Prospective study of healthcare utilisation and respiratory morbidity due to RSV infection in prematurely born infants

S Broughton, A Roberts, G Fox, E Pollina, M Zuckerman, S Chaudhry, A Greenough

Background: A study was undertaken to determine the impact of respiratory syncytial virus (RSV) infection, both in hospital and the community, on healthcare utilisation and respiratory morbidity in prematurely born infants and to identify risk factors for symptomatic RSV infection.

Methods: A hospital and community follow up study was undertaken of 126 infants born before 32 weeks of gestational age. Healthcare utilisation (hospital admissions and general practitioner attendances) in the first year, respiratory morbidity at follow up (wheeze and cough documented by parent completed diary cards), and RSV positive lower respiratory tract infections (LRTIs) were documented. Nasopharyngeal aspirates were obtained for immunofluorescence and culture for RSV whenever the infants had an LRTI, either in the community or in hospital.

Results: Forty two infants had an RSV positive LRTI (RSV group), 50 had an RSV negative LRTI (RSV negative LRTI group), and 32 infants had no LRTI (no LRTI group). Compared with the RSV negative LRTI and the no LRTI groups, the RSV group required more admissions (p = 0.392, p < 0.001) and days in hospital (p = 0.049, p = 0.006) and had more cough (p = 0.05, p = 0.038) and wheeze (p = 0.003, p = 0.003) at follow up. Significant risk factors for symptomatic RSV LRTI were number of siblings (p = 0.035) and maternal smoking in pregnancy (p = 0.005), for cough were number of siblings (p = 0.002) and RSV LRTI (p = 0.02), and for wheeze was RSV LRTI (p = 0.019).

Conclusion: RSV infection, even if hospital admission is not required, is associated with increased subsequent respiratory morbidity in prematurely born infants.

Methods: Infants born before 32 weeks of gestational age were eligible for entry into the study if they were delivered between February and September (that is, before the start of the RSV season defined as 1 October to 31 March consistent with UK experience) in either 2002 or 2003 and had no congenital abnormalities. The infants were all born in two tertiary perinatal centres. Those infants whose parent(s) gave informed written consent were entered into the study and were followed prospectively until a corrected age of 1 year. All hospital admissions and their duration were recorded, as was the number of attendances for respiratory illnesses made to general practitioners. To document respiratory morbidity at follow up, parents were asked to complete diary cards for a month when their infant reached 11 months corrected age.

Abbreviations: BPD, bronchopulmonary dysplasia; LRTI, lower respiratory tract infection; NICU, neonatal intensive care unit; RSV, respiratory syncytial virus.

PAEDIATRIC LUNG DISEASE

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We chose this age as we wished to determine whether the infant had suffered cough or wheeze at some time after any symptomatic RSV LRTI. The parent recorded on a daily basis whether their infant had symptoms of cough or wheeze.

Following discharge from the neonatal unit, during the RSV season the parent(s) were asked to contact the research team when their infant had signs consistent with a lower respiratory tract infection (LRTI)—that is, cough, wheeze and/or shortness of breath. In addition, the parent(s) were telephoned every 2 weeks throughout the RSV season by one of the researchers to ascertain whether the infant had been or was symptomatic. The telephone calls were limited to the RSV season as our aim was to record all possible RSV LRTI symptomatic cases.

The telephone calls were limited to the RSV season as our aim was to record all possible RSV LRTI symptomatic cases. The median number of days of mechanical ventilation required was 4 (range 0–116) and the median number of weeks of oxygen dependency was 33 (range 29–107). The only significant differences between the three groups were that antenatal infection (p = 0.016) and maternal smoking in pregnancy (p = 0.005) were more common in the no LRTI group than the RSV positive group (table 1). During the study period palivizumab was only prescribed to infants who had BPD, required supplementary oxygen until close to or after discharge from the NICU, and were being discharged during the RSV season. Thirteen of the infants received palivizumab, two of whom suffered an RSV positive LRTI.

