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

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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 use of palivizumab (Synagis), a humanised murine monoclonal antibody produced by recombinant technology, for the prevention of serious lower respiratory tract infection was examined.

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The population studied comprised high-risk infants. These were defined as those born at 35 weeks' gestation or less and who were less than 6 months old at the onset of the RSV season, or children younger than 2 years old who had received treatment for bronchopulmonary dysplasia in the previous 6 months.

Setting
The setting was secondary care. The economic study was carried out in the UK.

Dates to which data relate
The effectiveness evidence was gathered from studies dating from 1995 to 2000, with the majority of evidence coming from a study dated 1998. The resource use data were gathered from published data from 2000. The unit cost data were collected from a range of publications dating from 1999 to 2001.

Source of effectiveness data
The effectiveness data were derived from a systematic review of the literature.

Modelling
A decision analytic model, in the form of a basic deterministic decision tree, was used to project hospital admission rates and costs.

Outcomes assessed in the review
The primary outcome assessed was the hospitalisation rate. The secondary outcomes included receipt of intensive care, mechanical ventilation rates, morbidity and mortality. Adverse effects of the technologies were considered in the review, but were not included in the decision model.
Study designs and other criteria for inclusion in the review
Randomised controlled clinical trials comparing palivizumab with placebo or alternative prophylaxis were included in the review. However, only effectiveness data derived from the placebo trials were used to populate the decision tree. Other study designs were included for the purposes of background information.

Sources searched to identify primary studies
The authors searched MEDLINE (1966 to 2000), CINAHL, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, EMBASE (1980 to 2000), and databases provided by the Centre for Reviews and Dissemination (DARE, NHS EED, HTA). In addition, other sources (e.g. the Internet) were consulted, conference proceedings and relevant journals were handsearched, and experts were contacted.

Criteria used to ensure the validity of primary studies
The criteria used to ensure the validity of the primary studies included whether there had been a focused research question, randomisation, specific inclusion and exclusion criteria, clearly defined patient groups, intention to treat analysis and the reporting of loss to follow-up.

Methods used to judge relevance and validity, and for extracting data
Two reviewers independently assessed the quality of the studies (using the above criteria). Two reviewers also independently extracted the data, and any differences were resolved by discussion.

Number of primary studies included
One randomised controlled trial (the IMpact-RSV study) was used as the basis for the final analysis. Three other trials were included for background information and two further studies were included in the development of effectiveness model parameters.

Methods of combining primary studies
Most values were reported selectively from the IMpact-RSV study. The exception was the probability for intensive care, whereby the lesser of two study values was adopted.

Investigation of differences between primary studies
An investigation of differences between the primary studies was not reported, owing to the reliance upon one trial for evidence of effectiveness.

Results of the review
The results for effectiveness and prevalence parameters (taken from the Impact-RSV trial) were presented as percentage probabilities.

Hospitalisation for RSV in the absence of prophylaxis was 10.6%.

Admittance to intensive care was 25% (range: 25 - 36).

The reduction in risk of RSV hospitalisation resulting from the use of palivizumab was 55% (actual reduction in incidence was 10.6% to 4.8%).

The probability of death (taken from the placebo arm of the trial) was 1%.
Measure of benefits used in the economic analysis
The measures of benefit used were the number of hospital admissions prevented and the number of life-years gained (LYG). The discount rate for LYG was set at 1.5%, which was stated to reflect the standard rate used in practice.

Direct costs
Health service costs were included in the analysis. These related to nonintensive and intensive paediatric daily hospital care, along with the cost of a 6-month course of palivizumab. Administration costs (based on authors’ assumptions) relating to treatment with palivizumab were reported separately. The unit costs for nonintensive care were derived from primary studies. For intensive care, data were taken from Department of Health statistics while the drug costs were derived from the British National Formulary. The resource quantities and the costs were reported separately. Resource use data (length of hospital stay) were taken from Department of Health hospital episode statistics (1995 to 1999).

