Respiratory viral infections in infancy and school age respiratory outcomes

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Running head: School age respiratory outcomes after viral LRTIs

ABSTRACT

Objectives: To determine the impact of viral lower respiratory tract infections (LRTIs) in infancy, including rhinovirus (RV) and respiratory syncytial virus (RSV), on school age pulmonary function and healthcare utilisation of prematurely born children.

Working hypothesis: School age respiratory outcomes would be worse in children who had viral LRTIs in infancy.

Study design: Prospective study.

Subject selection: A cohort of prematurely born children was recalled, who had all LRTIs during infancy documented.

Methods: Pulmonary function was assessed at five to seven years of age and health related costs of care from aged one to follow-up determined.

Results*:* Fifty-one children, median gestational age 33^{+6} weeks, were assessed at a median (IQR) age 7.03 (6.37 – 7.26) years. Twenty-one children had experienced no LRTI, 14 RV LRTI, 10 RSV LRTI and 6 another viral LRTI (other LRTI). Compared to the no LRTI group, the RV group had a lower FEV_1 (p=0.033) and the other LRTI group a lower FVC (p=0.006). Non-respiratory medication costs were higher in the RV (p=0.018) and RSV (p=0.013) groups. Overall respiratory healthcare costs were relatively low in the RV (£153/year) and RSV (£27/year) groups and did not differ significantly from the no LRTI group; the other LRTI group had higher respiratory healthcare costs (p=0.042).

Conclusions: In moderately prematurely born children, RV and RSV LRTIs in infancy were not associated with higher respiratory healthcare costs after infancy. Children who experienced LRTIs caused by other respiratory viruses had higher respiratory healthcare costs and greater pulmonary function impairment.

INTRODUCTION

Chronic respiratory morbidity is common in prematurely born infants. The aetiology of that respiratory morbidity is multifactorial and includes respiratory syncytial virus (RSV) lower respiratory tract infections (LRTIs). Prematurely born infants are functionally [1 2] and genetically [3] predisposed to RSV LRTIs and have worse lung function in infancy after the LRTI [4 5]. Very prematurely born infants who had bronchopulmonary dysplasia (BPD) and then subsequently suffered an RSV LRTI hospitalization in the first two years had increased healthcare utilization and poorer pulmonary function at school age [6]. In an unselected cohort of prematurely born infants, RSV LRTIs in the first two years after birth were associated with higher healthcare costs in both the first and second years [7], but the longer term impact has not been reported in such a population. There are limited data regarding the impact of other respiratory viral infections on longer-term respiratory-related outcomes in prematurely born children. In eight prematurely born infants with BPD, development of rhinovirus (RV) LRTIs was associated with a worsening of their clinical status requiring the addition of new therapies for prolonged periods of time [8]. We demonstrated that prematurely born infants who had developed RV LRTIs followed up to one year of age had higher healthcare utilisation costs, greater numbers of hospital outpatient and respiratory-related general practitioner (GP) attendances than infants without a viral LRTI [9]. It is not known if RV has similar adverse effects in older children born prematurely. The aim, therefore, of this study was to determine the association between viral LRTIs in infancy, particularly RSV and RV LRTIs, on school age lung function and childhood health related costs of care in prematurely born children.

MATERIALS AND METHODS

All children were recruited from our previously reported cohort of children born at less than 36 weeks of gestational age [2]. The infants were consecutively recruited from the neonatal unit or postnatal wards of King's College Hospital NHS Foundation Trust (KCH) prior to the onset of the RSV season (defined as 1st October to 31st March) during 2008 and 2009. After discharge, parents contacted the research team on every occasion when their infants showed symptoms consistent with an LRTI. Whenever an LRTI was reported a researcher visited the infant at home or in hospital and obtained a nasopharyngeal aspirate (NPA). Real-time reverse transcriptase polymerase chain reaction (PCR) was performed on the NPA samples to test for thirteen viruses (rhinovirus, human metapneumovirus, influenza A and B, parainfluenza 1-3, RSV A and B, adenovirus, enterovirus, parechovirus and human bocavirus).

All participants from the initial cohort (n=159) were invited to participate in the current study, but those who had moved outside reasonable travelling distance to KCH were invited to give consent for interrogation of their healthcare record only. Up to three invitation letters were sent to parents, with follow-up phone calls made after each letter. The follow up study was approved by the National Research Ethics Service Committee West Midlands – Coventry & Warwickshire (reference 15/WM/0117). Parents gave informed, written consent for their child to participate. No child was tested within two weeks of any acute respiratory illness.

Assessment of pulmonary function

All pulmonary function testing was performed by the same operator (VMacB). Spirometry was conducted in accordance with ATS/ERS criteria [10] using a Jaeger Masterscreen device. Forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and FEV_1/FVC ratio were measured and expressed as standardized residuals ('z scores') relative to published predicted values taking into account sex, age and height [11]. Impulse oscillometry was conducted Jaeger Masterscreen IOS) in accordance with published guidelines [12], with the mean values for respiratory system resistance at 5Hz (R5) and 20Hz (R20) from three reproducible measurements reported and expressed as z scores relative to published predicted values [13].

