Rhinovirus infection and healthcare utilisation in prematurely born infants

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ABSTRACT Our aim was to determine whether rhinovirus (RV) lower respiratory tract infections (LRTIs) in prematurely born infants increase health-related cost of care during infancy.

153 infants born at <36 weeks of gestation were prospectively followed to 1 year. Cost of care was calculated from the National Health Service reference costing scheme and healthcare utilisation determined by examining hospital/general practitioner records.

20 infants developed RV LRTIs (RV group), 17 respiratory syncytial virus (RSV) LRTIs (RSV group), 12 both RV and RSV LRTIs (RV/RSV group) and 74 had no LRTI (no LRTI group). Compared with the no LRTI group, the RV/RSV LRTI group had the greatest increase in adjusted mean cost (difference GBP 5769), followed by the RV LRTI group (difference GBP 278) and, finally, the RSV LRTI group (difference GBP 172) ($p=0.045$). The RV group had more outpatient ($p<0.05$) and respiratory-related general practitioner ($p<0.05$) attendances, more wheezed at follow-up ($p<0.001$) than the no LRTI group and more had respiratory-related outpatient attendances than the RSV LRTI group ($p<0.05$).

We conclude that RV LRTIs were associated with increased health-related cost of care during infancy; our results suggest that the RV group compared with the RSV group suffered greater chronic respiratory morbidity.

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Introduction

Respiratory syncytial virus (RSV) lower respiratory tract infections (LRTIs) are associated with increased chronic respiratory morbidity and healthcare utilisation in prematurely born infants who did [1] or did not [2, 3] develop bronchopulmonary dysplasia (BPD). Amongst those who had had BPD, healthcare utilisation and the related cost of care were increased up to 7 years of age and lung function was lower than that of controls at 10 years of age [1]. In term-born children, rhinovirus (RV) infection is also associated with chronic respiratory morbidity [4–8]. There is some evidence that RV infection may also have long-term adverse effects on prematurely born infants, in that eight prematurely born infants with BPD who developed RV LRTIs subsequently had a sustained worsening of their clinical status, requiring the addition of new therapies for prolonged periods of time [9]. As a consequence, we hypothesised that prematurely born infants with or without BPD who suffered an RV LRTI would suffer increased healthcare utilisation in infancy and have greater health-related cost of care. The aim of this study was to test that hypothesis. In addition, we wished to determine whether the magnitude of any increase in healthcare utilisation and the health-related cost of care were similar to those associated with RSV LRTI.

Materials and methods

Study subjects

Infants born at <36 weeks of gestational age in 2008 or 2009 were eligible for entry into the study if they were born prior to the onset of the RSV season. The RSV season was defined as October 1 to March 31, consistent with the UK experience. Consecutive infants, including twins and triplets, who lived within the King's College Hospital NHS Foundation Trust (KCH) catchment area, and whose parents gave informed written consent, were recruited. The majority of the infants were born at KCH; the others had been born elsewhere because of a lack of maternity beds or neonatal intensive care unit cots at the time of delivery, but were transferred back to KCH for their ongoing neonatal care as soon as a cot became available. Infants were recruited either from the neonatal unit or postnatal ward. The study was approved by the research ethics committee of King's College Hospital NHS Trust.

Study design and methods

Following neonatal unit discharge, infants were followed prospectively until 1 year of corrected age. The parents were asked to contact the research team when their infant was symptomatic with signs consistent with an LRTI, that is, cough, wheeze, and/or shortness of breath. In addition, parents were telephoned every 2 weeks by researchers until the infants were 1 year of corrected age to ascertain whether their infant had been or was symptomatic. A researcher visited the home on every occasion that an infant had an LRTI and a nasopharyngeal aspirate (NPA) was obtained if the LRTI was confirmed by the researcher. NPAs were obtained on each occasion an infant was admitted with an NPA. Real-time reverse transcriptase polymerase chain reaction (PCR) was performed on the NPAs for nine viruses (rhinovirus, RSV A and B, human metapneumovirus, influenza A and B, and parainfluenza 1–3) in three multiplexes with a monoplex RNA internal control as previously described [10]. Adenovirus (DNA virus) was tested by real-time reverse transcriptase PCR in monoplex with a DNA internal control (also a monoplex) [10]. In addition, another multiplex, including an MS2 phage internal control, was developed using previously published primers and probes [11–14] that tested for enterovirus, parechovirus and human bocavirus.

