, coupled with limited treatment options and an increasing population of high-risk children has led to a shift in research toward providing passive immunity against RSV. Two products have been developed successfully, these are: palivizumab (Synagis®), a humanised monoclonal antibody, and RSV intravenous immunoglobulin, obtained from adult human plasma containing high titres of neutralising antibody to RSV.

4 Proposed Service Provision - Passive immunisation

4.1 The Intervention under Consideration

Palivizumab is a humanised murine monoclonal antibody, produced by recombinant technology designed to target an antigenic site on the F- protein of the RSV. This leads to failure of the virus to replicate thus preventing the development of clinical infection.[38] It is a genetically engineered antibody that mimics those produced naturally in humans.

Palivizumab was licensed in US by the Food and Drug Administration in June 1998 and has since been licensed for use in Europe. Palivizumab's licensed indication is for the prevention of serious lower respiratory-tract infection, requiring hospitalisation, caused by RSV, in children born at 35 weeks of gestation or less and who are less than 6 months old at the onset of the RSV season, or in children less than 2 years old who have received treatment for bronchopulmonary dysplasia (BPD) within the proceeding 6 months. It is licensed for monthly use during the RSV season.

Administration: It is advised that, where possible, the first dose of palivizumab be administered before the start of the RSV season. It is administered by intramuscular injection and the recommended dose is 15 mg/kg of body weight once a month. It can be administered in the community without the need to refer patients to hospital. However, as hospital-based neonatologists and paediatricians are most likely to assess at-risk babies the initial injection is likely to be given in hospital.[15]

Cost: There is only one supplier, Abbott Laboratories (Berkshire, UK), who supply palivizumab under the trade name of Synagis®. It is sold in the form of a powder for reconstitution in single vial packs of 50mg and 100mg with Water for Injections. The net price for a 50-mg vial is currently £424.00 and for a 100-mg vial is £706.00 (BNF, March 2001). [41] Once opened a vial must be used within 6 hours. The cost of a 6-month course for a 3kg child is £2544 and for a 6kg child is £4236, excluding administration costs and assuming use of a complete vial (50 or 100-mg) per child.

As a recombinant-derived product (not derived from human immune globulin), palivizumab presents no risk of transmission of blood-borne infections.[42] It also does not interfere with the immunisation schedule of young infants and can be produced in batch-lots ensuring that shortages are unlikely.[43]

4.2 Contra-indications

Known hypersensitivity to palivizumab or any other formulation components, or other humanised monoclonal antibodies.

4.3 Precautions

No data regarding more than 5 injections during one season are available. No data on infants with congenital heart disease are available. Injection of proteins such as palivizumab may be associated with a risk of allergic and anaphylactic reactions. A moderate to severe acute infection or febrile illness may warrant delaying the use of palivizumab. Palivizumab should be given with caution to patients with thrombocytopenia or any other coagulation disorder.

4.4 Interactions

No formal drug-drug interaction studies have been conducted however, no interactions have been described to date. Since palivizumab is RSV specific, interference with the immune response to vaccines is not expected.

4.5 Side Effects

Common (>1/100,<1/10) Adverse Drug Reactions (ADRs) include: fever (2.7%), injection site reactions (2.7%)and nervousness (2.3%).
Uncommon (>1/1000, <1/100) ADR's include: upper respiratory infection (0.4%), rhinitis (0.3%), cough (0.3%), wheeze (0.3%), leucopaenia (0.3%), rash (0.9%), diarrhoea (0.9%), vomiting (0.3%).

Palivizumab is not licensed for use in infants with congenital heart disease, however it is not expected to affect blood viscosity and is expected to be safe and efficacious in these infants.[11] The results of a randomised, controlled trial to evaluate the safety of palivizumab in children with a broad spectrum of congenital heart diseases are expected in 2002. A prospective, randomised, placebo- controlled trial of palivizumab in children with cystic fibrosis is also scheduled.

4.6 Current use of and policy on palivizumab in England

Sales analysis of the 1999/2000 RSV season in the UK suggested that approximately 180 infants received palivizumab which equates to approximately one third of the usage for other major European countries. The projection for the 2000/1 season suggests that approximately 300 infants will receive palivizumab in the UK.[44] A survey of 119 pharmaceutical advisers investigating policy on the prescribing of palivizumab was carried out in the Department of Public Health and Epidemiology at the University of Birmingham during November 2000. This revealed that 70 % of health authorities responding (n=60) did not at that time have a policy on the prescribing of palivizumab for the prevention of RSV. Of those that did have a policy (n=18), 11% allowed it's use for the licensed indication, 50% allowed it for restricted use only and 39% did not allow it's use. Restrictions of use included "for infants under the gestational age of ≤32weeks, who require ≥ 28 days of oxygen in neonatal care units and are discharged from intensive care units during the earlier part of the RSV season".

A study by Thomas et al[1] surveyed neonatal units in North and South Thames. Twenty-six out of thirty-nine units responding (81 % response rate) had no plans to use palivizumab in any infants, and of the five regional level III units in the Thames regions, only 1 planned to use palivizumab, and then on an individualised basis. It should be noted that this survey was carried out in 1999, just before palivizumab was licensed in the UK, unit policies may therefore have changed since the preparation has become more widely available.

