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Rhinovirus infection and healthcare utilisation in prematurely born infants

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ABSTRACT

Question of the study: Do rhinovirus lower respiratory tract infections (RV) LRTIs in prematurely born infants increase health related cost of care during infancy?

Patients and methods: 153 infants born <36 weeks of gestation were prospectively followed to one year. Cost of care was calculated from the NHS reference costing scheme and health care utilisation determined by examining hospital/general practitioner records.

Results: Twenty infants developed RV LRTIs (RV group), 17 RSV LRTIs (RSV group), 12 both RV and RSV LRTIs (RV/RSV group), 74 had no LRTI (no LRTI group). Compared to the no LRTI group, the RV/RSV LRTI group had the greatest increase in adjusted mean cost (difference = £5769), followed by the RV LRTI group (difference = £278), then the RSV LRTI group (difference = £172), p=0.045. The RV group had more out-patient ($p<0.05$) and respiratory related general practitioner ($p<0.05$) attendances and more wheezed at follow up ($p<0.001$) than the no LRTI group and more respiratory related out-patient attendances than the RSV LRTI group ($p<0.05$).

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

Key words: health care utilisation; health related cost of care; lower respiratory tract infection; respiratory syncytial virus; rhinovirus

INTRODUCTION

Respiratory syncytial virus (RSV) lower respiratory tract infections (LRTIs) are associated with increased chronic respiratory morbidity and health care utilisation in prematurely born infants who did [1] or did not [2, 3] develop bronchopulmonary dysplasia (BPD). Amongst those who had had BPD, health care utilisation and the related cost of care were increased up to seven years of age and lung function was lower than that of controls at ten 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 a RV LRTI would suffer increased health care 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 was similar to that associated with RSV LRTI.

MATERIALS AND METHODS

Study subjects

Infants born less than 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 1 October to 31 March, consistent with the UK

experience. Consecutive infants, including twins and triplets, who lived within the King's College Hospital NHS Foundation Trust (KCH) catchment, 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 NICU 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 one year of corrected age. The parents were asked to contact the research team when their infant was symptomatic with signs consistent with a LRTI, that is, cough, wheeze, and/or shortness of breath. In addition, parents were telephoned every two weeks by researchers until the infants were one 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 a 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 PCR in monoplex with a DNA internal control (also a monoplex) [10]. In addition another multiplex, including a MS2 phage internal control, was developed using

previously published primers and probes [11-14] which tested for enterovirus, parechovirus and human bocavirus.

Hospital records were examined to identify admissions, Accident and Emergency (A and E) and out-patient attendances and all medications prescribed. General Practitioner (GP) records were examined to identify any hospital readmissions, A and E attendances, the number of out-patient 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 one month when their infant was 11 months of corrected age and a respiratory health related questionnaire about their infant when the infant was one 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, antibiotics). To calculate the cost of care, the NHS reference costing scheme was used which gives national average costs for in- and out-patient hospital attendances 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:

(i) Infants who never had a symptomatic LRTI (no LRTI).

(ii) Infants who had at least one LRTI from which RV was detected from the NPA (RV LRTI)

(iii) Infants who had at least one LRTI from which RSV was detected from the NPA (RSV LRTI).

(iv) 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 a 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 Thomson [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 were 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 firstly 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 approximately 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

Two hundred and fifty one infants were eligible for inclusion into the study (Figure 1). The 153 (84 males) infants who completed the study had a median gestational age of 34 (range 23-35) weeks and a birth weight of 1890 (range 534-3610) g. Twenty infants developed RV LRTIs, 17 developed RSV LRTIs, 12 developed both RV/RSV LRTIs and 74 infants had no LRTI. Thirty 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 ($p<0.01$, $p<0.01$).

(i) 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), birth weight (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, $p<0.05$).

Table 1: Demographic data according to LRTI status.

Data presented as median (range) or n (%).

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	Overall p value
n	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
Birth weight (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**
Day Care	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

* 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, hayfever or an allergy

(ii) Healthcare utilisation

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

The RV LRTI group had more total ($p<0.05$) and respiratory related ($p<0.05$) out-patient attendances and general practitioner (GP) respiratory related attendances ($p<0.05$) than the no LRTI group and more respiratory related out-patient 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 ($p<0.05$) A and E attendances than the no LRTI group (Table 2). The RV/RSV group had more total and respiratory related hospitalisations than both the 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 ($p<0.05$) A and E attendances than the no LRTI group (Table 2). The RV/RSV LRTI group had more total out-patient attendances than the no LRTI group ($p<0.05$) (Table 2).