Hospital records were examined to identify admissions, accident and emergency and outpatient attendances and all medications prescribed. General practitioner (GP) records were examined to identify any hospital readmissions, accident and emergency attendances, the number of outpatient hospital appointments, the number of GP attendances and referrals to community support services and all medication prescribed. Regarding healthcare utilisation, all visits to practice nurses or routine visits to health visitors, for example, for immunisations, were not recorded as these were considered usual care for infants. Parents completed a respiratory diary card for 1 month when their infant was 11 months of corrected age and a respiratory health-related questionnaire about their infant when the infant was 1 year of corrected age. Parents were asked to record on a daily basis on the respiratory diary cards whether their infant coughed, wheezed or used any ''respiratory'' medications (inhalers, oral steroids or antibiotics). To calculate the cost of care, the National Health Service reference costing scheme was used; this gives national average costs for in- and outpatient hospital and GP attendances. For admissions, the number of days for each admission was multiplied by the national average cost for the diagnosis leading to admission.

Analysis

The infants were divided into four groups: 1) infants who never had a symptomatic LRTI (no LRTI); 2) infants who had at least one LRTI from which RV was detected from the NPA (RV LRTI); 3) infants who

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had at least one LRTI from which RSV was detected from the NPA (RSV LRTI); and 4) infants who had LRTI(s) with RV and RSV detected from NPA(s) (RV/RSV LRTI).

The results of infants who had other viral LRTIs, but not an RV or RSV LRTI, or had a symptomatic LRTI, but no virus was detected were excluded from the analysis.

Statistical analysis

Baseline factors were compared across the four groups using the Kruskal–Wallis test with *post hoc* tests adjusted for multiple comparisons. The cost data were summarised using means rather than medians to preserve the total sum of costs [15]. Baseline factors were compared across the four groups using the Kruskal–Wallis test with *post hoc* tests adjusted for multiple comparisons. To analyse the cost data, the approach advocated by BARBER and THOMPSON [16] was followed, fitting a generalised linear model with a gamma distribution and identity link for the total cost data, and a Poisson distribution with robust standard error and identity link for the respiratory cost data. In each case, models were chosen to give estimates as mean costs in a model with deviance residuals close to the normal distribution, as required by the method. In order to account for any differences in the demographics of the three groups, an adjusted analysis was performed with adjustment, first, for birthweight, gestational age, antenatal steroid use and surfactant, and, secondly, for those variables plus BPD. Principal components analysis was first used to reduce the birthweight, gestational age, antenatal steroid use and surfactant data to two principal components that explained almost ~80% of the total variability in those factors. Those two components were then used as covariates in a further generalised linear model to obtain adjusted estimates. Adjustment using a generalised linear model was not possible for the respiratory data as the majority of the ''no LRTI'' group had zero costs and so the model was unstable [17]. This is not a statistical power issue, but a consequence of the dominance of nil costs in the no LRTI group, as would be expected.

Results

251 infants were eligible for inclusion into the study (fig. 1). The 153 (84 male) infants who completed the study had a median gestational age of 34 (range 23–35) weeks and a birthweight of 1890 (range 534–3610) g. 20 infants developed RV LRTIs, 17 developed RSV LRTIs, 12 developed both RV/RSV LRTIs and 74 infants had no LRTI. 30 infants had other viral or viral negative LRTIs and their results were excluded from the analysis. Of the 12 infants developing both RV/RSV LRTIs, nine had RV or RSV detected during two separate LRTIs and three infants had detection of RV and RSV during one LRTI. The RV LRTI group had a median of two LRTIs, the RSV LRTI group a median of one LRTI and the RV/RSV LRTI group a median of two LRTIs ($p<0.001$ across the three groups with *post hoc* analysis showing no significant difference between the RV and the RV/RSV LRTI groups ($p=0.95$), but significant differences between both those groups and the RSV LRTI group ($p<0.01$ and $p<0.01$, respectively)).