There are currently no funds put aside for the provision of palivizumab.

4.7 Alternative RSV Prophylaxis

4.7.1 Respiratory Syncytial Virus immune globulin intravenous (RSV-IGIV) (RespiGam®, Massachusettes Public Health Biologic laboratories and MedImmune Inc).

RSV-IGIV was licensed by the Food and Drug Administration, in America, in January 1996 but is not currently licensed in the UK. It is prepared from donors selected for high serum titres of RSV neutralizing antibody and is used to confer passive immunity. It is administrated once a month, just prior to and during the RSV season, intravenously, over several hours, at a dose of 750 mg/kg.

RSV-IGIV provides additional protection against other respiratory viral illnesses and may be preferred for selected high-risk children including those receiving replacement intravenous immune globulin because of underlying immune deficiency or human immuno-deficiency virus infection.[43] RSV-IGIV does have several disadvantages. These include risk of fluid overload, the requirement of intravenous cannulation and infusion over several hours, the possibility of transmission of infection from donors and disruption of the routine childhood vaccination schedule. In addition to this its availability can be unreliable if there are a shortage of donors.

4.8 Current Use of RSV-IGIV

RSV-IGIV is currently not licensed in the UK.

4.9 Recommendations for use of the two prophylactics

The American Academy of Paediatrics (AAP) has made recommendations for the use of palivizumab and RSV immune globulin.[43] The AAP stress that neither preparation is approved by the FDA for infants or children with congenital heart disease. Their guidelines are outlined in Appendix 1.

5 Methods

5.1 Types of Study: Inclusion and Exclusion criteria

No language restrictions were applied. Studies were accepted if they complied with the following criteria:

5.1.1 Study design

All randomised controlled clinical trials comparing palivizumab with placebo or alternatives were included. Other study designs were considered for background information.

5.1.2 Population

Studies were included if the population were high-risk infants as defined by the licensed indication for palivizumab. These are children born at 35 weeks of gestation or less and who were less than 6 months old at onset of RSV, or in children less than 2 years old who had received treatment for BPD within the proceeding 6 months.

5.1.3 Intervention

Studies were included if the intervention was palivizumab versus placebo or any alternative prophylaxis (i.e. RSV-IGIV).

5.1.4 Outcomes

The primary outcome considered was hospitalisation rates. Secondary outcomes considered include receipt of intensive care, mechanical ventilation rates, morbidity and mortality.

5.2 Search Strategy

Reviews and primary studies were identified in the following databases:
Medline (1966 - 2000), CINAHL, Cochrane Database of Systematic Reviews, Cochrane Controlled Trials Register, EMBASE (1980 -2000), NHS Centre for Reviews and Dissemination (DARE, NEED, HTA)

The databases were searched in October 2000 and revisited in January 2001 to check for more recent papers.

The following MESH headings and text words were used:

MEDI-493, palivizumab, Synagis, RSV, respiratory syncytial virus

with the following search (adapted for each platform) being used:

(“MEDI-493”.mp) OR (“palivizumab”.mp) OR (“Synagis”.mp)
AND (respiratory syncytial virus, human/or respiratory syncytial viruses/) OR (“RSV”.mp)

The searches were inclusive, rather than restrictive, and reviews and primary studies with relevant subject matter were identified by inspection of titles and abstracts, obtaining papers where necessary.

The internet was searched with particular consideration been given to the FDA Centre for Drug Evaluation and Research site. Hand searches of Abstracts from the World Congress on Lung Health and 10th European Respiratory Society Annual Congress (Florence, Italy, August 30 –Sept 3, 2000) and from 94th, 95th, and 96th American Thoracic Society International Conferences (1998-2000) were carried out, in addition to hand searches of recent copies of relevant journals (Paediatric Respiratory Reviews). Contact was also made with Abbott Laboratories (manufacturers of palivizumab) and subject experts and references were sought from these sources. Citations in all papers obtained were checked for relevant references

5.3 Quality Assessment

An assessment of quality was undertaken independently by 2 researchers (AB,SS).
Information relating to the quality of included studies was collected, including whether:

- The study addressed a clearly focused question
- subjects were randomised to treatment groups,
- the randomisation method was specified
- the inclusion and exclusion criteria were specified
- there was clear definition of patient groups
- intention to treat analysis was used
- loss to follow-up was reported

5.4 Data Extraction Strategy

Two reviewers independently carried out data extraction and differences were resolved by discussion.

5.5 Economic Analysis

A search was made for economic analyses of palivizumab. Insufficient data on quality of life made it inappropriate for us to conduct a cost utility analysis. However, the evidence on effectiveness obtained from the trial identified and cost data on hospitalisation allowed a cost-effectiveness analysis of palivizumab compared to placebo to be carried out.

