PAEDIATRIC LUNG DISEASE

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

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Thorax 2005;**60**:1039–1044. doi: 10.1136/thx.2004.037853

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Received 18 November 2004
Accepted 25 September 2005
Published Online First 14 October 2005

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.

Prematurely born infants following discharge from the neonatal intensive care unit (NICU) have increased healthcare utilisation compared with that required by infants born at term. They are more likely to be admitted to hospital[1 2] and, as a result, the cost of hospital admissions for infants born before 32 weeks of gestation is 20 times that of term born infants.[2] In addition, prematurely born infants are more likely to have troublesome cough and wheeze requiring treatment and to need to be seen by their general practitioners.[3] RSV infection following NICU discharge has been shown to be associated with increased healthcare utilisation;[4 5] both retrospective and prospective studies have shown that prematurely born infants who have been hospitalised because of RSV infection subsequently require more hospital readmissions and more prolonged admissions.[4–6] Among infants born between 32 and 35 weeks of gestation, hospital admissions because of RSV infection were associated subsequently with more hospital admissions, physician contacts, inpatient procedures and days, and outpatient visits.[7] In addition, in children born prematurely who had developed bronchopulmonary dysplasia (BPD), hospital admissions for RSV were associated with a subsequent greater need for general practitioner (GP) attendances and medications for respiratory disorders in the preschool years.[8] It is possible, however, that those studies[4 5 6 8] underestimated the impact of RSV infection, as the prematurely born children were only diagnosed as having an RSV infection if they had required hospitalisation. Yet, in children born at term, RSV infection not meriting hospital admission has been associated with an increased risk of frequent wheeze in young children.[9]

The aim of this prospective study was to determine the impact of RSV infection (both in the hospital and community) on healthcare utilisation and respiratory morbidity in prematurely born infants. In addition, we wished to determine risk factors for symptomatic RSV infection. Treatment for RSV infection is supportive,[10] but results from randomised trials[11 12] have shown that immunoprophylaxis significantly reduces the requirement for hospitalisation for RSV infection. Unfortunately, immunoprophylaxis is expensive and studies have shown that, if palivizumab is prescribed for groups currently considered to be at high risk,[13] it is not cost effective, except perhaps in prematurely born infants who are receiving home oxygen therapy.[14] As a consequence, it is important to determine whether prematurely born infants at particularly high risk can be identified.

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[15]) 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

Table 1 Demographic data of the three groups of study subjects

				p values		
	No LRTI (n = 32)	RSV− LRTI (n = 50)	RSV+ LRTI (n = 44)	No LRTI vs RSV−	No LRTI vs RSV+	RVS− vs RSV+
Antenatal infection (n)	16 (50%)	13 (26%)	9 (20%)	0.06	0.02	1.00
Maternal smoking in pregnancy (n)	1 (3%)	6 (12%)	11 (25%)	0.34	<0.01	0.18
Antenatal steroids (n)	25 (78%)	43 (86%)	40 (91%)	0.97	0.36	1.00
Boys (n)	17 (53%)	27 (54%)	31 (70%)	1.00	0.39	0.32
Gestational age (weeks)	29.5 (23–31)	28 (24–31)	29 (23–31)	1.00	1.00	1.00
Birth weight (g)	1175 (500–1850)	1040 (650–2280)	1010 (570–1960)	1.00	1.00	1.00
Surfactant (n)	26 (81%)	37 (74%)	31 (70%)	1.00	1.00	1.00
Postnatal infection (n)	19 (59%)	23 (46%)	25 (57%)	0.72	1.00	0.89
Ventilator days (n)	6 (0–63)	3.5 (0–79)	4.5 (0–116)	0.97	1.00	0.47
Bronchopulmonary dysplasia (n)	13 (41%)	21 (43%)	17 (39%)	1.00	1.00	1.00
Duration of oxygen therapy (weeks)	33.5 (32–60)	35 (31–92)	32.5 (30–107)	1.00	1.00	1.00
Discharge August–November (n)	12 (38%)	20 (40%)	23 (52%)	1.00	0.61	0.70
Family history of atopy (n)	13 (41%)	22 (44%)	25 (57%)	1.00	0.50	0.65
No of school aged siblings (n)	0.5 (0–3)	0.5 (0–4)	1 (0–4)	1.00	0.51	0.23
Day care attendance (n)	4 (13%)	6 (12%)	9 (20%)	1.00	1.00	0.77
Parental smoking in the home (n)	5 (16%)	10 (20%)	13 (30%)	1.00	0.46	0.81
Breast feeding (n)	21 (66%)	33 (66%)	29 (66%)	1.00	1.00	1.00

Data are shown as n (%) or median (range).