Demographics

The significant differences in the demographics (table 1) between the four groups were in gestational age (but there were no significant differences on *post hoc* analysis), birthweight (the RV LRTI group was significantly lighter at birth than the no LRTI group; $p<0.05$), antenatal steroid use (a significantly greater proportion of the mothers in the RSV group had received antenatal steroids than the no LRTI group; $p<0.05$), surfactant use (a greater proportion of the RV/RSV LRTI group had more surfactant than either the RSV LRTI ($p<0.05$) or the no LRTI groups ($p<0.05$)), BPD (but there were no significant differences in *post hoc* analysis) and palivizumab use (a significantly greater proportion of the RV LRTI group had received palivizumab than the no LRTI group; $p<0.05$).

Healthcare utilisation

Nine (12%) infants of the no LRTI group had hospital admissions (all for nonrespiratory causes), two (10%) of the RV LRTI group had hospital admissions (one for an RV LRTI and one for a nonrespiratory cause), seven (41%) of the RSV LRTI group had hospital admissions (five for RSV LRTI, one for another viral LRTI and one for a nonrespiratory cause) and six (50%) of the RV/RSV LRTI group had hospital admissions (two for an RV/RSV LRTI, three for a RSV LRTI and one for an RV LRTI).

The RV LRTI group had more total ($p<0.05$) and respiratory-related ($p<0.05$) outpatient attendances and GP respiratory-related attendances ($p<0.05$) than the no LRTI group and more respiratory-related outpatient attendances than the RSV LRTI group ($p<0.05$). The RSV LRTI group had more total ($p<0.05$) and respiratory-related ($p<0.05$) hospitalisations than the no LRTI group and more total ($p<0.05$) and respiratory-related ($p<0.05$) hospitalisations than the RV LRTI group. The RSV LRTI group had more total ($p<0.05$) and respiratory-related ($p<0.05$) accident and emergency attendances than the no LRTI group (table 2). The RV/RSV group had more total and respiratory-related hospitalisations than both the

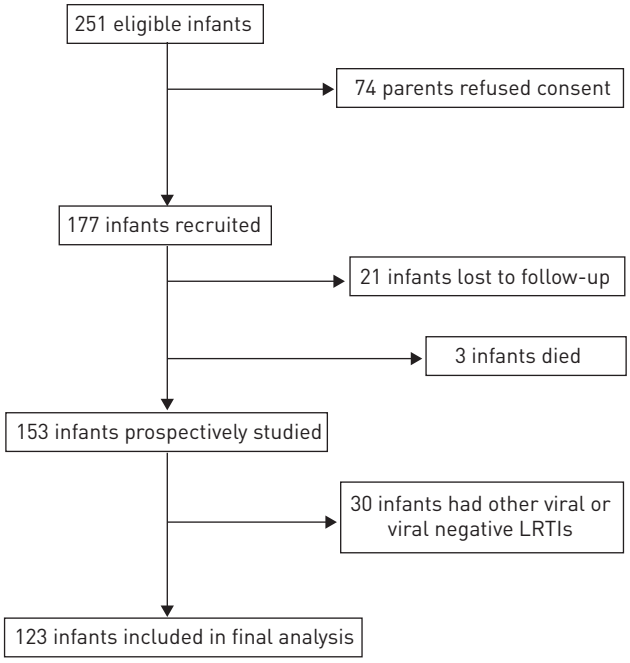

FIGURE 1 Consort diagram of recruitment. LRTI: lower respiratory tract infection.

no LRTI ($p<0.05$) and RV LRTI ($p<0.05$) groups. The RV/RSV group had more total ($p<0.05$) and respiratory-related ($p<0.05$) accident and emergency attendances than the no LRTI group (table 2). The RV/RSV LRTI group had more total outpatient attendances than the no LRTI group ($p<0.05$) (table 2).