6 Results

One existing systematic review was identified but the primary objective of this review was to assess the effects of polyclonal respiratory syncytial virus hyperimmune globulin (RSV-IGIV) and palivizumab was included with these in the analysis.[45]

One large randomised, double-blind, placebo-controlled, multi-centre trial was identified - the Impact-RSV study.[35] A further phase I/II multicentre, randomized, double blind, placebo-controlled, dose escalation study was identified[46] but the objective of this study was to describe the safety, tolerance, immunogenicity and pharmacokinetics of palivizumab and did not consider any of the primary or secondary outcomes listed in our study inclusion criteria. This study is described below in the section on safety.

6.1 IMpact RSV study[35]

The IMpact RSV study was conducted at 139 centres in the United States (119), the United Kingdom (11) and Canada (9) during the 1996 to 1997 RSV season. 1502 children were randomized centrally (500 to the placebo group and 1002 to the palivizumab group), using an interactive voice randomization system, to receive five injections of either palivizumab (15 mg/kg) or an equivalent volume of placebo* by intramuscular injection every 30 days. Sample size calculations were based on observations from the PREVENT trial of RSV-IGIV with a minimum of 1281 being required.[47] The 2:1 randomisation was prompted by some concern of randomizing subjects to placebo (especially since a polyclonal gamma globulin preparation was commercially available for RSV).[48] Children were eligible to enter the trial if they were either ≤ 35 weeks gestation and 6 months of age or younger; or 24 months old or younger and had clinical diagnosis of BPD requiring ongoing medical treatment (e.g. supplemental oxygen, steroids, bronchodilators, or diuretics within the past 6 months). Children with congenital heart disease other than patent ductus arteriosus or hemodynamically insignificant septal defect were excluded. Patients were also excluded if they were presently hospitalised and had an expected hospitalisation time of >30 days or if they required mechanical ventilation at the time of entry. In addition, patients who suffered from hepatic or renal dysfunction, seizure disorder or immunodeficiency or who had received immunoglobulins within the past three months were excluded. As were those patients who had active or recent RSV infection, had previously received monoclonal antibodies, were exposed to experimental drugs, or were afflicted by a condition that decreased life expectancy to six months or less. Both groups were balanced at entry for demographics and RSV risk factors; slightly more people in the palivizumab arm of the study had at least one smoker in the household (p=0.039). Overall the mean age of the subjects was 6 months and the mean weight 5kg. Most of the subjects were premature and had been hospitalized at least once since birth. Approximately 80% of the subjects had a gestational age ≤ 32 weeks and around a third of subjects were twins (multiple births).

6.1.1 Primary endpoint

The primary endpoint of the study was hospitalisation for a respiratory illness with confirmed RSV infection (tested for RSV antigen in respiratory secretions using commercially available

* the placebo was identical in appearance to palivizumab – the same formulation without anti-body with 0.02% Tween-80 added.

tests). Those with hospitalisation as a result of RSV infection were evaluated for total number of days in the hospital, total days with increased supplemental oxygen, total days with moderate or severe lower respiratory tract illness, and incidence and total days of intensive care and mechanical ventilation. The incidence of hospitalisation for respiratory illness not caused by RSV and the incidence of otitis media were also evaluated. Adverse events were reported throughout the study period.

The rate of completion of the study was 99% for both the placebo and palivizumab arms and >95% of both groups received at least four injections. All infants were followed for 150 days (30 days from the last injection) regardless of the amount of drug received. Reasons for non-completion included death (n=7), withdrawal of consent (n=4), or loss to follow-up (n=5). All randomised patients were included in the safety and efficacy analyses and were thus performed on an intention to treat basis.[47]

The results demonstrated a 55% reduction in the risk of hospitalisation attributable to RSV with palivizumab (see

Table 4). Statistically significant decreases in hospitalisation were seen in both subgroups: children with BPD experienced a 39% reduction and premature infants without BPD experienced a 78% reduction. Trends in reduction of RSV hospitalisation rates were similar in all countries participating in the study. In general, palivizumab appears effective in both patients who are premature but do not have BPD and those who are premature and have BPD. However, the greatest effect is within the subset of premature patients without BPD.

Table 4 - Number (%) of RSV hospitalisations in the Impact-RSV trial by all infants and sub-groups

	Placebo	**palivizumab**	**% reduction in hospitalizations (RRR) (95% CI)**	**P Value (Fishers exact test)**	**ARR**	**NNT**
All infants (n=1502)	53/500 (10.6%)	48/1002 (4.8%)	55% (38,72)	0.0004	5.8	17
Infants with BPD (n=762)	34/266 (12.8%)	39/496 (7.9%)	39% (20,58)	0.038	4.9	20
Infants without BPD (n=740)	19/234 (8.1%)	9/506 (1.8%)	78% (66,90)	<0.001	6.3	16
Infants≤ 32 weeks (n=1257)	47/417 11.3%	44/840 5.2%	54%	<0.05	6.1	16
Pre-term infants born > 32 weeks (n=245)	6/83 7.2%	4/162 2.5%	66%	<0.05	4.7	21
Infants >5kg (n=617)	23/215 10.7%	21/402 5.2%	51%	0.014	5.5	18
Infants ≤5kg (n=885)	30/285 10.5%	27/600 4.5%	57%	0.001	6.0	17

NB: RRR= relative risk reduction, ARR= absolute risk reduction, NNT = number needed to treat
Source of primary data: IMpact RSV trial[35] and FDA Centre for Biologics Evaluation and Research.[48]

6.1.2 Secondary endpoints

The secondary outcomes of the trial are reported in Table 5. Children randomised to palivizumab had significantly fewer total days (per 100 children) of RSV hospitalisation, days with increased oxygen and days with an LRI score[⊗⊗] of 3 or greater. There were 4 deaths in the palivizumab group but none of these were deemed to be related to palivizumab. Two children in the palivizumab group and none in the placebo group died during hospitalisation for RSV; one following surgery for tympanostomy tubes and the other a child with BPD who had complications.