The infants were divided into three groups: (1) those with an RSV positive LRTI (RSV group); (2) those with an RSV negative LRTI (RSV negative LRTI group); and (3) those without LRTI (no LRTI group). RSV infection was identified by immunofluorescence and/or a positive culture from the nasopharyngeal aspirates.

### Table 2

Healthcare utilisation of the three groups

<table>
<thead>
<tr>
<th>No LRTI (n = 32)</th>
<th>RSV– LRTI (n = 50)</th>
<th>RSV+ LRTI (n = 44)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospital admissions (n)</td>
<td>0 (0%)</td>
<td>14 (28%)</td>
<td>18 (41%)</td>
</tr>
<tr>
<td>Length of stay (days)</td>
<td>0 [0]</td>
<td>0 (0–15)</td>
<td>4 [3.8]</td>
</tr>
<tr>
<td>PICU admission</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>4 (9%)</td>
</tr>
<tr>
<td>GP attendances (n)</td>
<td>0 [0.4]</td>
<td>1 [0.92]</td>
<td>1 [1.9]</td>
</tr>
</tbody>
</table>

Data are shown as n (%) or median (range).
illnesses), respiratory morbidity (cough and wheeze at follow up), and symptomatic RSV infection were related to potential explanatory variables which included infant, parental, and family characteristics. The variables explored had been previously identified as risk factors for healthcare utilisation in prematurely born infants. Antenatal variables recorded were infection (maternal positive blood culture, histologically proven choioamnionitis, maternal urinary tract infection, or maternal temperature with a positive culture from a high vaginal swab and rupture of membranes of longer than 24 hours), maternal smoking, and antenatal corticosteroid administration. Postnatal variables were sex, gestational age, birth weight, use of surfactant, postnatal infection (positive blood culture or suspected clinical infection with a raised C reactive protein, increased or decreased neutrophil count and/or decreased platelet count), the number of days of mechanical ventilation, BPD (defined as oxygen dependency beyond 36 weeks postmenstrual age), discharge home in oxygen, duration of supplementary oxygen dependency beyond 36 weeks postmenstrual age, and discharge from the neonatal unit between August and November. Family variables were a family history of atopy (asthma or hay fever in a parent or sibling), number of siblings, attendance at day care, parental smoking, and antenatal corticosteroid administration. Postnatal variables were sex, gestational age, birth weight, use of surfactant, postnatal infection (positive blood culture or suspected clinical infection with a raised C reactive protein, increased or decreased neutrophil count and/or decreased platelet count), the number of days of mechanical ventilation, BPD (defined as oxygen dependency beyond 36 weeks postmenstrual age), discharge home in oxygen, duration of supplementary oxygen dependency, and discharge from the neonatal unit between August and November. Family variables were a family history of atopy (asthma or hay fever in a parent or sibling), number of siblings, attendance at day care, parental smoking, and antenatal corticosteroid administration.

Regression analysis demonstrated that parental smoking and RSV positive LRTI were significant risk factors for hospital admission (table 4); duration of oxygen therapy, parental smoking in the home, and RSV positive LRTI were significant risk factors for length of hospital stay; antenatal infection appeared protective (table 5). The only significant risk factor for GP attendances was RSV positive LRTI (table 5).

### Table 3 Respiratory morbidity of the three groups

<table>
<thead>
<tr>
<th></th>
<th>No LRTI (n = 21)</th>
<th>RSV – LRTI (n = 32)</th>
<th>RSV+ LRTI (n = 35)</th>
<th>p values</th>
<th>No LRTI vs RSV</th>
<th>No LRTI vs RSV+</th>
<th>RSV – vs RSV+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough (days per month)</td>
<td>0 [2.6] (0–11)</td>
<td>0 [2.8] (0–14)</td>
<td>5 [6.7] (0–31)</td>
<td>1.000</td>
<td>0.050</td>
<td>0.038</td>
<td></td>
</tr>
<tr>
<td>Wheeze (days per month)</td>
<td>0 [0.6] (0–4)</td>
<td>0 [1.1] (0–13)</td>
<td>3 [5.1] (0–31)</td>
<td>1.000</td>
<td>0.003</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Reliever use (days per month)</td>
<td>0 [0.2] (0–4)</td>
<td>0 [0.4] (0–10)</td>
<td>0 [2.7] (0–18)</td>
<td>1.000</td>
<td>0.120</td>
<td>0.103</td>
<td></td>
</tr>
</tbody>
</table>

Data are shown as median [mean] (range).

