Direct cost analyses of palivizumab treatment in a cohort of at-risk children: evidence from the North Carolina Medicaid Program

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 (Synagis prophylaxis) against respiratory syncytial virus (RSV) was compared with no prophylaxis among infants born at 32 to 35 weeks’ estimated gestational age (EGA).

Type of intervention
Primary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised infants born between 1 March 2002 and 28 February 2003 at 32 to 35 weeks’ EGA, and who were enrolled in the AccessCare Medicaid programme during the study period. Participants were excluded if they had a diagnosis of chronic lung disease and/or haemodynamically unstable congenital heart disease.

Setting
The setting was primary care and tertiary care. The economic study was conducted in North Carolina, USA.

Dates to which data relate
The effectiveness and resource use data were gathered from 1 October 2002 to 31 May 2003. The price year was not reported.

Source of effectiveness data
The evidence for the effectiveness outcomes was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
A power calculation estimated that 16 patients per study group were needed to detect an effect size of 1.92 or greater using projected average monthly costs with 90% power (0.05 level of significance, 1-sided). A further power calculation estimated that 114 patients per group were required to detect a difference in hospitalisation proportions with a relative risk of 0.2.

Potential study participants were identified through a review of palivizumab prior authorisation forms, Medicaid
Of the 714 infants who were identified as being potentially eligible to receive palivizumab, 374 were born during the study period. Of these, 367 infants met the study criteria (see 'Study Population' section) and were enrolled in the study. Participants were assigned to the prophylaxis group when there was documented evidence of having received at least one palivizumab injection during the study period. In the absence of such evidence, the participant was assigned to the non-prophylaxis group. Inpatient claims and RSV rapid antigen test results were screened to establish whether hospitalisation was caused by an RSV-related condition. Ambulatory care claims were based on diagnosis alone since RSV testing was not routinely performed by providers of ambulatory services. Four patients who were hospitalised with an RSV-related illness and subsequently received palivizumab prophylaxis were assigned to the non-prophylaxis group. This included one participant who was hospitalised with an RSV infection both before and after prophylaxis. A total of 185 patients were assigned to the prophylaxis group and 182 to the non-prophylaxis group.

**Study design**

The study employed a prospective cohort design and was multi-centred, with data being collected from 28 paediatric practices in North Carolina. The follow-up did not extend beyond the study period, which the authors variously described as being 7 or 8 months. Surveys were partially or fully completed for all study participants and risk factor data were completed for 98.4%.

**Analysis of effectiveness**

All of the patients included in the study were accounted for in the analysis. The primary health outcomes assessed were the number of hospitalisations for RSV-related conditions and the number of deaths. Other reported health care use was the average number of ambulatory care and emergency department visits, and the average number of palivizumab injections per participant.

A descriptive analysis was conducted to compare the predisposing, enabling and need factors between the two groups. The predisposing variables were those that "describe the propensity of individuals to use services" (i.e. in the study: race, gender, and age of participant's mother at the infant's date of birth). The enabling variables referred to resources that the patients and families required to use services (i.e. in the study: the highest educational level attained by the infant participant's mother and the number of miles the infant lived from a hospital that cares for infants or children or has an emergency department). The need variables referred to one's illness level or perceived need for care, as evaluated by the individual or the health care delivery system. The need variables selected for the study included whether an infant participant had a sibling in school, attended day care during the study period, was exposed to cigarette smoke in the home, or was part of a multiple birth.

Differences were tested using the chi-squared test for dichotomous variables and the t-test for continuous variables. The groups were similar in terms of patient gender, mother's age, distance to a health care facility for children, siblings in school, smoking exposure in the home, and the number of positive risk factors per participant. However, the prophylaxis group had a significantly greater percentage of white infants, a lower percentage of black and Hispanic infants, a higher percentage of multiple births, and were of slightly lower gestational age and weight at birth compared with the non-prophylaxis group. Multivariate regression analyses were undertaken to control for confounding by assessing the potential influence of risk factors on hospitalisation and costs.