Diary card and respiratory healthcare data

Analysis of the diary card data highlighted that the RV/RSV LRTI group had more days of inhaler use than any of the other three groups ($p<0.05$, $p<0.05$ and $p<0.05$, respectively) (table 3). Analysis of the

TABLE 1 Demographic data according to lower respiratory tract infection (LRTI) status

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	Overall p-value
Subjects	74	20	17	12	
Gestational age weeks	34.1 (25.7–35.9)	32.9 (27.4–35.7)	32.6 (28.9–35.6)	32.1 (23.0–35.9)	0.044
Birthweight g	2070 (895–3610)	1558 (670–2512)	1756 (1080–2650)	1595 (610–2546)	0.002
Males	39 (53)	9 (45)	9 (53)	5 (42)	0.85
Ethnicity					0.043
Caucasian	28 (38)	2 (10)	3 (18)	2 (17)	
Black Caribbean	19 (26)	2 (10)	5 (29)	2 (17)	
Black African	12 (16)	4 (20)	5 (29)	2 (17)	
Asian	3 (4)	2 (10)	1 (6)	0 (0)	
Hispanic	1 (1)	0 (0)	0 (0)	1 (8)	
Mixed race	11 (15)	10 (50)	3 (18)	5 (41)	
Antenatal smoking[#]	11 (15)	4 (20)	2 (12)	2 (17)	0.91
Antenatal steroids	40 (54)	16 (80)	16 (94)	8 (67)	0.014
Surfactant	11 (15)	7 (35)	1 (6)	6 (50)	0.005
Duration of ventilation days	0 (0–82)	1 (0–103)	1 (0–17)	1.5 (0–81)	0.39
Bronchopulmonary dysplasia	4 (5)	5 (25)	0 (0)	3 (25)	0.008
Family history of atopy[¶]	52 (70)	13 (65)	8 (47)	7 (58)	0.32
Breastfeeding	62 (84)	15 (75)	11 (65)	8 (67)	0.20
Eczema	20 (28)	3 (16)	2 (12)	2 (17)	0.45
Daycare attendance	2 (3)	0 (0)	1 (6)	1 (8)	0.52
Number of siblings	1 (0–5)	1 (0–5)	1 (0–4)	1 (0–4)	0.91
Palivizumab	0 (0)	3 (15)	0 (0)	1 (8)	0.005

Data are presented as n, median (range) or n (%), unless otherwise stated. RV: rhinovirus; RSV: respiratory syncytial virus. [#]: all mothers who smoked antenatally also smoked postnatally; [¶]: a family history of atopy was defined as a first degree relative (parent or sibling) with asthma, eczema, hay fever or an allergy.

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TABLE 2 Healthcare utilisation to 1 year corrected age according to lower respiratory tract infection (LRTI) status

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	p-value
Admissions	74	20	17	12	
Total	0 (0.1) (0–2)	0 (0.1) (0–1)	0 (0.6) (0–3)	1 (1.8) (0–11)	0.001
Respiratory	0 (0) (0–0)	0 (0.1)(0–1)	0 (0.4) (0–1)	0 (1.3) (0–11)	<0.001
Accident and emergency attendances					
Total	0 (0.7) (0–6)	1 (1.2) (0–5)	1 (1.6) (0–8)	1 (2.5) (0–14)	0.015
Respiratory	0 (0.1) (0–3)	0 (0.3) (0–4)	0 (0.7) (0–3)	1 (1.9) (0–12)	<0.001
Outpatient attendances					
Total	2 (3.3) (0–14)	5 (6.9) (0–18)	4 (4.0)(0–10)	5 (7.3) (1–15)	0.002
Respiratory	0 (0) (0–0)	0 (1.1) (0–9)	0 (0) (0–0)	0 (0.8) (0–8)	<0.001
GP attendances					
Total	5 (5.3) (0–20)	6 (6.8) (1–15)	5 (6.1) (2–14)	9 (8.3) (3–15)	0.069
Respiratory	0 (0.4) (0–2)	1 (1.4) (0–4)	1 (0.8) (0–3)	1 (1.8) (0–6)	0.002

Data are presented as n or median (mean) (range), unless otherwise stated. RV: rhinovirus; RSV: respiratory syncytial virus; GP: general practitioner.

respiratory health-related questionnaire data (table 4) demonstrated that a greater proportion of the RV LRTI group wheezed than the no LRTI group ($p<0.001$). Greater proportions of the RV/RSV LRTI group wheezed ($p<0.001$) and used bronchodilators ($p<0.01$) or preventers ($p<0.001$) than the no LRTI group (table 4). A greater proportion of the RV/RSV LRTI group used preventers compared with the RSV LRTI group ($p<0.001$) (table 4).