### RESULTS

Ninety four of the 126 infants suffered a total of 134 LRTIs; 39 infants had one, 29 had two, 11 had three, and two infants had four LRTIs. Forty four of the infants suffered RSV positive LRTIs on 48 occasions; four of the infants had two RSV positive LRTIs. Six infants had influenza A and four had parainfluenza type 3 positive LRTIs; for all analyses these infants were included in the RSV negative LRTI group.

The RSV group required significantly more admissions, longer hospital admissions, and more GP attendances than the no LRTI group; and significantly longer hospital admissions, more PICU admissions and GP attendances than the RSV negative LRTI group (table 2). The number of hospital admissions per 100 children was 41 in the RSV group and 21 in the RSV negative LRTI group. The number of hospital days per 100 children in the RSV group was 380 compared with 120 in the RSV negative LRTI group. The RSV negative LRTI group required more hospital admissions than the no LRTI group (number of admissions per 100 children in the no LRTI group being 0, table 2). Eighty eight parents completed diary cards. The demographic data of the infants whose parents did and did not complete diary cards did not differ significantly (data not shown). The RSV group had significantly more days of cough and wheeze than either the no LRTI or the RSV negative LRTI groups, but there were no significant differences in respiratory morbidity between the no LRTI and the RSV negative LRTI groups (table 3).

Exclusion of the data on infants who required hospitalisation showed that the RSV group (median 1, mean 1.3, range 0–6) required more GP attendances than the no LRTI group (median 0, mean 0.4, range 0–4) (p = 0.049) and that they had significantly more wheeze (median 3, mean 3.7, range 0–18 days) than both the no LRTI (median 0, mean 0.6, range 0–4 days) (p = 0.005) and the RSV negative LRTI (median 0, mean 0.7, range 0–4 days) groups (p = 0.004).

Regression analysis demonstrated that parental smoking and RSV positive LRTI were significant risk factors for hospital admission (table 4); duration of oxygen therapy, parental smoking in the home, and RSV positive LRTI were significant risk factors for length of hospital stay; antenatal infection appeared protective (table 5). The only significant risk factor for GP attendances was RSV positive LRTI (table 5).
Table 5 Risk factors for length of hospital stay and GP attendances

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Length of hospital stay p value</th>
<th>GP attendances p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antenatal infection</td>
<td>0.018</td>
<td>0.913</td>
</tr>
<tr>
<td>Maternal smoking in pregnancy</td>
<td>0.150</td>
<td>0.574</td>
</tr>
<tr>
<td>Antenatal steroids</td>
<td>0.120</td>
<td>0.970</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.847</td>
<td>0.832</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.930</td>
<td>0.154</td>
</tr>
<tr>
<td>Birth weight</td>
<td>0.555</td>
<td>0.950</td>
</tr>
<tr>
<td>Surfactant</td>
<td>0.090</td>
<td>0.151</td>
</tr>
<tr>
<td>Postnatal infection</td>
<td>0.078</td>
<td>0.989</td>
</tr>
<tr>
<td>Duration of ventilator days</td>
<td>0.139</td>
<td>0.244</td>
</tr>
<tr>
<td>Duration of oxygen therapy</td>
<td>&lt;0.001</td>
<td>0.184</td>
</tr>
<tr>
<td>Discharge August-November</td>
<td>0.061</td>
<td>0.127</td>
</tr>
<tr>
<td>Family history of atopy</td>
<td>0.731</td>
<td>0.307</td>
</tr>
<tr>
<td>Number of school aged siblings</td>
<td>0.611</td>
<td>0.390</td>
</tr>
<tr>
<td>Day care attendance</td>
<td>0.824</td>
<td>0.277</td>
</tr>
<tr>
<td>Parental smoking in the home</td>
<td>&lt;0.001</td>
<td>0.085</td>
</tr>
<tr>
<td>Bottle feeding</td>
<td>0.756</td>
<td>0.624</td>
</tr>
<tr>
<td>RSV LRTI</td>
<td>0.010</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Significant risk factors for cough were number of siblings (p = 0.002) and RSV positive LRTI (p = 0.02) and, for wheeze, RSV positive LRTI was a significant risk factor (p = 0.019). Significant risk factors for symptomatic RSV positive LRTI were maternal smoking in pregnancy and number of siblings (table 6).