Table 2: Health care utilisation to one year corrected age according to LRTI status

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

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	p value
n	74	20	17	12	
Admissions					
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
A and E 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
General Practice 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

(iii) Diary card and respiratory health care 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 $p<0.05$) (Table 3). Analysis of the 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 to the RSV LRTI group ($p<0.001$) (Table 4).

Table 3: Diary card data at one year corrected age.

Data presented as median [mean] (range). Not all patients completed the diary card

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	p
n	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

Table 4: Respiratory health related questionnaire data.

Data presented as n (%) responding yes to the question.

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	
N*	71	19	17	12	p
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, 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

*not all parents completed the questionnaire

(iv) Health related cost of care

There was a significant difference overall across the four groups in the mean costs for out-patient attendances, GP respiratory attendances and medication (Table 5). The costs for out-patient attendances were greater in the RV LRTI group compared to the no LRTI group ($p<0.05$) and compared to 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 to the no LRTI group, the RV/RSV LRTI group had the highest mean cost (difference = £7035), then the RV LRTI group (difference = £1086), followed by the RSV LRTI group (difference = £678). These differences were reduced after adjusting for birth weight, gestational age, antenatal steroid and surfactant use, but overall the differences remained statistically significant. Further adjustment for BPD in addition, 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.

Table 5: Costs of care (UK£) to one year corrected age according to LRTI status
Data are presented as mean [SD]

	No LRTI	RV LRTI	RSV LRTI	RV/RSV LRTI	Overall p value
n	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
A and E					
Total cost	59 [100]	109 [148]	158 [228]	286 [509]	0.09
Respiratory cost	5 [33]	35 [116]	77 [113]	247 [486]	0.73
Out-patient					
Total cost	445 [418]	1402 [1689]	522 [321]	1227 [1317]	0.002
Respiratory cost	0 [0]	605 [1444]	0 [0]	362 [1210]	Not able to calculate[1]
General practice					
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

[1] Generalised linear model did not converge and so the p value is unobtainable

Table 6: Unadjusted and adjusted mean total costs (UK £) according to LRTI status

	Unadjusted mean Difference[1] (UK £)	95% CI for difference	Adjusted mean difference[2] (UK £)	95% CI for difference	Adjusted mean difference[3] (UK £)	95% CI for difference
No LRTI (n=74)	Reference group	Overall p value: p=0.001		Overall p value: p=0.040		Overall p value: p=0.045
RV LRTI (n=20)	1086	54 to 2019	323	-441 to 1087	278	-448 to 1005
RSV LRTI (n=17)	678	-141 to 1497	151	-655 to 957	172	-631 to 975
RV/RSV LRTI (n=12)	7035	2497 to 11573	5851	1789 to 9912	5769	1711 to 9828

[1] Difference in means between the reference group and each other group in turn

[2] Adjustment for birth weight, gestational age, antenatal steroid use and surfactant use

[3] Adjustment for all as in [2] plus BPD

Table 7: Unadjusted mean difference in respiratory costs (UK £) according to LRTI status

	Unadjusted mean difference[1] (UK £)	95% CI for difference
No LRTI (n=74)	Reference group	Overall p value: p=0.003
RV LRTI (n=20)	713	79 to 1346
RSV LRTI (n=17)	418	98 to 738
RV/RSV LRTI (n=12)	4125	-952 to 9203

[1] Difference in means between the reference group and each other group in turn. An adjusted model could not be fitted due to convergence problems

DISCUSSION

We have demonstrated that prematurely born infants developing RV LRTIs had increased health related cost of care during infancy compared to infants who did not develop a LRTI. Our results demonstrating 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, as the RSV group, had significantly more admissions and A and E 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] were more likely to develop a severe LRTI, as evidenced by requirement for a pediatric 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 premorbid lung function [20]. In addition, amongst infants with a wider range of gestational ages, those who required hospitalisation for an RSV LRTI had significantly poorer premorbid lung function [21]. In infants born at term, poorer premorbid lung function, that is a higher resistance of the respiratory

system in the first two months after birth was associated with an increased risk of the occurrence and duration of RV-associated wheeze during infancy [22]. It is thus possible that poorer premorbid 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-gamma (IFN-γ) responses in infancy in children with atopy may partly explain why atopy is a risk factor for HRV-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 did skin prick test the infants, as our experience is 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 one 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 which resulted in the increased costs of care compared to 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 one year so 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 birth weight and less likely to have received antenatal steroids. Our findings of increased health related costs of care compared to 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 out-patient and respiratory related general practitioner 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.