Health-related cost of care

There was a significant difference overall across the four groups in the mean costs for outpatient attendances, GP respiratory attendances and medication (table 5). The costs for outpatient attendances were greater in the RV LRTI group compared with the no LRTI group ($p<0.05$) and compared with the RSV LRTI group ($p<0.05$). There were no significant differences between the four groups on *post hoc* analysis for the costs for GP respiratory attendances or medications.

Compared with the no LRTI group, the RV/RSV LRTI group had the highest mean cost (difference GBP7035), followed by the RV LRTI group (difference GBP1086) and, finally, the RSV LRTI group (difference GBP678). These differences were reduced after adjusting for birthweight, gestational age, antenatal steroid and surfactant use, but overall the differences remained statistically significant. In addition, further adjustment for BPD reduced the differences slightly more, but the overall differences in costs between groups remained significant ($p=0.045$) (table 6). The health-related cost of care of the RV LRTI group was similar to that of the RSV LRTI group ($p=0.83$) (table 6). The ordering of costs was the same for total respiratory costs and the differences in mean costs were statistically significant ($p=0.003$) (table 7). Adjustment for neonatal factors for total respiratory costs was not possible as models with possible confounders would not converge.

Discussion

We have demonstrated that prematurely born infants developing RV LRTIs had increased health-related cost of care during infancy compared with infants who did not develop an LRTI. Our results demonstrating

TABLE 3 Diary card data at 1 year corrected age

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	p-value
Subjects#	49	16	11	9	
Days of cough	0 (3.3) (0–31)	0.5 (4.9) (0–18)	0 (6.5) (0–23)	3 (7.8) (0–30)	0.40
Days of wheeze	0 (0.7) (0–12)	0 (2.4) (0–27)	0 (0.1) (0–1)	0 (4.4) (0–30)	0.035
Days using antibiotics	0 (0) (0–2)	0 (0) (0–0)	0 (0.6) (0–7)	0 (1.1) (0–5)	0.042
Days using inhalers	0 (0) (0–0)	0 (1.9) (0–30)	0 (0) (0–0)	0 (4.3) (0–30)	<0.001

Data are presented as n or median (mean) (range), unless otherwise stated. LRTI: lower respiratory tract infection; RV: rhinovirus; RSV: respiratory syncytial virus. #: not all patients completed the diary card.

TABLE 4 Respiratory health-related questionnaire data

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	p-value
Subjects[#]	71	19	17	12	
Did your child cough in the first year?	66 (93)	19 (100)	17 (100)	12 (100)	0.47
Did your child wheeze in the first year?	11 (15)	13 (68)	8 (47)	9 (75)	<0.001
Did your child use any medication for a chest problem in the first year?	17 (24)	10 (53)	9 (19)	7 (58)	0.008
Bronchodilators, *e.g.* salbutamol?	6 (8)	6 (32)	6 (35)	6 (50)	<0.001
Antibiotics?	13 (18)	9 (47)	7 (37)	6 (50)	0.01
Preventers, *e.g.* steroids or montelukast?	0 (0)	2 (11)	0 (0)	3 (25)	0.001
Has your child ever been diagnosed with asthma by a doctor?	0 (0)	0 (0)	0 (0)	1 (8)	0.10

Data are presented as n or n (%), unless otherwise stated. LRTI: lower respiratory tract infection; RV: rhinovirus; RSV: respiratory syncytial virus. [#]: not all parents completed the questionnaire and those reported responded yes to the question.

the RV LRTI group suffered chronic respiratory morbidity are in keeping with previous findings in eight prematurely born infants [9]. In that series, however, all of the infants were born very prematurely, had had BPD and were hospitalised with the RV LRTI [9]. Whereas, the 20 infants in the RV group presently studied were born at a higher gestational age, only 25% had had BPD and only one of the 20 infants had been hospitalised with the RV LRTI.