The parasternal intercostal electromyogram was recorded from the second intercostal space during ten minutes of tidal breathing as per our previous work [14]. Full methodological details are given in the online supplementary material. EMGpara was log-transformed and expressed relative to predicted based on previously published data [14].

On the day of testing, pulmonary function and EMGpara were measured twice, once at baseline and then repeated twenty minutes after administration of 400µg salbutamol via a metered-dose inhaler and spacer device.

Healthcare utilization and health related cost of care

Participants' General Practitioners (GP) records were inspected to identify any hospital admissions, emergency department visits, hospital outpatient appointments,

other contacts with health professionals, GP attendances and all medication prescriptions. All visits for routine immunisations or health screening were not included in the analysis as these were deemed usual care for children. GP and hospital costs were calculated using the National Health Service (NHS) reference costing scheme [15] and medication costs using the NHS indicative costs listed within the British National Formulary [16]. Each healthcare contact or prescription was defined as respiratory-related or non-respiratory related through examination of clinical records to determine the primary reason for presentation. Non-respiratory costs included both childhood illnesses and injuries (such as gastrointestinal conditions and fractures) and a small number of children with complex conditions requiring extensive input from multiple clinical specialties. Respiratory medications were antibiotics taken for respiratory disorders, preventers and treatment for asthma. All other medications were classified as non respiratory. All healthcare costs were divided by the number of years of follow-up and expressed as UK pounds (£) per year for medication costs, hospital costs (inpatient stays, outpatient appointments and emergency department visits) and overall health related costs of care, with GP attendances expressed as number of visits per year. Healthcare utilization and health related cost of care were not reported for the first year after birth as these were previously reported [9].

Analysis

Comparisons were made between those children who did not have an LRTI (no LRTI group) and the virus groups (RSV, RV or other virus). Children were included in the RSV group if they had at least one RSV LRTI regardless of whether they had another viral LRTI. Children were included in the RV group if they had at least one RV

LRTI, but not RSV LRTI regardless of whether they had another viral LRTI. Children were included in the other LRTI group if they had a viral LRTI, but neither RSV nor RV was detected. Due to substantial skew in several variables non-parametric statistics were used for all analyses, with the Kruskal Wallis test used to examine differences across groups and the Mann-Whitney test used *post hoc* to compare individual virus groups to the no LRTI group. The healthcare costs data are presented as mean (95% CI) in order to preserve total costs as per our previous work [9].

RESULTS

Fifty-one children were recruited, healthcare utilisation data only were available from four children due to geographical distance precluding attendance for full testing. A flow chart detailing reasons for non-participation is included within the online supplementary material. The characteristics of the children included did not differ significantly from those that did not with regard to birth weight, gestational age at birth, sex, duration of mechanical ventilation at birth or the proportion who were very low birth weight (birth weight <1500g). There were, however, significantly greater proportions of extremely low birth weight babies (birth weight <1000g, p=0.006) and those who had had BPD (oxygen dependency, p=0.006) in those included in the current study (Table 1).

Compared to the no LRTI group, at the time of study, the RV group was older (p=0.018) and the median BMI of the 'other LRTI' group was higher (p=0.035), though with all values remaining within normal limits. The across-group comparison demonstrated a significant difference in birth weights, but this did not reach statistical significance on *post hoc* testing. There were no other significant differences between the groups (Table 2).

Several children within each virus group had experienced multiple viral LRTIs or viral co-infections (Table 3). Three children within the RSV group required hospital admission, one of whom had two admissions. There were no admissions in the RV or other LRTI groups. Within the 14 children with RV LRTI, five had experienced RV type C, one type B, two type A and in six infants the subtype was not identified.

Pulmonary function

Spirometry, IOS and EMGpara assessments were attempted in all of the 47 children attending for pulmonary function testing. It was possible to assess more children with EMGpara than the other two techniques. Spirometry was successfully undertaken in 33 (70%) children, IOS in 39 (83%) and EMGpara in 43 (91%) ($p=0.028$).

FEV_1 and FVC differed significantly across the virus groups (Table 4). Compared to the no LRTI group, the RV group had a lower median FEV_1 ($p=0.033$) and the other LRTI group a lower median FVC ($p=0.009$). There were no other significant differences in lung function between the groups.

Health related cost of care

Overall respiratory-related healthcare costs and respiratory-related GP attendances were higher in the other LRTI group ($p=0.042$ and $p=0.012$ respectively). The overall respiratory related healthcare costs did not differ significantly between the RV, RSV and the no LRTI group. Non-respiratory medication costs were significantly higher in both the RV ($p=0.018$) and RSV ($p=0.013$) groups (Table 5).