**Effectiveness results**

The total number of hospitalisations for RSV-related conditions was 5 in the prophylaxis group versus 12 in the non-prophylaxis group, (p=0.0782). The participants in the prophylaxis group were hospitalised a total of 22 days (including 2 days in intensive care), compared with 45 days of hospitalisation (including 13 days in intensive care) for the non-prophylaxis group. When multivariate logistic regression was used to control for possible confounding factors, prophylaxis and non-prophylaxis participants did not differ in the incidence of hospitalisation for RSV-related conditions (odds ratio 0.27; p=0.058).

The average number of ambulatory care department visits per participant was 0.57 in the prophylaxis group and 0.63 in the non-prophylaxis group, (p=0.6539).
The average number of emergency department visits per participant was 0.05 in the prophylaxis group and 0.03 in the non-prophylaxis group, \((p=0.3524)\).

The average number of palivizumab injections per participant was 4.10 in the prophylaxis group versus 0.07 in the non-prophylaxis group, \((p<0.0001)\).

No deaths occurred in either group.

**Clinical conclusions**

There was no significant difference in the total number of hospitalisations for RSV-related conditions between participants who received prophylaxis and those who did not. The incidence of hospitalisation was still not statistically significantly different between the two groups when possible confounding factors were controlled for.

**Measure of benefits used in the economic analysis**

The measure of benefit used was the number of hospitalisations avoided.

**Direct costs**

Only the direct costs to the Medicaid programme were included in the analysis. These were for hospitalisation, emergency department care, ambulatory care (outpatient and office visit), and palivizumab prophylaxis. Resource use was taken from parental survey, medical record abstraction and North Carolina Medicaid claims. All costs were derived from Medicaid claims. Palivizumab costs were adjusted for the manufacturer's discount to the state Medicaid programmes according to the federal rebate programme, drug handling fees, and nurse visits for conservative cost estimates. The average per person seasonal cost was reported separately to the average resource use. Discounting was, appropriately, not undertaken. The cost data were collected for the years 2002 to 2003 and, although not explicitly stated, the costs were presumed to be expressed in these prices.

The study reported the average and standardised costs per person for the RSV season (i.e. 7 months). Standardised costs were used to account for those infants who were born during the study and did not complete the full study period. Standardised costs were calculated as the actual per person cost divided by the number of months the patient was in the study, and then multiplied by 7 months.

**Statistical analysis of costs**

The authors standardised the costs, as previously described (see 'Direct Costs' section). A linear regression of individual seasonal total costs was undertaken as a function of palivizumab intervention and other covariates, using both actual and standardised costs. A log-transformed regression of the seasonal costs was also undertaken in an attempt to minimise the highly skewed distribution of the cost data.

**Indirect Costs**

The indirect costs were not included in the analysis.

**Currency**

US dollars ($).

**Sensitivity analysis**

The authors reported that a sensitivity analysis was conducted to investigate uncertainty in the number of RSV-attributed hospitalisations. This was undertaken because the rapid antigen test used to detect RSV had a sensitivity of 80 to 90%. The additional hospitalisation costs for non-RSV-related bronchiolitis were included in the sensitivity analysis.
**Estimated benefits used in the economic analysis**
The authors did not report the number of hospitalisations that were averted by palivizumab prophylaxis.

**Cost results**
The undiscounted average seasonal cost of prophylaxis was $4,996.46 (standardised: $5,297.50) for the intervention group and $57.52 (standardised: $73.86) for the comparator group, owing to 4 patients from the non-prophylaxis group subsequently receiving palivizumab, (p<0.0001).

The undiscounted average per person seasonal cost of treatment and prophylaxis was $5,116.55 (standardised: $5,434.20) for the intervention group and $371.18 (standardised: $504.79) for the comparator group, (p<0.0001).

The cost of adverse events due to treatment was not specifically addressed. The cost study was limited to the study period.