The RV/RSV group, like the RSV group, had significantly more admissions and accident and emergency attendances than the no LRTI group. It has been previously reported that infants who develop a dual infection either with RSV and human metapneumovirus [18] or RSV and RV [19] are more likely to develop a severe LRTI, as proven by requirement for a paediatric intensive care unit admission. In this study, however, only three of the infants had RV and RSV detected during the same LRTI. The higher admission rate of the RV/RSV group may reflect a functional predisposition to severe viral LRTIs. We have previously shown that very prematurely born infants who developed an RSV LRTI and subsequent chronic respiratory morbidity had significantly worse pre-morbid lung function [20]. In addition, among infants with a wider range of gestational ages, those who required hospitalisation for an RSV LRTI had significantly poorer pre-morbid lung function [21]. In infants born at term, poorer pre-morbid lung function, that is, a higher resistance of the respiratory system in the first 2 months after birth, was associated with an increased

TABLE 5 Costs of care (GBP) to 1 year corrected age according to lower respiratory tract infection (LRTI) status

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	Overall p-value
Subjects	74	20	17	12	
Admission					
Total cost	188±654	139±450	665±1006	5771±10168	0.51
Respiratory cost	0±0	48±214	337±627	3470±7740	0.83
Accident and emergency					
Total cost	59±100	109±148	158±228	286±509	0.09
Respiratory cost	5±33	35±116	77±113	247±486	0.73
Outpatient					
Total cost	445±418	1402±1689	522±321	1227±1317	0.002
Respiratory cost	0±0	605±1444	0±0	362±1210	Unable to calculate[#]
GP					
Total cost	287±252	439±380	313±196	731±931	0.05
Respiratory cost	16±25	55±52	32±37	75±95	0.02
Medication					
Total cost	109±173	672±1218	104±150	719±1334	0.04
Respiratory cost	2±3	484±1195	3±5	286±963	0.09
Overall					
Total cost	980±958	2067±1794	1658±1299	8015±12072	0.001
Respiratory cost	27±78	740±1477	446±691	4153±9335	0.003

Data are presented as n or mean± SD, unless otherwise stated. RV: rhinovirus; RSV: respiratory syncytial virus; GP: general practitioner. [#]: generalised linear model did not converge and so the p-value was unobtainable.

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TABLE 6 Unadjusted and adjusted mean total costs (GBP) according to lower respiratory tract infection (LRTI) status

	Subjects n	Unadjusted mean difference[#]	95% CI for difference	Adjusted mean difference[¶]	95% CI for difference	Adjusted mean difference[+]	95% CI for difference
No LRTI	74	Reference group	Overall p=0.001		Overall p=0.040		Overall p=0.045
RV LRTI	20	1086	54–2019	323	-441–1087	278	-448–1005
RSV LRTI	17	678	-141–1497	151	-655–957	172	-631–975
RV/RSV LRTI	12	7035	2497–11573	5851	1789–9912	5769	1711–9828

RV: rhinovirus; RSV: respiratory syncytial virus. [#]: difference in means between the reference group and each other group in turn; [¶]: adjustment for birthweight, gestational age, antenatal steroid use and surfactant use; [+]: adjustment for birthweight, gestational age, antenatal steroid use, surfactant use and bronchopulmonary dysplasia.

risk of the occurrence and duration of RV-associated wheeze during infancy [22]. It is thus possible that poorer pre-morbid lung function might explain the chronic respiratory morbidity of our RV group.

In infants born at term, RV seems to preferentially affect the lower airways, causing bronchiolitis in atopic children prone to wheezing [23–25]. It has been suggested that the reduced interferon (IFN)-γ responses in infancy in children with atopy may partly explain why atopy is a risk factor for human rhinovirus-induced wheezing [5]. Interferon responses in early life are inversely associated with the severity of viral respiratory illnesses [26]. In addition, infants with low *ex vivo* IFN-γ responses in early life are more likely to have frequent viral respiratory illnesses, including those associated with wheezing [27]. In this study, we performed skin prick tests on the infants, despite our experience being that parents of prematurely born infants frequently refuse skin prick testing in a research setting, as do prematurely born children [1]. We did not, however, see any significant differences between our groups in a family history of atopy or the proportion of infants who had eczema. Whether atopy does predispose prematurely born infants to RV LRTIs needs further investigation.