DISCUSSION

We have demonstrated that respiratory viral infections in infancy were associated with poorer respiratory outcomes at school age, as demonstrated by a lower FEV_1 in children who had had RV LRTI and lower FVC in the other LRTI group. Furthermore, higher healthcare utilisation costs were seen in children who had experienced other viral LRTIs. In a previous study, prematurely born infants had a higher airway resistance at one year of age following respiratory viral infections [17]. Those results [17] are in keeping with findings in term born infants [18] and the lung function abnormalities and increased occurrence of wheezing at school age in term born children following RSV infections in infancy [19-23]. The abnormalities we report differ from those previous findings, as there were no differences in FEV_1/FVC across the groups. Hence, we have not demonstrated a consistent obstructive lung function deficit (though FEV_1 was lower in the RV group) and the results suggest a restrictive rather than an obstructive pattern. The reduced FVC in the other LRTI group may indicate reduced lung growth, though full lung volume measurements would be required to confirm this. We, therefore, suggest that they may not be a consequence of the viral infections, but rather indicate a long-standing lung function defect which may have put the infants at increased risk of becoming symptomatic from a viral LRTI.

A range of tests were used to assess respiratory function, as we felt that the use of non-volitional tests of pulmonary function would be advantageous in the assessment of a population known to exhibit higher rates of motor and cognitive impairments. There was indeed a significant difference in the success of the children being able to

perform three tests, with spirometry being the least successfully accomplished and EMGpara being the most successfully accomplished. Indeed, only 70% of the children, despite the majority being born moderately prematurely, were able to perform spirometry at school age. The EMGpara results, however, did not differ significantly between the three groups. It is possible that EMGpara, which is measured during tidal breathing, may be less sensitive to small deficits in pulmonary function that are apparent during the forced manoeuvres required of spirometry, Furthermore, the reference data are more limited for this technique due to its novelty and, therefore, subtle abnormalities may be not be detected.

The median gestational age at birth of the children was 34 weeks indicating that the majority had been born moderately prematurely. Such subjects, do, however, suffer morbidity following RSV infections. A systematic review demonstrated amongst infants born between 29 and 35 weeks the rates of RSV hospitalization varied from 2.3 to 10% and recurrent wheezing rates ranged from 20.7% to 42.8% one to two years after RSV hospitalization [24]. Other studies have shown consistently higher healthcare costs in the first year after birth in those infants experiencing LRTI, whether or not hospitalisation was required [25]. In this study, the overall respiratory healthcare costs in all groups were relatively low. We did not, however, include the first year's costs in this study (these have been previously reported [7 9]) and it is in infancy the majority of hospitalizations occur, which are responsible for the majority of healthcare costs. We suggest, therefore, that the greatest burden associated with respiratory viral infections is encountered in the first year after birth.

The overall respiratory healthcare costs were significantly higher in those children who had had a viral LRTI not due to RSV or RV and this was associated with them having had significantly more respiratory related GP attendances, and significantly reduced FVC. The "other" viruses included adenovirus, parainfluenza types 1 and 3, influenza A and human metapneumovirus. We have previously shown that human metapneumovirus is associated with elevated airways resistance at one year of age [17]. A number of the children in the RV group had experienced coinfection with other viruses. While the differences in healthcare costs between the RV and no LRTI groups did not reach statistical significance, they tended to be higher. It is possible therefore that coinfection with RV may influence outcome ; larger studies with detailed multivariate analysis would be required to ascertain this.

In both the RV and RSV groups compared to the no LRTI group, the non respiratory medication costs were significantly higher, suggesting the children had other non-respiratory co-morbidities. It is possible then that symptomatic viral LRTIs may occur in already vulnerable infants, rather than being causative of later morbidity. Although the differences did not reach statistical significance, the proportions of children with a history of bronchopulmonary dysplasia were higher in each LRTI group than the no LRTI group, suggesting that these groups may be at risk of LRTIs.

The study has strengths and some limitations. The children had all their LRTIs during infancy documented regardless of whether they were hospitalized or remained at home. We used a multiplex PCR to identify 13 common respiratory viruses from NPAs taken at the time of the LRTI. Detailed healthcare utilisation was assessed and hence health related cost of care determined. We were, however, only able to follow

up a proportion of the original study cohort, and we recognise the limitations of the small numbers within each virus subgroup. Nevertheless, we were able to report significant differences between the groups. Other studies in comparable populations have shown high drop-out rates, particularly in observational studies, even when contact is ongoing [26 27]. Furthermore, it has been suggested that study participation in paediatric populations decreases upon commencement of formal schooling [28]. Nevertheless, the children included in the current study were representative of the original cohort with regard to gestational age and birth weight.

In conclusion, in moderately prematurely born children, RV and RSV LRTIs in infancy were not associated with significantly higher overall respiratory healthcare costs after infancy. Indeed, the respiratory healthcare costs in both groups were low with implications for the cost effectiveness of prophylactic agents in such a population. Differences in pulmonary function were small and only detected using spirometry; these data therefore suggest a balance is required between the feasibility of non-volitional measures such as EMGpara and the greater sensitivity to small changes offered by spirometry.

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Authors contribution: AG, VMacB and GFR designed the study; SD recruited the original cohort; VMacB and MNY collected the data at follow up, VMacB, AG and JLP analysed the data. All authors were involved in interpretation and writing up the data and approved the final manuscript.

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