Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis

Stevens T P, Sinkin R A, Hall C B, Maniscalco W M, McConnochie K M

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
Prophylaxis with either respiratory syncytial virus (RSV) immune globulin (RSV-Ig) or RSV monoclonal antibody (palivizumab) for preventing RSV hospitalisation in a cohort of preterm infants born at 32 weeks' gestation or earlier.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population consisted of a cohort of preterm infants born at 32 weeks' gestation or earlier, surviving until discharge from the regional neonatal intensive care unit.

Setting
Tertiary care. The economic analysis was carried out in the USA.

Dates to which data relate
Effectiveness data for the cohort not using RSV prophylaxis corresponded to a 5-year period, which included the RSV seasons of 1992 through 1996. The rates of reduction in RSV hospitalisation after RSV prophylaxis were obtained from two studies published in 1997 and 1998. The price year was not reported.

Source of effectiveness data
The evidence for the final outcomes was based on a single study and a literature review.

Link between effectiveness and cost data
Costing appears to have been conducted retrospectively on the same patient sample as that used in the effectiveness analysis; applying the RSV reduction rates obtained from the literature.

Study sample
Power calculations were not used to determine the sample size. The study sample consisted of 1,029 consecutive premature infants born at 32 weeks' gestation or earlier, surviving to discharge from the regional neonatal intensive care unit. Cohort members were grouped for analysis by gestational age (165 in the age group 26 weeks and under, 171 in the 27-28 week age group, 240 in the over 28-30 week age group and 453 in the over 30-32 week age group) and duration of respiratory support in the neonatal period, expressed as weeks of postconceptual age (PCA) (131 in the 36
and over group, and 898 in the under 36 group). In an attempt to extrapolate the results to the entire study region, a regional database was used which showed that 2,051 children younger than 1 year were admitted to regional hospitals with a lower respiratory tract infarction (LRTI) during the study period. Of these 2,051 infants, 1,390 (67.8%) were admitted to a university hospital.

**Study design**
This was a retrospective cohort study, carried out in a 12-county neonatal network served by a regional centre (children's hospital). The duration of follow-up was until 1 year of corrected age (1 year past 40 weeks of PCA). No information was given regarding loss to follow-up. Children who were hospitalised with RSV infections at university hospitals were identified through a database of all hospitalised children with a positive RSV culture or antigen detection assay. The authors extrapolated from data collected at the university hospitals to generate estimates for the entire study region. In extrapolating to the region, the fundamental assumption was that the ratio of university hospital to regional admissions for the cohort of premature infants was the same as the ratio of university hospital to regional admissions for infants admitted with any LRTI.

**Analysis of effectiveness**
The principle (intention to treat or treatment completers only) used in the analysis of effectiveness was not explicitly specified. The clinical outcome measure was RSV hospitalisation rate; which was ascertained directly at the study hospitals and estimated for hospitals throughout the study region. The rates were also reported in terms of subgroups of infants.

**Effectiveness results**
The effectiveness results were as follows:

The probability of hospitalisation with an RSV-associated illness for infants born at 32 weeks' gestation or earlier was estimated at 11.2%.

The incidence of RSV hospitalisation increased with decreasing gestational age (13.9% versus 4.4% for infants born at 26 weeks' or less gestation versus those born at 30-32 weeks' gestation).

Infants requiring respiratory support at 36 weeks PCA or older had a higher hospitalisation rate (16.8% versus 6.2%) than infants requiring respiratory support at less than 36 weeks PCA did.

For infants requiring respiratory support at less than 36 weeks PCA, the incidence of RSV hospitalisation still increased with decreasing gestational age (10.2% versus 4.3% for infants of 26 weeks' or less gestation versus those of 30-32 weeks' gestation).

**Clinical conclusions**
The study results show that gestational age as well as duration of respiratory support contribute to the need for hospitalisation with an RSV-associated illness.

**Outcomes assessed in the review**
Estimated percent reductions in the RSV hospitalisation for all subjects, those 36 weeks of PCA or older, and those less than 36 weeks of PCA.

**Study designs and other criteria for inclusion in the review**
Not reported.
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
Two studies were included in the review.

Methods of combining primary studies
Each set of values was based on an individual study.

Investigation of differences between primary studies
Not reported.

Results of the review
The estimated percentage reductions in RSV hospitalisation for RSV-Ig were 41% for all subjects, 49% for those of 36 weeks or less PCA, and 20% for those of less than 36 weeks PCA.

The estimated reductions for palivizumab were 55% for all subjects, 39% for those of 36 weeks or less PCA, and 78% for those of less than 36 weeks PCA.

Measure of benefits used in the economic analysis
The measure of benefits used was the number of RSV hospitalisations prevented, which was estimated by multiplying the number of RSV hospitalisations (when there was no RSV prophylaxis) by the percentage reduction in these hospitalisations (due to the RSV prophylaxis) obtained from the literature.