DISCUSSION

In a prospective study we have shown that RSV infection in prematurely born infants was associated with increased healthcare utilisation and respiratory morbidity at follow up. A strength of this study is that RSV positive LRTIs were identified both in hospital and in the community and thus, compared with previous studies, which excluded infants who had had an RSV infection resulting in hospitalisation, showed that even RSV infection which did not merit hospital admission was associated with significantly more GP attendances and greater wheeze at follow up.

Parents were requested to contact the research team on each occasion that their infant had a symptomatic LRTI. It is possible some parents failed to do so but, to minimise the risk of missing infants with LRTIs, we also contacted the parents at 2 weekly intervals. The proportion (31%) of our cohort who tested positive for RSV infection is similar to that found in other community based studies by Legg et al24 (31.8%) and Ray et al25 (22.2%). Although we cannot be completely confident that we included every infant with a symptomatic RSV infection, we found that symptomatic RSV infection was associated with a significantly greater requirement for hospital admission, prolonged hospital admission, more GP attendances, and greater respiratory morbidity at follow up.

As part of this study protocol, we only investigated whether the infants had an RSV, influenza, adenoavirus, or parainfluenza virus LRTI. We cannot therefore comment on the relative impact of rhinovirus or metapneumovirus on healthcare utilisation or chronic respiratory morbidity which needs further investigation. Several of the infants in the non-RSV positive LRTI group had proven influenza or parainfluenza virus infections and it is possible that others may have had other non-investigated viral infections. This group fared significantly worse than the non-LRTI group in respect of the number of hospital admissions, but were significantly better than the RSV positive group with regard to the duration of hospital admissions, numbers of PICU admissions and GP attendances, and days of cough and wheeze. These findings are compatible with our previous report8 in which we found differences in healthcare utilisation between infants with BPD admitted with an RSV proven infection and those with either probable bronchiolitis or no respiratory problem.

As in studies undertaken in infants born at term,9 26–28 we assessed the infants with regard to their RSV status only when they were symptomatic. Neither the previous studies9 26–28 nor this one can therefore comment on the impact of asymptomatic RSV infections on respiratory morbidity. However, as almost all children will have suffered an RSV infection by the age of 2 years,29 it seems likely that only those RSV infections sufficiently severe to cause clinically significant symptoms will result in chronic respiratory morbidity.9 26–28

We were unable to follow approximately one third of eligible infants. Those not followed, however, did not differ significantly from the study population with regard to their birth weight, gestational age, or BPD status—all factors known to affect the severity of RSV infection.3 It therefore seems unlikely that our results were biased by loss to follow up. Indeed, our RSV hospitalisation rate of 10.1% was not significantly different from the study population with regard to their RSV status only when they were symptomatic. Neither the previous studies9 26–28 nor this one can therefore comment on the impact of asymptomatic RSV infections on respiratory morbidity.9 26–28

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infants may therefore be less likely to develop asthma-like symptoms with an LRTI and to require a prolonged admission.

In conclusion, in our prospective study we have identified that RSV infection is associated with increased healthcare utilisation and respiratory morbidity in infants born prematurely. Importantly, RSV infections in the community as well as those resulting in a hospital admission are associated with increased respiratory morbidity at follow up. Our results indicate that, in situations where prophylaxis with palivizumab is not routinely given to infants born at less than 32 weeks of gestation, consideration should be given to the use of prophylactic palivizumab in those infants who have siblings and whose mothers smoked during pregnancy.

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