Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The administration of prophylactic palivizumab against respiratory syncytial virus (RSV) was compared with no prophylaxis among infants with haemodynamically significant congenital heart disease (CHD). It was assumed that a 90-mg dose of palivizumab (Synagis; MedImmune Inc.) was administered to each patient. Each patient received five doses during the RSV season.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis and cost-utility analysis.

Study population
The study population comprised a hypothetical cohort of 10,000 paediatric patients with CHD. The average age of the patients was not specified but was inferred to be 0.55 years. Only children diagnosed with haemodynamically significant CHD (such as cyanosis, congestive heart failure, pulmonary hypertension, and some ventricular septal defects) were included in the study. Diagnoses such as transposition of the great arteries were excluded because, after surgical repair, these patients have normal postoperative haemodynamics.

Setting
The study settings were primary and tertiary care. The economic study was conducted in the USA.

Dates to which data relate
The effectiveness evidence data were gathered from studies and statistics published between 1992 and 2004. The cost data were taken from published and electronic sources relating to 1982 to 2004, and were adjusted to 2002 prices.

Source of effectiveness data
The estimates for the final outcomes were derived from a synthesis of published studies. In addition, one of the estimates of effectiveness was based on authors’ assumptions.

Modelling
A decision analysis model was used to estimate the costs and benefits of each strategy. Half of the cohort was assigned to receive palivizumab, and half was assigned to the no-prophylaxis group. The time horizon of the analysis was established so as to cover the costs until discharge from hospital. However, the benefits were estimated over the patient’s lifetime.
Outcomes assessed in the review
The following outcomes were assessed from an ad hoc review of the literature:

the percentages of patients with various heart lesions in the cohort;
the probability of hospitalisation for RSV among paediatric patients who did and did not receive palivizumab prophylaxis;
the length of hospital stay for patients who did and did not receive palivizumab prophylaxis; and
the number of days in an intensive care unit (ICU) for patients who did and did not receive palivizumab prophylaxis.

Study design and other criteria for inclusion in the review
Most of the parameter estimates were taken from a single multi-centre placebo-controlled trial (Feltes et al. 2003, see 'Other Publications of Related Interest' below for bibliographic details). The authors also referred to a population-based study and census data for the derivation of an estimate of disease prevalence (Botto et al. 2001, see 'Other Publications of Related Interest' below for bibliographic details). The remaining 6 data sources were not described.

Sources searched to identify primary studies
Not reported.

Criteria used to ensure the validity of primary studies
Not reported.

Methods used to judge relevance and validity, and for extracting data
Not reported.

Number of primary studies included
The values for the parameters in the model were obtained from 9 published studies and reports.

Methods of combining primary studies
In general, the primary studies were not combined.

Investigation of differences between primary studies
Not reported.

Results of the review
The following parameters were used in the model.

The proportions of patients with various heart lesions in the cohort were as follows:
heterotaxy 3.3%,
tetralogy of fallot 14.1%,
double outlet right ventricle 3.9%,
truncus arteriosus 2.3%,
arteriovenous canal 9.7%,
total anomalous pulmonary veins 2.7%,
Ebstein's anomaly 1.4%,
tricuspid atresia 1.2%,
pulmonary atresia intact ventricular septum 1.9%,
pulmonary atresia other 6.3%,
hypoplastic left heart syndrome 7.6%,
aortic arch hypoplasia 2.3%,
ventricular septal defect 15.5%,
other major defects 23.9%, and
cardiomyopathy 3.5%.

The probability of hospitalisation was 5.3% for patients who received palivizumab prophylaxis and 9.7% for those who did not.
The length of hospital stay was 10.7 days for patients who received palivizumab prophylaxis and 13.3 days for those who did not.
The number of days in the ICU was 15.9 days per 100 children who received palivizumab prophylaxis and 71.2 days per 100 children who did not.

Methods used to derive estimates of effectiveness
The authors made some assumptions in their model, which supplemented the data derived from the literature.

Estimates of effectiveness and key assumptions
For patients with ventricular septal defect, only 25% would have a haemodynamically significant lesion.