Our study has a number of strengths and some limitations. We prospectively followed a large cohort of prematurely born infants from birth to 1 year of corrected age. We were able to investigate symptomatic LRTIs, not only in hospitalised infants, but also in those with LRTIs in the community. This is important, as we have previously demonstrated that infants with RSV LRTI not requiring hospitalisation also suffer increased respiratory morbidity [2]. In addition, the NPAs were tested by real-time PCR multiple assay that had the advantage of high sensitivity to detect a wide range of respiratory viruses [28, 29]. A limitation of our study, however, is that we only obtained NPAs when the infants were symptomatic and thus we cannot comment as to whether asymptomatic LRTIs increase healthcare utilisation at follow-up. Both the RV LRTI and the RV/RSV LRTI groups had a median of two LRTIs, but the RSV LRTI group had a median of one LRTI, which might have influenced differences in the cost of care. The RV LRTI and RSV LRTI groups, however, had similar costs of care, but the type of healthcare utilisation that resulted in the increased costs of care compared with the no LRTI group differed between the two groups. Infants were recruited before the RSV season to ensure all infants were exposed to a whole RSV season. All infants, however, were followed for 1 year so that seasonal variations between viruses would not affect our results. Our groups differed significantly in respect to certain of their demographics; the no LRTI group were more mature at birth, of higher birthweight and were less likely to have received antenatal steroids. Our findings of

TABLE 7 Unadjusted mean difference in respiratory costs (GBP) according to lower respiratory tract infection (LRTI) status

	Subjects n	Unadjusted mean difference[#]	95% CI for difference
No LRTI	74	Reference group	Overall p=0.003
RV LRTI	20	713	79–1346
RSV LRTI	17	418	98–738
RV/RSV LRTI	12	4125	-952–9203

RV: rhinovirus; RSV: respiratory syncytial virus. [#]: difference in means between the reference group and each other group in turn. An adjusted model could not be fitted due to convergence problems.

increased health-related costs of care compared with the no LRTI group, however, remained statistically significant after adjusting for neonatal factors.

In conclusion, RV LRTIs in prematurely born infants were associated with an increased health-related cost of care during infancy. The increased health-related cost of care in the RV LRTI group was due to more outpatient and respiratory-related GP attendances and a greater proportion of the group wheezed at follow-up, whereas in the RSV LRTI group it was due to more admissions. Those data suggest the RV LRTI group suffered greater chronic respiratory morbidity than the RSV LRTI group.