We chose this age as we wished to determine whether the infants suffered cough and/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.[16] 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 during the RSV season rather than to look at seasonal variation in respiratory symptoms. A researcher visited the infants at home on every occasion that the infants had a LRTI. A nasopharyngeal aspirate was then obtained. Nasopharyngeal aspirates were also obtained from all infants admitted to hospital with an LRTI. Immunofluorescence and culture for RSV, influenza A and B, adenovirus and parainfluenza strains 1, 2 and 3 were performed on the aspirates.

Study patients

One hundred and ninety infants were eligible for inclusion in the study; 40 parent(s) declined to take part, a further 21 initially consented but defaulted from follow up, and three infants died before discharge from the neonatal unit. The remaining 126 infants had a median gestational age at birth of 29 weeks (range 23–31) and a birth weight of 1045 g (range 500–2080); neither their gestational age nor birth weight differed significantly from those who did not take part (data not presented). The study population consisted of 75 boys (60%); 38 of the mothers (30%) had had an antenatal infection and 108 (86%) had received antenatal steroids; 94 of the infants (75%) had received surfactant, 67 (53%) had a postnatal infection, and 51 (40%) developed BPD. None of the infants had suffered a nosocomial viral infection while on the NICU. 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.

The research ethics committees of King's College NHS trust and Guy's and St Thomas' NHS trust approved the study.

Analysis of data

Differences between the three groups were assessed for statistical significance using the multivariate analysis of variance with a Bonferroni post hoc correction for multiple comparisons. A subanalysis was also undertaken which excluded infants who had required hospital admission. Healthcare utilisation (number and duration of total hospital admissions and number of GP attendances for respiratory

Table 2 Healthcare utilisation of the three groups

				p values		
	No LRTI (n = 32)	RSV− LRTI (n = 50)	RSV+ LRTI (n = 44)	No LRTI vs RSV−	No LRTI vs RSV+	RSV− vs RSV+
Hospital admissions (n)	0 (0%)	14 (28%)	18 (41%)	0.009	<0.001	0.392
Length of stay (days)	0 [0] (0)	0 [1.2] (0–15)	0 [3.8] (0–46)	0.709	0.006	0.049
PICU admission	0 (0%)	0 (0%)	4 (9%)	1.000	0.074	0.035
GP attendances (n)	0 [0.4] (0–4)	1 [0.92] (0–4)	1 [1.9] (0–7)	0.422	<0.001	0.004

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

Table 3 Respiratory morbidity of the three groups

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

Data are shown as median [mean] (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.[2 4 5 17–21] Antenatal variables recorded were infection (maternal positive blood culture, histologically proven chorioamnionitis, 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[22]), 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[23]), 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 type of feeding (bottle or breast). For each outcome, several possible explanatory variables showed significant associations so multivariate linear or binary logistic regression as appropriate was used to explore the relationships further.

Analysis was performed using SPSS version 12.0 (SPSS Inc, Chicago, IL, USA).

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 4 Risk factors for hospital admission

	p value	Odds ratio	95% confidence intervals
Antenatal infection	0.165	0.414	0.119 to 1.438
Maternal smoking in pregnancy	0.849	1.190	0.200 to 7.072
Antenatal steroids	0.976	0.976	0.198 to 4.821
Male sex	0.787	0.864	0.299 to 2.495
Gestational age	0.723	0.933	0.634 to 1.373
Birth weight	0.074	1.002	1.000 to 1.004
Surfactant	0.127	2.165	0.802 to 5.842
Postnatal infection	0.237	0.469	0.134 to 1.646
Duration of ventilator days	0.852	0.994	0.937 to 1.055
Duration of oxygen therapy	0.676	1.020	0.930 to 1.118
Discharge August–November	0.056	2.868	0.973 to 8.455
Family history of atopy	0.361	1.698	0.545 to 5.292
Number of school aged siblings	0.906	1.030	0.633 to 1.674
Day care attendance	0.821	0.837	0.181 to 3.883
Parental smoking in the home	0.003	3.39	1.080 to 10.634
Breast feeding	0.175	0.456	0.147 to 1.417
RSV LRTI	0.013	3.09	1.277 to 7.532

Table 5 Risk factors for length of hospital stay and GP attendances

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

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,[4–6 8] we could assess the impact of RSV infection on the healthcare utilisation of prematurely born infants more accurately. Our sub-analysis, 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 al*[24] (31.8%) and Ray *et al*[25] (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, adenovirus, 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 report[8] 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 studies[9 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.[8 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.[4] It therefore seems unlikely that our results were biased by loss to follow up. Indeed, our RSV hospitalisation rate of 10.1% was not dissimilar to that reported in previous studies by Stephenson *et al*[3] (5.2%) and Joffe *et al*[4] (7.2%),