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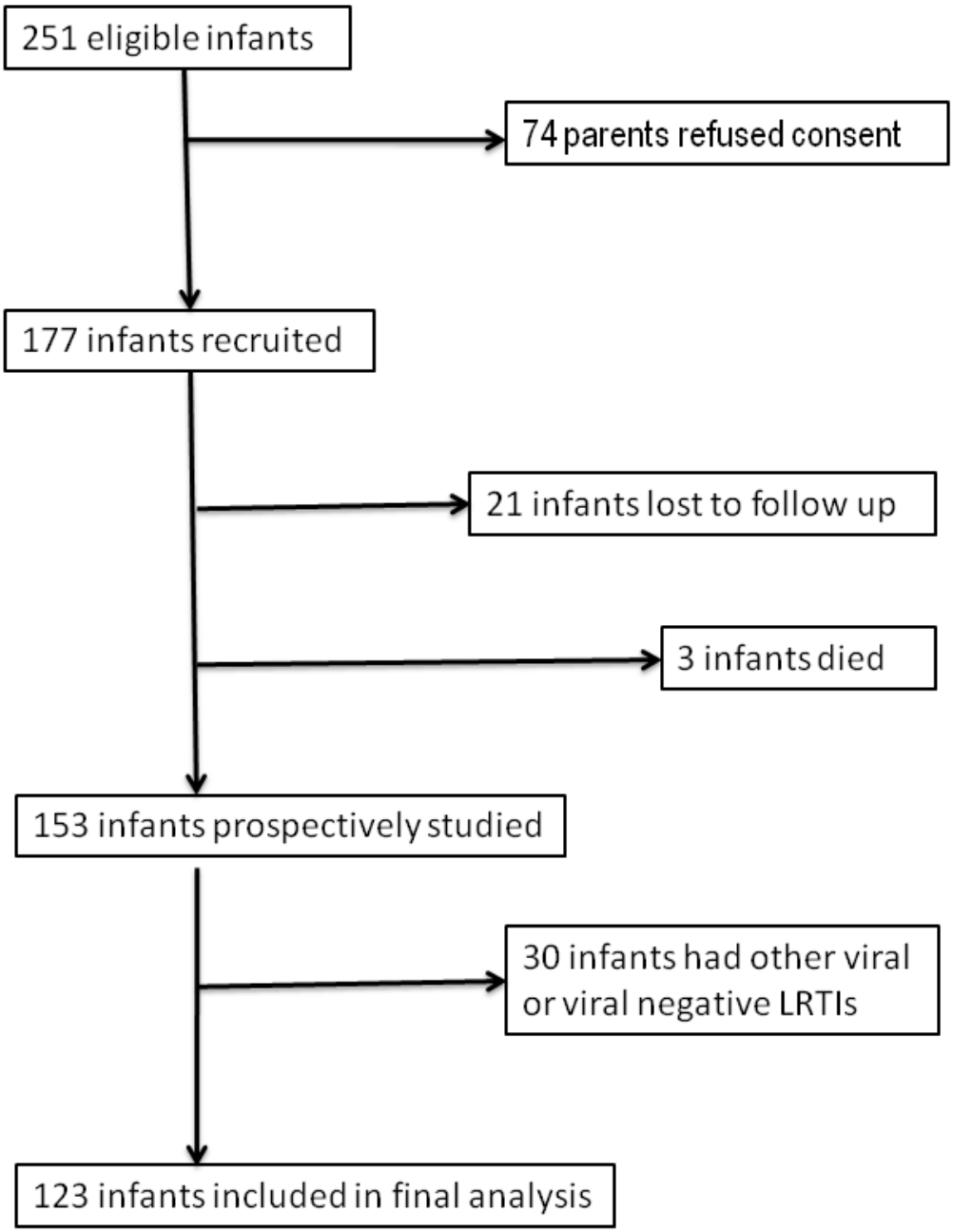
FIGURE LEGEND

Figure 1: Consort diagram of recruitment.


251 eligible infants
74 parents refused consent
177 infants recruited
21 infants lost to follow up
3 infants died
153 infants prospectively studied
30 infants had other viral or viral negative LRTIs
123 infants included in final analysis