Direct costs
Costs were not discounted due to the one-year time frame of the cost analysis. Quantities were reported separately from the costs (in general categories) and cost items were reported separately. The cost analysis covered the costs of RSV prophylaxis and hospital charges due to RSV hospitalisation (based on the percentage reduction in RSV hospitalisation due to RSV prophylaxis). The perspective adopted in the cost analysis was not explicitly specified. The cost calculations were based on the assumption that a 3.5kg patient would receive 5 doses of drug per RSV season at the manufacturers recommended dosage (750 mg/kg for RSV-Ig and 15 mg/kg for palivizumab); with the assumption of no drug wastage. The price year was not given.

Indirect Costs
Indirect costs were not included.

Currency
US dollars ($).
Sensitivity analysis
No sensitivity analysis was conducted.

Estimated benefits used in the economic analysis
See review results above.

Cost results
The costs of RSV-Ig and palivizumab were estimated to be $2,841 and $2,774, respectively.

Synthesis of costs and benefits
The cost-effectiveness ratio was the net cost (cost of RSV prophylaxis minus anticipated savings in hospital charges) per hospitalisation prevented.

The net cost per hospitalisation prevented for the entire cohort was $54,485 for RSV-Ig and $37,612 for palivizumab.

When analysed by duration of respiratory support expressed as weeks of PCA, the values for infants of 36 weeks or over PCA were $11,468 for RSV-Ig and $16,851 for palivizumab. For infants of less than 36 weeks PCA the values were $148,002 for RSV-Ig and $32,792 for palivizumab.

For the subgroups of patients classified in terms of those requiring respiratory support at less than 36 weeks PCA, analysed by gestation age, were as follows:

PCA 26 weeks or less: $87,389 for RSV-Ig and $15,511 for palivizumab;
27-28 weeks: $105,591 for RSV-Ig and $20,403 for palivizumab;
older than 28-30 weeks: $140,283 for RSV-Ig and $32,829 for palivizumab;
older than 30-32 weeks: $218,223 for RSV-Ig and $50,888; and for palivizumab
for the entire subgroup: $148,002 for RSV-Ig and $32,792 for palivizumab.

Authors' conclusions
This analysis suggests that available forms of RSV prophylaxis would increase the net cost of care, not only for the entire cohort, but also for each of the subgroup studies. However, the RSV hospitalisation rate and the cost-effectiveness of prophylaxis varied markedly by subgroup.

CRD COMMENTARY - Selection of comparators
The strategy of usual care (not using any RSV prophylaxis) was regarded as the comparator. This appropriately allowed the active value of the intervention to be evaluated.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results may have been adversely affected by the retrospective nature of the single study (used as the source of the rate of RSV hospitalisation when no prophylaxis is used) and the apparent lack of a systematic literature review (including appraisal of the quality of the primary studies included and differences between studies) for the studies used as sources for the effectiveness outcomes of the RSV prophylaxis. The study sample appears to have been representative of the study population.

Validity of estimate of measure of benefit
The estimate of the benefit measure was directly derived from the effectiveness analysis. The choice of the benefit measure was appropriate and justified by the authors.

Validity of estimate of costs
Good features of the cost analysis were as follows: quantities were reported separately from the costs (although only in general categories such as hospital stay); and cost items were reported. However, the price year and perspective adopted in the cost analysis were not specified; statistical analysis was not conducted on resource use or cost data; the cost data were based on charges rather than true costs; the effects of alternative preventive methods on indirect costs were not addressed; sensitivity analysis was not performed to assess the robustness of the cost results. The inclusion of such elements would have enhanced the generalisability of the results to other settings.

Other issues
Given the limitations of the study design, and the lack of sensitivity analysis and statistical analysis of the costs, the study results may need to be treated with some caution. The issue of generalisability to other settings (outside the study region) or countries was not specifically addressed, although comparisons were made with other studies. The degree to which the study sample was representative of the study population was addressed by pointing out that the authors chose a 32 week or lower gestational age cut-off for this study because this is the age group commonly at high risk for severe RSV illness.

Implications of the study
Further study is needed to characterise the effect of RSV prophylaxis on outpatient direct and indirect medical and social costs. Further study of subgroups of high-risk patients, including those living in high-risk environments (parental smoking, overcrowding, and so on), may also improve the cost-effectiveness of RSV prophylaxis. This analysis supports the general American Academy of Pediatrics Red Book Committee recommendation that RSV prophylaxis should be considered on a risk-stratified basis for both premature infants and infants requiring prolonged respiratory support in the neonatal period. Precisely where along the risk continuum the threshold for use of RSV prophylaxis should lie remains a question for families, providers, payers, and society.

Source of funding
None stated.

Bibliographic details

PubMedID
10632251

Indexing Status
Subject indexing assigned by NLM

MeSH
Antibodies, Monoclonal /economics /therapeutic use; Antibodies, Monoclonal, Humanized; Cohort Studies; Cost-Benefit Analysis; Costs and Cost Analysis; Hospitalization /economics /statistics & numerical data; Humans; Immunoglobulins, Intravenous /economics /therapeutic use; Infant; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases /economics /epidemiology /prevention & control; Palivizumab; Respiratory Syncytial Virus Infections /economics /epidemiology /prevention & control; Respiratory Syncytial Viruses

AccessionNumber