Twenty five percent of the infants we followed required at least one hospital admission. The rates of hospitalisation previously reported for prematurely born infants vary from

Table 6 Risk factors for RSV positive LRTI

	p value	Odds ratio	95% confidence intervals
Antenatal infection	0.081	0.331	0.100 to 1.095
Maternal smoking in pregnancy	0.005	4.845	1.610 to 14.582
Antenatal steroids	0.109	3.589	0.751 to 17.560
Male sex	0.069	2.627	0.936 to 6.430
Gestational age	0.238	0.812	0.575 to 1.147
Birth weight	0.431	1.001	0.999 to 1.003
Surfactant	0.391	0.667	0.265 to 1.683
Postnatal infection	0.373	1.646	0.546 to 4.969
Duration of ventilator days	0.148	1.041	0.986 to 1.099
Duration of oxygen therapy	0.438	0.967	0.887 to 1.053
Discharge August–November	0.202	1.892	0.710 to 5.041
Family history of atopy	0.591	1.290	0.509 to 3.269
Number of school aged siblings	0.035	1.454	1.027 to 2.059
Day care attendance	0.264	2.145	0.562 to 8.192
Parental smoking in the home	0.771	0.809	0.194 to 3.368
Bottle feeding	0.966	0.977	0.331 to 2.881

5.7%[3] to 29.5%,[4] although they tended to be higher in infants who had suffered BPD.[8] We noted, however, that infants who had suffered a symptomatic RSV infection had a greater need for hospitalisation and a greater total length of hospital admission (table 1). They also had more GP attendances for respiratory illnesses, possibly because they had significantly more cough and wheeze at follow up. Our finding in a prospective study that symptomatic RSV infection increases subsequent morbidity is supported by the finding in infants of 32–35 weeks gestation at birth that hospitalisation for RSV infection was associated with subsequent significantly greater hospitalisation, inpatient days, physician contacts, and outpatient attendances. Unfortunately, in that study[7] classification of RSV hospitalisation was not based on RSV testing but rather on the International Classification of Diseases (9th revision) clinical modification code. In contrast, in the present study infants were only diagnosed as being RSV positive if RSV was identified by immunofluorescence and/or culture of nasopharyngeal aspirates, so we are confident that our infants suffered RSV infections. A further advantage of our study was that its design also allowed us to capture RSV infections in the community and thus, uniquely, we report the impact of non-hospitalisation RSV infection on prematurely born infants.

Respiratory morbidity was assessed by analysis of diary cards which were completed sometime following the RSV infection. The analysis showed that those infants who had an RSV infection had significantly more days of cough and wheeze at follow up. In addition, linear regression analysis showed that RSV infection as well as BPD status was a significant risk factor for wheeze. These data suggest that, as in infants born at term,[9 26–28] RSV infection is associated with chronic respiratory morbidity in preterm infants. This is supported by the results of a retrospective study which found increased health care following RSV infection in preschool children born prematurely who had developed BPD.[30] The duration of the increased respiratory morbidity in prematurely born children merits further investigation.

A number of risk factors for healthcare utilisation in prematurely born infants have been identified in previous studies: in addition to RSV infection, these are birth weight,[5 17] BPD,[4 5 17–19] NICU discharge 3 months before the RSV season,[4 5] number of siblings,[4 5 18–20] tobacco exposure,[4 5 18 19] male sex,[19] day care attendance,[18 20 21] and bottle feeding.[2] As a consequence, we determined their relative importance by including these potential risk factors in our multivariate analysis. RSV positive LRTI was a significant risk factor for all three assessments of healthcare utilisation. Parental smoking was a significant risk factor for both a requirement for hospital admission and a longer total length of hospital admission, agreeing with findings from previous studies.[4 5 20 21] Antenatal smoking was a significant risk factor for symptomatic RSV infection, further highlighting the importance of counselling mothers against smoking, particularly during pregnancy. The likely mechanism is that antenatal smoking is associated with impaired lung function,[31 32] as infants with impaired lung function are more likely to have a symptomatic RSV infection.[33–35] Another risk factor we identified for RSV infection was the number of siblings, consistent with greater exposure to infected children. Antenatal infection differed significantly on univariate analysis between infants who subsequently developed an RSV positive LRTI and no LRTI. Antenatal infection has been associated with a significantly increased risk of BPD,[36 37] yet regression analysis showed that antenatal infection appeared protective against a prolonged hospital admission. A possible explanation for the findings from the regression analysis is that, as intrauterine inflammation has been found to be associated with an increase in type I cytokines,[38] affected 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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Ms Alison Roberts was supported by a peer reviewed grant from WellChild, who received funding from Abbott Laboratories.

There is no financial conflict of interest.

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