The mortality rate for patients who were admitted to the hospital would be 3% whether they had received palivizumab or not.

By reducing the hospital admission rate for RSV bronchiolitis, palivizumab would result in a 0.13% reduction in overall mortality.

The average life expectancy of infants in the cohort was 77.2 years, based on the US average life expectancy in 2002.

Measure of benefits used in the economic analysis
The measures of health benefit used were the life-years saved (LYS) and quality-adjusted life-years (QALYs) saved. These were derived from the model and were discounted at an annual rate of 3%. The utility value of adult congestive heart failure (CHF) patients was used as a proxy for CHD lesions that resulted in long-term exercise limitations. Health-related quality of life scores for adults with CHF were obtained from a single published study (Fryback et al. 1993, see 'Other Publications of Related Interest' below for bibliographic details) that assessed utility using the time trade-off method. The utility value of adult CHF patients was 0.71. The model assumed that CHD patients with lesions that were not associated with long-term exercise limitation had a utility value of 1.0.
The model also estimated the number of RSV-related deaths averted per 5,000 patients.

Direct costs
The direct costs of health care and the direct costs to the patients’ parents were included in the analysis. The costs included were for palivizumab and its administration, ICU and non-ICU hospital care, and the parents’ travel costs associated with administration of the prophylaxis. Overhead allocation and office staff time were considered to be negligible and, hence, were not included in the analysis. The drug costs came from average wholesale prices, while drug administration costs were based on physician and nursing mean hourly wages estimated from US Department of Labor sources. The costs of hospitalisation were derived from a published analysis of bronchiolitis hospitalisation costs from a consortium of 10 children’s hospitals and were compared with data from published literature. Travel costs were calculated from the Internal Revenue Service mileage reimbursement rate.

The cost estimates were reported separately from other model parameters. Discounting was applied at a rate of 3%. The costs were adjusted to 2002 prices, although the method used was not reported. The total costs were derived using modelling.

Statistical analysis of costs
The costs were treated deterministically. No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs were included, which was appropriate given the study perspective. The indirect costs reported were the productivity losses incurred by the parent as a consequence of attending appointments for the administration of prophylaxis, or for staying with the infant during periods of hospitalisation. The number of work days lost and the value of each day were reported separately. The number of work days lost was based on the number of days of hospitalisation, which was taken from a published study. The value of a work day was based on the average wage, as reported by the US Bureau of Labor and Statistics 2002. Discounting was applied at a rate of 3%.

Currency
US dollars ($).

Sensitivity analysis
A sensitivity analysis was conducted to investigate the robustness of the results under the uncertainty surrounding the parameters of the model. The methods used were not described. However, it is likely that one-way sensitivity analyses were undertaken. The authors did not justify the ranges over which the variables were tested. The ranges appear to have been based on their assumptions rather than being derived from the literature. The parameters investigated were the RSV-related hospital mortality rate, the utility value for CHD lesions that resulted in long-term exercise limitation, and a differential reduction in hospital mortality between patients who received prophylaxis and those who did not.

Estimated benefits used in the economic analysis
The number of RSV-related deaths averted by prophylaxis was 6.6 per 5,000 patients. The authors calculated the duration of benefits over the patient's remaining lifetime, which was estimated to be 76.65 years.

Compared with a non-prophylaxis strategy, prophylaxis with palivizumab resulted in 505.89 undiscounted LYS per 5,000 patients. Applying a 3% discount rate reduced this to 203.33 LYS.

The number of QALYs gained was not reported.

Cost results
The total discounted costs of the intervention strategy were $37,406,643 (i.e. $32,815,000 total cost of the palivizumab regimen plus $4,591,643 total hospital costs), while the total discounted costs of the comparator strategy were $16,990,890. This included the costs of hospitalisation for RSV-related bronchiolitis. The palivizumab strategy resulted in a net loss of $20,415,753. A discount rate of 3% was applied.

Synthesis of costs and benefits
The costs and benefits were summarised in the form of a cost-effectiveness ratio and a cost-utility ratio by dividing the net costs by the number of LYS or QALYs saved.