Table 5 - Secondary endpoints of the RSV IMpact trial

	Placebo	**palivizumab**	**P value**
Total days (per 100 children) of RSV hospitalisation	62.6	36.4	<0.001
Days with increased oxygen	50.6	30.3	<0.001
Days with an LRI score of 3 or greater	47.4	29.6	<0.001
Incidence of intensive care (ICU) admissions (%)	3.0	1.3	0.026
Total ICU days	12.7	13.3	0.023
Incidence of mechanical ventilation (%)	0.2	0.7	0.280
Proportion of children with at least one episode of otitis media (%)	40	42	0.505
Incidence of all hospitalisations (%)	31	24	0.011
Total days (per 100 children) of all hospitalisations	242	191	0.005
Incidence of respiratory hospitalisations (%)	22	16	0.008
Total days (per 100 children) of respiratory hospitalisation	180	124	0.004
Incidence of RSV of respiratory hospitalisations unrelated to RSV (%)	14	13	0.470
Total days (per 100 children) of hospitalisations unrelated to RSV	118	88	0.369
Proportion of children reporting adverse events related to study drug (%)	10	11	
Number of deaths	5 (1.0%)	4 (0.4%)	

6.2 Additional trials included for information

Three large uncontrolled follow-up studies that took place over the 1998-9 RSV season in Europe and the US have endorsed the findings of the IMpact-RSV study.[49-51] These report rates of RSV-related hospitalisation in patients receiving palivizumab to be even lower than reported in the IMpact-RSV study in infants (with the infants fulfilling the same inclusion criteria as in the IMpact-RSV study). The Expanded Access study[51] found a hospitalisation rate due to RSV in the range of 1.2-3.7% (n=565). The REACH study[49] found a hospitalisation rate due to RSV of 1.5% (n=7013) and the Outcomes study[49; 50] found an RSV hospitalisation rate of 2.3% (n=1839) in a group of patients in whom 21% had BPD.

A case series studies reported at the 2000 meeting of the American Thoracic Society reported incidences of hospitalisation from RSV following a course (of varying lengths) of palivizumab to be 1.4%.[52]

[⊗⊗] LRI Score: 0 = no respiratory illness/infection; 1= upper respiratory tract illness/infection; 2= mild lower respiratory tract illness/infection; 3 = moderate LRI; 4 =severe LRI; 5= mechanical ventilation.

6.3 Safety

Two studies performed during the development of palivizumab have shown palivizumab to be well tolerated and capable of producing adequate antibody levels from monthly doses of 10 or 15 mg/kg. [46; 53]

An Expanded Access study with palivizumab (protocol (W98-271))[51] was initiated in the 1998-99 RSV season to collect additional safety data in countries in which palivizumab was not yet available. The phase III/IV study included infants with a gestation of ≤35 weeks who were less than 6 months old or children ≤24 months old with a history of BPD requiring medical intervention. A total of 665 children were involved at 97 centres in 20 countries. Two deaths were reported both judged to be unrelated to palivizumab. 101 serious adverse events were reported: 100 were hospitalisations and 1 was an RSV infection that did not require hospitalisation. None were considered to be related to palivizumab. Of the hospitalisations, 71 were for respiratory illness: 11 of which were RSV positive, 29 of which were RSV-negative and 31 which were not tested for RSV.

The immunogenicity and safety of palivizumab given to infants for a second season has been assessed at 6 centres, in 88 patients from the RSV-Impact study.[54]

There are still a number of questions regarding palivizumab that need to be addressed. These are mainly to do with it's safety and efficacy in other groups of high-risk patients such as those with congenital heart disease and those with cystic fibrosis. There are a number of trials involving palivizumab that are currently in progress. These include two studies one looking at the use of palivizumab in infants with congenital heart disease and one looking at its use in infants with Cystic Fibrosis, both are expected to be completed in 2002.[44]

7 Economic analysis

7.1 Available studies identified

Two cost -effectiveness studies applicable to the USA were identified. Joffe et al[55] use population-based RSV re-hospitalisation data in their calculation. Marchetti at al.[56] evaluated the economic impact of using palivizumab in a cost-benefit model that compiled data from multiple clinical trials.

A number of papers were also identified that contained some commentary on costs associated with palivizumab but these were not full economic evaluations. Of these there were three published studies applicable to the UK.