**Synthesis of costs and benefits**
The costs and benefits were summarised by the net cost to avoid one hospitalisation. The authors reported that the undiscounted net cost of prophylaxis needed to prevent one RSV-related hospitalisation was $102,073.

The sensitivity analysis showed that the cost results were robust to variations in the total costs when hospitalisation costs for non-RSV bronchiolitis were included.

**Authors’ conclusions**
From the perspective of the US Medicaid programme, prophylaxis against respiratory syncytial virus (RSV) with palivizumab did not provide direct cost-savings related to hospitalisation or ambulatory care when administered to infants of 32 to 35 weeks’ estimated gestational age (EGA). The large difference observed in costs between the two groups was directly attributable to palivizumab prophylaxis.

**CRD COMMENTARY - Selection of comparators**
Although no explicit justification was given for the comparator used, it would appear to represent current practice in the authors’ setting. If another prophylaxis for RSV-related bronchiolitis had been available it would have been more appropriate to include that, rather than no prophylaxis, as the comparator. You should decide if the comparator chosen represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The analysis was based on a prospective cohort design, which was appropriate given the study question. The study sample is likely to have been representative of the study population since patients from 28 dispersed practices were included in the effectiveness analysis. In addition, the demographic characteristics and risk factors of the patients in the two groups were compared, and a regression analysis was used to address possible confounding factors. Assigning participants who received prophylaxis after a hospital admission to the non-prophylaxis group ensured conservative cost estimates. Power calculations were reported and an appropriate sample size was used. These facts improve the internal validity of the effectiveness analysis.

**Validity of estimate of measure of benefit**
The summary measure of benefit used was hospitalisations avoided. The authors did not report this adequately. In addition, this measure of benefit does not permit comparisons across health technologies.

**Validity of estimate of costs**
The analysis of the costs was performed from the perspective of the US Medicaid programme. It appears that all the
relevant categories of costs were included in the analysis. Some relevant costs were omitted from the analysis. For example, the authors did not include the costs of side effects of treatment, and it is unclear whether their omission would have affected the authors’ conclusions. Average per person seasonal costs were reported separately to average per person seasonal health care use, thus enhancing the reproducibility of the study in other settings. However, the accuracy of the estimates of the average costs is uncertain as the authors reported that the data were collected from 1 October 2002 to 31 May 2003 (i.e. 8 months), yet the study was conducted over 7 months.

No statistical analyses of either the quantities or prices were performed. A sensitivity analysis was undertaken to explore the impact of RSV test sensitivity on the costs, and the rational for the range used appears to have been appropriate. Discounting was not applied, which was appropriate given that the costs were incurred only during a short time. Costs, rather than charges, were reported. The price year was inferred to be 2002 to 2003, and this increases the generalisability of the results.

Other issues
The authors did not directly compare their findings with those from other studies. However, they did report results from published studies and presented a selection of findings. The issue of the generalisability of the results to other settings was not directly addressed. Although the summary measure of benefit was not adequately reported, in general, the authors do not appear to have presented their results selectively and their conclusions reflected the scope of the analysis.

The authors acknowledged three limitations to their study. First, the study did not consider the societal costs or the possible long-term health effects of RSV bronchiolitis, such as the development of asthma and allergies. Second, significant differences were observed between patient attributes in the two study groups, although the authors attempted to address this concern in the regression analysis. Finally, the selection of inpatient costs was based on RSV testing procedures which were not completely accurate. This limitation was explored in the sensitivity analysis.

Implications of the study
The authors stated that consideration must be given to the continued use of palivizumab in infants born at 32 to 35 weeks’ EGA because the costs of RSV prophylaxis far exceed the costs of treatment for RSV-attributed infections. In addition, there are no clear data to support long-term outcome differences in this gestational age group, with or without palivizumab treatment. Public health measures to reduce premature births and low birth weight, and to promote a healthy environment for the infant, are alternatives that could reduce RSV infections but have not been widely implemented.

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