The findings were sensitive to the hospital mortality rate for RSV-related bronchiolitis, and to a differential rate of hospital mortality among infants who had received prophylaxis. The results were relatively robust to changes in the utility value.

Authors' conclusions
The cost of routine palivizumab prophylaxis against respiratory syncytial virus (RSV)-related bronchiolitis for young children with haemodynamically significant congenital heart disease (CHD) is relatively high for the benefit gained. Palivizumab does not result in cost-savings in relation to the direct and indirect costs of RSV hospitalisation.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was given for the comparator used (i.e. no prophylaxis) it would appear to represent current practice in the authors' setting. If another prophylaxis for RSV-related bronchiolitis were available it would be more appropriate to have included that as the comparator. You should decide if the comparator represents current practice in your own setting.

Validity of estimate of measure of effectiveness
A systematic review of the literature was not undertaken. Although this is common practice with models, it does not always ensure that the best data available are used in the model. The authors gave few details of the methodology undertaken in their review. The parameters were not derived from a synthesis of the primary studies, and the authors based half of their estimates on the results from a single trial. Full details of the primary studies were not provided. The authors made several assumptions in the model, which were explicitly reported. A sensitivity analysis was conducted on three of the parameters, but it was unclear how the ranges were derived and whether they were appropriate.

Validity of estimate of measure of benefit
The summary measures of benefit were the LYS and QALYs saved. These were obtained from the decision analysis model. Owing to a lack of quality of life studies among children, the utility values were extrapolated from a study among adult patients with CHF that used the time trade-off approach to estimate utility. The validity of the QALYs saved relies on the unproven assumption that the quality of life for children with CHD who suffer with long-term exercise intolerance is the same as that for adults with CHF. The authors explored a range of utility values in the sensitivity analysis. The benefits were appropriately discounted.

Validity of estimate of costs
The analysis of the costs was performed from a societal perspective. As such, it appears that all the relevant categories of costs were included in the analysis. However, some relevant costs were omitted from the analysis. In particular, the authors did not include the outpatient costs for treating RSV bronchiolitis. They justified this by referring to other studies that had shown that the direct costs of an outpatient RSV infection among CHD patients were relatively low. The productivity losses incurred by the parents after hospital discharge and in cases of outpatient RSV infections were also not included. The authors reported that determining the indirect costs for illness and hospitalisation of a child was
controversial. It was unclear whether the consideration of these costs would have altered the authors’ conclusions.

The costs were reported separately from other model parameters, thus enhancing the reproducibility of the study in other settings. The estimates of resource use were taken from the literature. The costs were treated deterministically, and the robustness of the estimates used was not explored in a sensitivity analysis. Discounting was applied to the costs. It was unclear whether costs or charges were reported. The cost data were taken from sources published between 1982 and 2004, and were reported for a single price year. The method used to adjust the costs was not reported.

**Other issues**

The authors compared their findings with those from other studies that had investigated prophylaxis with palivizumab in different patient groups. They found their cost-effectiveness results were in agreement with published studies. The authors did not directly address the issue of the generalisability of the results to other settings. The estimated number of QALYs saved was not reported. The authors referred to the patient population variously as infants, young children and children, and it was unclear as to precisely which age group their findings related to.

The authors acknowledged several limitations associated with their study. First, there was no research to support the potential benefit that palivizumab lowers the risk of in-hospital mortality. Second, the authors assumed a normal life expectancy for all CHD patients despite evidence to the contrary, and this could result in an overestimation of the benefits of prophylaxis. Finally, if CHD patients experienced adverse long-term effects as a consequence of an RSV infection, such as delayed surgery, the benefits of prophylaxis would be underestimated.

**Implications of the study**

The authors stated that, given the relatively high cost of palivizumab and the large number of potential recipients, further evaluation of its use in this patient group is necessary. Research should focus on identifying cardiac lesions associated with the highest risk of mortality, and patients who are most able to benefit from prophylaxis. The practitioners' adherence to guidelines on RSV prophylaxis should also be analysed.

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None stated.

**Bibliographic details**


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**Other publications of related interest**


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