Thomas et al[1] presented a cost comparison from the perspective of a large regional neonatal unit. A cohort of 82 infants born at a gestation of less than 32 weeks and previously treated at a regional neonatal unit was studied retrospectively. The study classified the infants in to four groups:

1. Infants < 2 years with CLD on home oxygen
2. Infants < 2 years with CLD who had stopped oxygen in the prior 6 months
3. Infants not in groups 1 or 2, <29 weeks gestation
4. Infants not in groups 1 or 2, 29-32 weeks gestation

The potential cost of palivizumab for infants in Group 1 was similar to the high cost of hospitalisation for the one infant admitted with RSV-LRTI from this group, i.e, cost neutral. However, for all other groups in the cohort, the potential cost of palivizumab was deemed to be far higher than the actual cost of hospitalisation for RSV. The authors concluded that treating infants with CLD on home oxygen would be relatively cost effective compared with other infants, although an incremental outlay may still be required.

A prospective study by Clarke et al[30] aimed to, determine the hospital admission rate with RSV infection of a high-risk cohort (n=656) from a health authority population in the North of England, and to assess the potential impact that RSV prophylaxis would have had for these patients and the health authority over two RSV seasons. A weakness of the study was the failure to test for RSV in all admissions but based on those that were tested, RSV caused 4.2 admissions per hundred high-risk infants in the seasons studied. Prophylaxis may have saved up to £195,341 in hospital costs over the two years, but would have cost £1.1 million in drug acquisition costs. In other words, for the 28 admissions in the study, the net cost would be £90,4659 giving a cost of £32,309 per hospitalisation prevented.

A study of health economic outcomes associated with RSV in premature infants with BPD has recently been published as a poster.[57] One of the studies primary objectives was to evaluate the use of healthcare resources and the associated cost of treatment (primary and hospital costs) of RSV infection in infants born <32 weeks gestational age (GA) with BPD. It was a 4 centre, UK, retrospective study which identified neonates born <32 weeks GA who were admitted to neonatal intensive care units (NICU) between 1st July 1994 and 30th June 1997 and who developed BPD. A retrospective review of hospital notes was carried out in order to evaluate any community care, hospital outpatient attendances, readmissions and treatment received by these infants up to the age of 2, and these interventions were costed.

235 infants were entered into the study. These infants were split into 4 categories; those hospitalised for proven RSV infection, those hospitalised for bronchiolitis but with RSV status unproven, those hospitalised for another respiratory illness and those either hospitalised for a non-respiratory cause or not hospitalised at all. The mean costs incurred by the infants in their first two years of life in each group were £12,638, £6,059, £5,684 and £2,461 respectively. The study concluded that, during the first two years of life, costs incurred by infants hospitalised with RSV infection were significantly higher than those incurred by infants in any of the other three groups. It is the first UK specific health economic data looking at the health care costs associated with RSV infection that comprehensively considers both primary and hospital costs in the economic evaluation.

The IMpact RSV study was not designed to provide economic data on the cost effectiveness of the product.[58]

7.2 Cost effectiveness analysis

Insufficient data on quality of life of infants with RSV made it inappropriate to conduct a cost utility analysis. Therefore we used the evidence on effectiveness obtained from the one randomised controlled trial identified and cost data on hospitalisation to undertake a cost-effectiveness analysis of palivizumab compared to placebo.

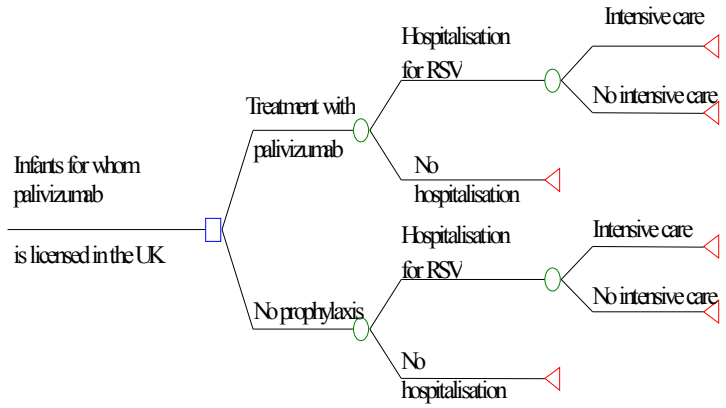
Cost-effectiveness is measured as a ratio of cost to effectiveness with an incremental cost effectiveness ratio (ICER) being the cost-effectiveness of using one treatment in preference to another.[59] This section examines the incremental cost-effectiveness of prophylaxis using palivizumab compared with a strategy of no prophylaxis for the prevention of RSV related lower respiratory tract infection and subsequent hospitalisation. It is written from an NHS perspective and does not take in to account any potential costs or savings external to the NHS e.g. community and parental costs.

We calculate cost per hospital admission prevented and cost per life year gained.

7.2.1 Decision analytic model description

The decision tree used in the decision analytic model for hospital admission rates and costs is shown in **Figure 2** below. The tree represents the scenario for infants for who palivizumab is licensed in the UK.