Statistical analysis of costs
The costs were presented as a mixture of deterministic and descriptive data.

Indirect Costs
No indirect costs were reported.

Currency
UK pounds sterling (£).

Sensitivity analysis
A one-way, simple, sensitivity analysis was used to show the effects of varying the data (costs, resource use and effectiveness parameters) upon the costs per hospital admission and per LYG. The range of values used was not fully justified for each parameter, although it appears that sub-group data from the Impact-RSV trial has been used for the probability of hospitalisation.

Estimated benefits used in the economic analysis
The authors presented incremental benefits for hospitalisations prevented and LYG, only in the context of a base-case incremental cost-effectiveness ratio (ICER; see ‘Synthesis of Costs and Benefits’ section).

Cost results
The cost of a 6-month course of palivizumab was 2,544 for a 3-kg child.

The associated administration cost was 100.

The costs of nonintensive and intensive paediatric hospital care were 310 and 1,065 per day, respectively.

Synthesis of costs and benefits
The base-case ICER for palivizumab was 43,000 per hospital admission prevented, and 96,000 per LYG if used for all children who met the licensed indication.

The results of the sensitivity analysis showed that the ICERs were generally insensitive to variations in all parameters. The exception was the probability of hospitalisation for RSV in the absence of prophylaxis.

The probability of RSV-related admission to hospital would need to be 31% or above for the intervention drug to be a cost-effective alternative to no prophylaxis.
Authors’ conclusions
Palivizumab was an effective prophylaxis for preventing serious respiratory tract infections caused by respiratory syncytial virus (RSV) and requiring hospitalisation in high-risk children. However, the drug is not cost-effective when used in all children who meet the licensed indication for use. It only becomes so in those at the highest risk and when the probability of hospitalisation increases to 31% or above.

CRD COMMENTARY - Selection of comparators
It would appear that palivizumab was chosen to represent a newly developed passive immunisation against RSV infection in comparison with other agents (e.g. RSV intravenous immunoglobulin, which is not currently licensed for use in the UK). Comparisons with placebo were also considered, allowing the active value of the drug to be evaluated without an active agent as an alternative. You should decide if these represent widely used technologies in your own setting.

Validity of estimate of measure of effectiveness
The authors described the systematic identification, selection and synthesis of evidence to form estimates of effectiveness. The review methodology was sufficiently robust to identify relevant research and reduce potential biases. Estimates of effectiveness were largely derived from one, apparently well-conducted, trial, which reflects the early stage of research in this area. Indeed, the authors pointed to future studies to investigate the generalisability of the results and safety of this intervention to other populations (such as those with congenital heart disease and cystic fibrosis).

Validity of estimate of measure of benefit
The chosen benefit measures (hospital admissions prevented and LYG) were appropriate, although the measurement tool was not reported for LYG.

Validity of estimate of costs
The authors included relevant items in relation to hospital costs, as part of the NHS perspective, although community-based costs might also have been relevant to reflect any follow-up services beyond the initial injection. The costs were reported separately from resource use, thus enhancing the reproducibility of the results in other settings. The resource quantities were derived from a published source and a sensitivity analysis was appropriately conducted. The costs, which were derived from a mixture of published sources and authors’ assumptions, were also appropriately explored in a sensitivity analysis, although not all of the ranges of values used were fully justified. This potentially limits the interpretation of the findings. The price year was not reported, thus limiting any future reflation exercise.

Other issues
There appears to have been limited scope for comparing the results with those from other studies, given that palivizumab is a relatively new intervention. However, three large uncontrolled follow-up studies were cited to endorse the findings in relation to hospitalisation rates. The issue of generalisability was not directly addressed. The findings of the study were presented in full and the conclusions reflected the scope of the analysis.

Implications of the study
The authors recommended no changes to the current clinical practice of using palivizumab only in infants at high risk of hospitalisation in the UK. They also recommended the commissioning of a systematic review of prognostic factors for hospital admission, to enable the development of clinical guidelines for identifying the most appropriate patients for treatment with the drug.

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