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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Authors' objectives
To address the question of how effective and cost-effective palivizumab (Synagis) is, compared with placebo or alternative prophylaxis, in the prevention of respiratory syncytial virus (RSV) infection in infants at high risk of infection.

Searching
The following databases were searched for reviews and primary studies: MEDLINE (from 1966 to 2000), CINAHL, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, EMBASE (from 1980 to 2000), DARE, NHS EED and HTA. The databases were searched in October 2000 and revisited in January 2001 to check for more recent papers.

The MeSH and textwords 'MEDI-493', 'palivizumab', 'Synagis', 'RSV' and 'respiratory syncytial virus' were used with the following search (adapted for each platform): ("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. Reviews and primary studies with relevant subject matter were identified by inspection of the titles and abstracts, and by obtaining papers where necessary. Papers written in any language were considered.

The Internet was searched, in particular, the FDA Centre for Drug Evaluation and Research site. Abstracts from the World Congress on Lung Health and 10th European Respiratory Society Annual Congress, and from the 94th, 95th and 96th American Thoracic Society International Conferences were handsearched, as were recent copies of Paediatric Respiratory Reviews). Abbott Laboratories (the manufacturer of palivizumab) and subject experts were contacted for further references. Citations in all the papers obtained were checked for additional references.

A search for economic analyses of palivizumab was also conducted.

Study selection
Study designs of evaluations included in the review
All randomised controlled clinical trials comparing palivizumab with placebo or alternatives were included.

Specific interventions included in the review
Studies were included if the intervention was palivizumab versus placebo or any alternative prophylaxis (i.e. RSV intravenous immunoglobulin). The participants in the one identified study were randomised to receive five injections of either palivizumab (15 mg/kg) or an equivalent volume of placebo by intramuscular injection every 30 days. The placebo was identical in appearance to palivizumab; the same formulation without antibody with 0.02% Tween-80 added.

Participants included in the review
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' gestation or less and who were younger than 6 months old at the onset of RSV, or children less than 2 years old who had received treatment for bronchopulmonary dysplasia (BPD) within the preceding 6 months.

In the one identified study, children with congenital heart disease other than patent ductus arteriosus or hemodynamically insignificant septal defect, were excluded. Children were also excluded if they were hospitalised and...
had an expected hospitalisation time of more than 30 days, or if they required mechanical ventilation at the time of entry. In addition, infants were excluded if they suffered from hepatic or renal dysfunction, seizure disorder or immunodeficiency; had received immunoglobulins within the past 3 months; 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 6 months or less.

Overall, the mean age of the participants was 6 months and the mean weight was 5 kg. Most of the participants were premature and had been hospitalised at least once since birth. Approximately 80% of the participants had a gestational age equal to or less than 32 weeks, and around one third of the participants were twins (multiple births).

Outcomes assessed in the review
The primary outcome considered was hospitalisation rates. The secondary outcomes included receipt of intensive care, mechanical ventilation rates, morbidity and mortality.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Information relating to the quality of the included studies was collected. This included whether: the study addressed a clearly focused question; the participants were randomised to treatment groups; the randomisation method was specified; the inclusion and exclusion criteria were specified; there was clear definition of the treatment groups; intention to treat analysis was used; and loss to follow-up was reported. The quality assessment was undertaken independently by two researchers. It was not stated how any disagreements were resolved.

Data extraction
Two reviewers independently extracted the data and resolved any differences by discussion.

Methods of synthesis
How were the studies combined?
It was not possible to combine the studies, as only one study was found that met the inclusion criteria. Publication bias was not assessed.

How were differences between studies investigated?
It was not possible to investigate differences between the studies, as only one study was found which met the inclusion criteria.

Results of the review
One large randomised, double-blind, placebo-controlled, multicentre trial with a total of 1,502 participants was included in the review.

The results demonstrated a 55% reduction in the risk of hospitalisation attributable to RSV with palivizumab (95% confidence interval, CI: 38, 72, P=0.0004). Statistically-significant decreases in hospitalisation were seen in both subgroups: children with BPD experienced a 39% reduction (95% CI: 20, 58, P=0.038), while premature infants without BPD experienced a 78% reduction (95% CI: 66, 90, P<0.001). Trends in reduction of RSV hospitalisation rates were similar in all of the countries participating in the study, i.e. USA, UK and Canada. In general, palivizumab appeared to be effective in both patients who are premature but do not have BPD, and those who are premature and have BPD. However, the greatest effect was within the subset of premature patients without BPD.

Children randomised to palivizumab had significantly fewer total days (per 100 children) of RSV hospitalisation (P<0.001), days with increased oxygen (P<0.001), and days with a lower respiratory illness score of at least three (P<0.001).
**Cost information**
The authors state that insufficient data on quality of life made it inappropriate for them to conduct a cost-utility analysis. However, the evidence on effectiveness obtained from the trial identified, along with the cost data on hospitalisation, allowed a cost-effectiveness analysis of palivizumab in comparison with placebo to be carried out.

The economic analysis was based on effectiveness data from the RCT and cost data on hospitalisation. The base-case incremental cost effectiveness ratio was found to be £43,000 per hospital admission prevented, and £96,000 per life-year gained if used for all children who meet the licensed indication.

**Authors' conclusions**
Palivizumab appeared to be effective in preventing serious lower respiratory tract infection caused by RSV and 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. This is not how the drug is currently used by clinicians in the UK; they reserve it for those children at greatest risk.

**CRD commentary**
The authors stated their review question and the inclusion criteria clearly. The literature search was adequate and included handsearches of abstracts from conferences, and contact with the manufacturers of palivizumab and subject experts, in an attempt to identify grey literature. No analyses were conducted to assess publication bias. No language restrictions were applied.

The validity of the individual studies was systematically assessed. The authors did not report details relating to the decision-making process for selecting the studies, such as how many of the reviewers were involved, whether the studies were examined independently, or whether the reviewers were blinded to the source.

Details of the studies were reported thoroughly in the text, with the results presented in tabular format and supplemented by a narrative discussion.

Only one study was identified that was eligible for inclusion in the review, which is a potential source of bias. However, the authors' conclusions appear to be justified.

**Implications of the review for practice and research**
Practice: The authors state that the recommendation for the use of palivizumab (Synagis), in the prevention of 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 also fall. However, although the trial results were consistent with such a fall, the trial was not large enough to demonstrate a statistically significant reduction in the 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.

Research: The authors state that a systematic review of the prognostic factors for hospital admission should be undertaken. This should permit the development of clinical guidelines, to enable clinicians to identify the most appropriate children to be treated with palivizumab.

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**Bibliographic details**
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