Figure 2 - Decision tree



For either treatment strategy (palivizumab or no prophylaxis) there is a chance that a child will have to be hospitalised for RSV, and having been hospitalised, there is a further chance that the child will have to be admitted to an intensive care unit. There are costs and probabilities associated with each of these strategies, defined in terms of 8 parameters. The parameters used in this model together with the base-case values and the sources from which these are derived are given in Table 6.

Table 6 : Parameters and base-case values for the decision model

Parameter	Base-case value	Source
Resource use parameters		
Length of stay in hospital (applies to both intensive and non-intensive care)	4 days	HES data for the West Midlands[60]
Unit cost		
Cost of non-intensive paediatric hospital care per day	£310 per day	Netton & Curtis[61], Deshpande[62]
Cost of paediatric intensive hospital care per day	£1065 per day	National Schedule of Reference Costs Critical Care Services[63]
Cost of 6 month course of palivizumab (excluding administration costs)	£2544 for a 3kg child	Costs from BNF[41]
Administration cost of treatment with palivizumab	£100	Assumption made by authors
Effectiveness and prevalence parameters		
Probability of hospitalisation for RSV in the absence of prophylaxis	0.106	The IMpact RSV Study Group[35]
Probability of intensive care conditional on hospitalisation for RSV	0.25	Wang et al. PICNIC study[19], Carbonell-Estrany X et al[36]
Reduction in risk of hospitalisation due to prophylaxis using palivizumab	0.55	The IMpact RSV Study Group[35]
Probability of death from RSV amongst those admitted to hospital	0.01	Placebo arm of The IMpact RSV Study Group[35]
Discount rate for benefits (LYG)	0.015	Current practice

7.2.2 Discussion of parameter values

Resource use parameters and unit costs
Netton and Curtis[61] calculate the cost of non-intensive paediatric hospital care to be £310 per day. The 1999 NHS National Schedule of Reference[63] costs gives a mean average cost of £1065 per day for a paediatric intensive care unit, with costs ranging from £425 to £1,757 for all NHS trusts. The hospital episode statistics for the West Midlands indicated an average length of stay of around 4 days per episode.[60] This is confirmed by Clarke et al[30] with the average length of stay for all at risk infants found to be 4 days for non-intensive paedriatric care and 4 days for intensive care. The cost of a 6-month course of palivizumab (excluding administration costs) is £2544 for a 3kg child, and £4236 for a 6kg child assuming the use of a single 50-mg or 100-mg vial per child each month.[41] It should be noted that the IMpact-RSV[35] trial used a 5-month course of palivizumab, but it is presumed that 6 doses would be given in the UK as the duration of the RSV season runs from October to March. Data on the administration costs associated with palivizumab over a six month period were not available, however, a base-line figure of £100 has been used.

Effectiveness and prevalence parameters
Probabilities of hospitalisation for RSV (in the absence of prophylaxis) vary from 0.005 to as high as 0.37, depending on such factors as length of gestation, whether or not infants have received treatment for BPD, whether or not infants were oxygen-dependent at 28 days, whether or not there are cardiac problems, and so on. The IMpact-RSV study found the incidence of hospitalisation in the placebo group to be 10.6% and the study by Clark et al[30] found that there were 10.4 admissions per 100 at risk infants for a respiratory illness consistent with bronchiolitis. As these studies both consider high risk infants for which the use of palivizumab is indicated the probability of hospitalisation used in the base-case scenario is 10.6% as in the IMpact-RSV study. A number of hospitalised infants with RSV will require admission to an intensive care unit (ICU). The proportions are again highly dependent on degree of prematurity, presence or absence of heart disease or lung disease and so on. One study suggests rates between 25% to 36%[19] and another[36] 25%, a base-case probability of admission to ICU of 0.25 is used. The IMpact-RSV study[35] found that the incidence reduction of RSV hospitalization resulting from the use of palivizumab was 10.6% to 4.8%, a reduction in risk of 55%. For the purposes of the cost-effectiveness analysis, 0.55 is therefore used as the base-case figure for reduction in risk of hospitalisation.

The death rate amongst those receiving no prophylaxis was taken from the placebo arm of the trial. Because most deaths will occur in children who are hospitalised, we have assumed that death rate will be reduced at the same rate as hospital admissions are reduced i.e. RR of death in palivizumab infants of 0.45. The figures from the trial are consistent with this assumption where 1% of children died in the placebo group and 0.4% in the palivizumab group, even though the difference did not reach statistical significance. The discount rate for benefits used in the calculation of cost per life year gained has been set at 1.5% which is the standard figure currently used[64].

7.2.3 Base Case Incremental cost-effectiveness ratio for palivizumab

ICER per hospital admission prevented
The base-case ICER for a was found to be £43,000 per hospital admission prevented.

ICER per life-year gained (LYG)
The base-case ICER was £96,000 per LYG if used for all children who meet the licensed indication.

7.3 Sensitivity Analysis

A sensitivity analysis was carried out varying parameters as detailed in Table 7.