References

1 Greenough A, Alexander J, Boit P, *et al.* School age outcome of hospitalisation with respiratory syncytial virus infection of prematurely born infants. *Thorax* 2009; 64: 490–495.
2 Broughton S, Roberts A, Fox G, *et al.* Prospective study of health care utilisation and respiratory morbidity due to RSV infection in prematurely born infants. *Thorax* 2005; 60: 1039–1044.
3 Broughton S, Sylvester KP, Fox G, *et al.* Lung function in prematurely born infants following viral lower respiratory tract infections. *Pediatr Infect Dis J* 2007; 26: 1019–1024.
4 Jackson DJ, Gangnon RE, Evans MD, *et al.* Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008; 178: 667–672.
5 Jartti T, Korppi M. Rhinovirus induced bronchiolitis and asthma development. *Pediatr Allergy Immunol* 2011; 22: 350–355.
6 Midulla F, Pierangeli A, Cangiano G, *et al.* Rhinovirus bronchiolitis and recurrent wheezing: 1 year follow up. *Eur Respir J* 2012; 39: 396–402.
7 Guilbert TW, Singh AM, Danov Z, *et al.* Decreased lung function after preschool wheezing rhinovirus illnesses in children at risk to develop asthma. *J Allergy Clin Immunol* 2011; 128: 532–538.
8 Lemanske RF, Jackson DJ, Gangnon RE, *et al.* Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005; 116: 571–577.
9 Chidekel AS, Rosen CL, Bazzy AR. Rhinovirus infection associated with serious lower respiratory illness in patients with bronchopulmonary dysplasia. *Pediatr Infect Dis J* 1997; 16: 43–47.
10 Auburn H, Zuckerman M, Broughton S, *et al.* Detection of nine respiratory RNA viruses using three multiplex RT-PCR assays incorporating a novel RNA internal control transcript. *J Virol Methods* 2011; 176: 9–13.
11 Brittain-Long R, Nord S, Olofsson S, *et al.* Multiplex real-time PCR for detection of respiratory tract infections. *J Clin Virology* 2008; 41: 53–56.
12 Lu X, Chittaganpitch M, Olsen S, *et al.* Real-time PCR assays for detection of bocavirus in human specimens. *J Clin Microbiology* 2006; 44: 3231–3235.
13 Nix WA, Maher K, Johansson ES, *et al.* Detection of all known parechoviruses by real-time PCR. *J Clin Microbiology* 2008; 46: 2519–2524.
14 Rolfe KJ, Parmar S, Mururi D, *et al.* An internally controlled, one-step, real-time RT-PCR assay for norovirus detection and genogrouping. *J Clin Virology* 2007; 39: 318–321.
15 Thompson SG, Barber JA. How should cost data in pragmatic randomised trials be analysed. *BMJ* 2000; 320: 1197–2000.
16 Barber J, Thompson S. Multiple regression of cost data: use of generalised linear models. *J Health Serv Res Policy* 2004; 9: 197–204.
17 Peacock J, Peacock P. The Oxford Handbook of Medical Statistics, Chapter 12. Oxford, Oxford University Press, 2010.
18 Semple MG, Cowell A, Dove W, *et al.* Dual infection of infants by human metapneumovirus and human respiratory syncytial virus is strongly associated with severe bronchiolitis. *J Infect Dis* 2005; 191: 382–386.
19 Richard N, Komurian-Pradel F, Javouhey E, *et al.* The impact of dual viral infection in infants admitted to a pediatric intensive care unit associated with severe bronchiolitis. *Pediatr Infect Dis J* 2008; 27: 213–217.
20 Broughton S, Bhat R, Roberts A, *et al.* Diminished lung function, RSV infection, and respiratory morbidity in prematurely born infants. *Arch Dis Child* 2006; 91: 26–30.
21 Drysdale SB, Wilson T, Alcazar M, *et al.* Lung function prior to viral lower respiratory tract infections in prematurely born infants. *Thorax* 2011; 66: 468–473.
22 van der Zalm MM, Uiterwaal CS, Wilbrink B, *et al.* The influence of neonatal lung function on rhinovirus associated wheeze. *Am J Respir Crit Care Med* 2011; 183: 262–267.
23 Gern JE, Busse WW. Association of rhinovirus infections with asthma. *Clin Microbiol Rev* 1999; 12: 9–18.
24 Eirnarsson O, Geba GP, Zhu Z, *et al.* Interleukin-11: stimulation *in vivo* and *in vitro* by respiratory viruses and induction of airways hyperresponsiveness. *J Clin Invest* 1996; 97: 915–924.
25 Gern JE, Vrtis R, Grindle KA, *et al.* Relationship of upper and lower airway cytokines to outcome of experimental rhinovirus infection. *Am J Respir Crit Care Med* 2000; 162: 2226–2231.
26 Papadopoulos NG, Stanciu LA, Papi A, *et al.* A defective type I response to rhinovirus in atopic asthma. *Thorax* 2002; 57: 328–332.
27 Copenhaver CC, Gern JE, Li Z, *et al.* Cytokine response patterns, exposure to viruses and respiratory infections in the first year of life. *Am J Respir Crit Care Med* 2004; 170: 175–180.
28 Kuypers J, Wright N, Ferrenberg J, *et al.* Comparison of real-time PCR assays with fluorescent-antibody assays for diagnosis of respiratory virus infections in children. *J Clin Microbiol* 2006; 44: 2382–2388.
29 van de Pol AC, van Loon AM, Wolfs TF, *et al.* Increased detection of respiratory syncytial virus, influenza viruses, parainfluenza viruses, and adenoviruses with real-time PCR in samples from patients with respiratory symptoms. *J Clin Microbiol* 2007; 45: 2260–2262.

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