Table 7 - Range of values for parameters used in the sensitivity analysis

Parameter	**Range of Values**
Cost of non-intensive hospital care per day	£200, £600
Cost of intensive hospital care per day	£425, £1757
Cost of course of palivizumab (excluding administration costs)	£2120 for a 3kg child for 5 months £4236 for a 6kg child for 6 months
Administration cost of treatment with palivizumab	£50, £200
Length of stay in hospital (applies to both intensive and non-intensive care)	5 days for both intensive and non-intensive care
Probability of hospitalisation for RSV in the absence of prophylaxis	Varied continuously. (Subgroup data from trials are shown in Table 4)
Probability of intensive care conditional on hospitalisation for RSV	0.1, 0.5

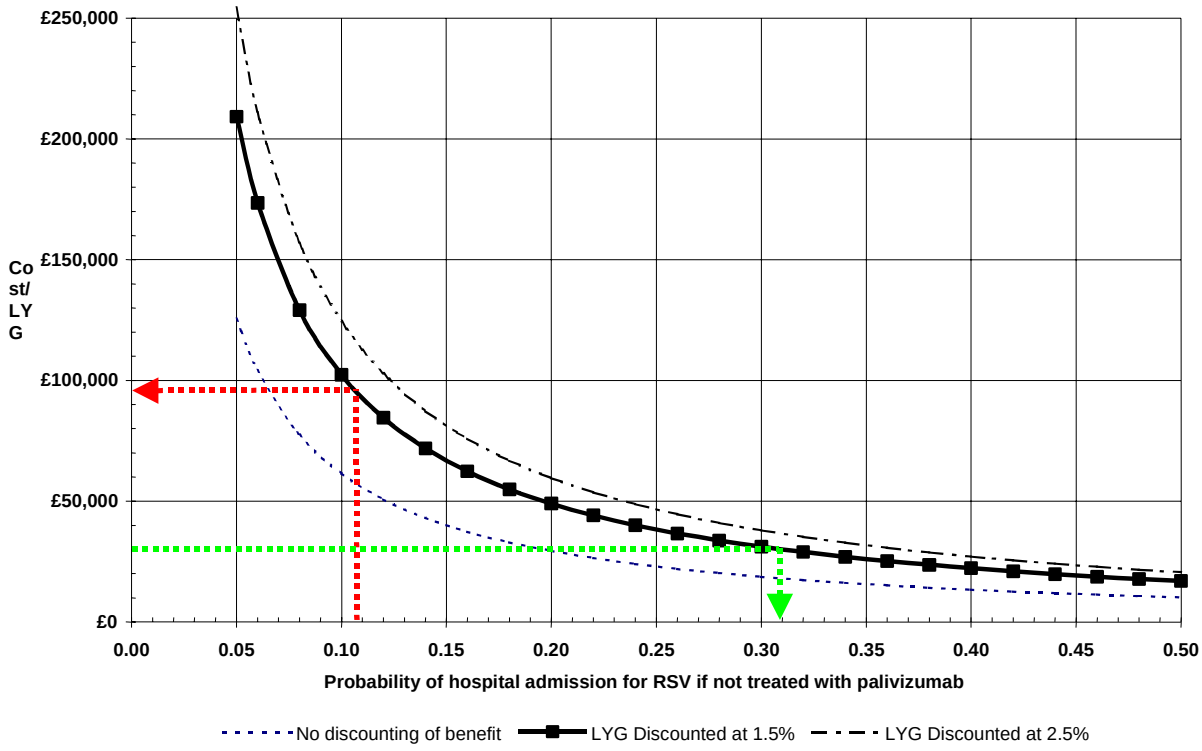
The results of the sensitivity analysis are displayed in Table 8.

Table 8 - Results of the sensitivity analysis

Parameter varied	Value/£	Cost/ admission prevented	Cost/LYG
Cost of non-intensive hospital care	200	£44,000	£97,000
	600	£42,000	£94,000
Cost of intensive hospital care per day	425	£44,000	£98,000
	1757	£43,000	£95,000
Cost of palivizumab reduced to 5 months treatment	2120	£36,000	£80,000
Cost of palivizumab increased for 6kg child (for 6/12)	4236	£72,000	£161,000
Administration cost of treatment with palivizumab	50	£42,000	£94,000
	200	£45,000	£100,000
Length of stay in hospital (applies to both intensive and non-intensive care)	5	£43,000	£95,000
Probability of intensive care conditional on hospitalisation for RSV	0.1	£44,000	£97,000
	0.5	£43,000	£95,000
Probability of hospitalisation for RSV in the absence of prophylaxis	See Figure 3 -Cost/LYG as the level of risk of hospitalisation of the infants treated increases		

The sensitivity analysis indicates that the ICERs are relatively insensitive to variations in all parameters in the table apart from 'probability of hospitalisation for RSV in the absence of prophylaxis' (see below).

Figure 3 - Cost/LYG as the level of risk of hospital admission of the infants treated increases



7.3.1 Varying probability of hospital admission for RSV in the absence of prophylaxis

Not all infants who meet the licensed indication for RSV prophylaxis will have the same probability of hospital admission or death. Paediatricians using palivizumab in the West Midlands Region have up until now generally reserved its use for those infants they perceive to be at highest risk of being hospitalised for an RSV related lower respiratory tract infection. Figure 3 shows what happens to the cost per life year gained when the probability of hospitalisation of the infants treated is varied between 5and 50%. The RR of hospitalisation for children receiving palivizumab compared to those who are not is the same as in the IMpact RSV trial at 0.45. This model assumes that the threshold for hospital admissions remains the same and that therefore the proportion of children admitted to hospital who die remains the same.

The red dotted line shows the baseline probability of hospitalisation for RSV across all infants for whom palivizumab is indicated (i.e 10.6% taken from the placebo arm of the IMpact RSV trial). This shows that the ICER for palivizumab when used generally in accordance with the licensed indications is over £95,000 per hospital admission prevented. The green dotted line shows what the probability of admission would have to be for palivizumab to be a cost effective alternative to no prophylaxis i.e., a probability of hospitalisation for RSV of 31% or above.

8 Conclusions

Palivizumab appears to be an effective prophylaxis for the prevention of serious lower respiratory-tract infection caused by RSV and requiring hospitalisation in high-risk infants. This conclusion is based on one large randomised controlled trial and is consistent the results of a number of post-marketing uncontrolled follow-up studies. In the Impact-RSV study palivizumab reduced the likelihood of hospitalisation for RSV by 55%.

In our base case cost-effectiveness model palivizumab did not represent good value when used in all children who meet the licensed indication for palivizumab. However, this is not how the drug is being used by clinicians in the UK who reserve it for those infants with the highest risk. A sensitivity analysis varying the probability of hospitalisation in the absence of prophylaxis shows that palivizumab becomes cost effective as the probability of hospitalisation increases. When the probability is 31% or greater the ICER drops to below £30,000 per life year gained. Reports[1] have indicated that the highest risk group are those infants that have bronchopulmonary dysplasia (chronic lung disease) that are supported by oxygen at home, however, the IMpact RSV published trial data does not permit an estimation of prognostic indicators.

The findings of this report are consistent with the current judicious use by clinicians. The current practice of providing palivizumab to infants at high risk of hospitalisation appears to be cost-effective. As this is a new drug, if palivizumab is used the morbidity and mortality from RSV should be studied in those high-risk infants who do and do not receive prophylaxis.

9 Further Research

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.

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Appendix 1

American Academy of Paediatrics Guidelines for the Use of palivizumab and RSV-IGIV

1. Palivizumab or RSV-IGIV prophylaxis should be considered for infants and children younger than 2 years of age with CLD who have required medical therapy for their CLD within 6 months before the anticipated RSV season. Palivizumab is preferred for most high-risk children because of it's ease of administration, safety and effectiveness. Patients with more severe CLD may benefit from prophylaxis for two RSV seasons, especially those who require medical therapy. Decisions regarding individual patients may need additional consultation from neonatologists, intensivists, or pulmonologists. There are limited data on the efficacy of palivizumab during the second year of age; risk of severe RSV disease exists for children with severe CLD who require medical therapy. Although those with less severe underlying disease may receive some benefit for the second season, immunoprophylaxis may not be necessary.

2. Infants born at 32 weeks of gestation or earlier without CLD or who do not meet the criteria in recommendation 1 may also benefit from RSV prophylaxis. In these infants, major risk factors to consider are gestational age and chronological age at the start of the RSV season. Infants born at 28 weeks of gestation or earlier may benefit most from prophylaxis up to 12 months of age. Infants born at 29-32 weeks of gestation may benefit most from prophylaxis up to 6 months of age. Decisions regarding duration of prophylaxis should be individualised, according to the duration of the RSV season. Practitioners may want to use RSV rehospitalization data from their own region to assist in the decision making process.

3. Given the large number of patients born between 32 to 35 weeks and the cost of the drug, the use of palivizumab in the population should be reserved for those infants with additional risk factors until more data are available.

4. Palivizumab or RSV-IGIV are not licensed by the FDA for patients with CHD. Available data indicate that RSV-IGIV is contraindicated in patients with cyanotic CHD. However, patients with CLD who are premature, or both, who meet the criteria in 1 and 2 and who also have asymptomatic acyanotic CHD may benefit from prophylaxis.

5. Palivizumab or RSV-IGIV prophylaxis has not been evaluated in randomised controlled trials in immunocompromised children. Although specific recommendations for immunocompromised patients cannot be made, children with severe immunodeficiencies may benefit from prophylaxis. If these infants are receiving standard immune globulin intravenous monthly, physicians may consider substituting RSV-IGIVIV during the RSV season.

6. RSV prophylaxis should be initiated at the onset of the RSV season and terminated at the end of the RSV season.

7. RSV is known to be transmitted in the hospital setting and to cause serious disease in high risk infants. In high risk hospitalised infants, the major means to prevent RSV disease is strict observance of infection control practices, including the use of rapid means to identify and cohort RSV-infected infants. If an RSV outbreak is documented in a high-risk unit, primary emphasis should be placed on proper infection control practices. The need for and efficacy of prophylaxis in these situations has not been evaluated.

Source: American Academy of Pediatrics[43]