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Respiratory-syncytial-virus- and rhinovirus-related bronchiolitis in children aged <2 years in an English district general hospital

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SUMMARY

Background: Bronchiolitis is the most common reason for hospitalization in young children. In addition to respiratory syncytial virus (RSV), other viruses have been increasingly implicated. Guidance on testing has also changed.

Aims: To compare clinicopathological outcomes in young children admitted with bronchiolitis due to RSV in comparison with rhinovirus (RV), and identify associated risk/epidemiological factors.

Methods: Children aged less than two years admitted to hospital with a clinical diagnosis of bronchiolitis with positive results for either RSV or RV were included in this study. Polymerase-chain-reaction-negative cases using an extended respiratory virus panel served as a control group. Retrospective data were collected on sex, risk factors, respiratory support, intravenous fluids and antibiotics. Outcomes such as length of stay (LOS) and need for transfer to the high-dependency unit/paediatric intensive care unit were included.

Findings: Two hundred and twenty-seven out of 437 nasopharyngeal aspirate samples were positive for either RSV ($N = 162$) or RV ($N = 65$). The median age of cases was three months and 75% had at least one risk factor. Risk factors were higher in the RV group ($P = 0.004$). RV accounted for the majority of cases outside the RSV season ($P < 0.01$). RV-associated bronchiolitis had a longer LOS (more than seven days) ($P < 0.05$) and increased need for chest X-rays and/or antibiotics ($P < 0.05$). Use of intravenous fluids and respiratory support were higher in the RV group, but the difference was not significant.

Conclusions: RV is the second most common pathogen associated with bronchiolitis and is isolated all year round. This may be important in those with risk factors resulting in prolonged LOS. Further research is necessary to establish the exact role of RV in this common condition, particularly outside the traditional RSV season.

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Introduction

Acute viral bronchiolitis is common in children aged less than two years. It is a major reason for admission to hospital, and secondary spread can lead to hospital-associated infections and outbreaks. It usually presents with cough and increased work of breathing, and often affects a child's ability to feed [1]. Respiratory syncytial virus (RSV) is the most common pathogen detected in hospitalized children, particularly during the winter months in temperate climates. A nasopharyngeal aspirate (NPA) has traditionally been used to inform cohorting of infectious patients (i.e. to minimize secondary spread) and to aid clinical decision making (e.g. avoiding unnecessary antibiotics). However, bronchiolitis remains primarily a clinical diagnosis, and recent studies have highlighted a large number of other viral pathogens such as adenovirus, influenza virus, parechovirus, bocavirus, human metapneumovirus and rhinovirus (RV) as pathogens associated with this clinical condition [2]. Neither the American Academy of Pediatrics (AAP, 2014) nor the National Institute for Health and Care Excellence (NICE, 2015) guidelines recommend routine use of NPA testing for RSV in the diagnosis of infants with bronchiolitis [1,3].

Extended polymerase chain reaction (PCR) testing for viral respiratory tract pathogens, including those associated with bronchiolitis, is now available for routine use in most diagnostic microbiology laboratories. As part of a review of the use of this technology, the role of RV as a cause of non-RSV-associated cases, particularly those occurring outside the traditional RSV season (October–February in the Northern hemisphere), was examined. As RV is a common virus in both children and adults, there is also a risk of nosocomial spread involving healthcare workers and visitors, adding to the challenge of controlling these infections in hospitals.

The aim of this study was to determine the clinicopathological outcomes in a cohort of infants and young children aged less than two years admitted with bronchiolitis, where the presence of either RSV or RV as a single pathogen was detected on analysis of NPA samples. NPA samples that were negative on PCR using an extended panel of respiratory viruses served as a control group.

Methods

An extended panel of respiratory viruses has been available for a number of years from the microbiology laboratory at the study hospital. RV was included as part of the extended panel from April 2012 onwards. Until December 2013, the extended panel was undertaken by the South West Virology (Public Health England) Laboratory in Bristol. From January 2014, the local microbiology laboratory provided the extended PCR panel (Respiratory Pathogens 21, Fast Track Diagnostics, Slierna, Malta). Pathogens detected included influenza A, influenza A (H1N1 pdm09), influenza B, rhinovirus, coronavirus (NL63, 229E, OC43, HKU1), parainfluenza (1, 2, 3 and 4), human metapneumovirus A/B, bocavirus, RSV A/B, adenovirus, enterovirus, parechovirus and *Mycoplasma pneumoniae*. All NPA samples were initially screened by testing for RSV using antigen detection (Binax NOW RSV card), and those that tested negative went on to have extended PCR panel testing (Figure 1). This was in accordance with the hospital policy at the time to support diagnosis while limiting unnecessary tests.

Children aged less than two years admitted to hospital with a clinical diagnosis of bronchiolitis with a positive NPA for RSV or RV were identified from a search of the microbiology department's electronic database. Data were collected over a period of three years and nine months (April 2012–December 2015). Infants who only had a single pathogen (either RSV or RV) were included in the study. NPA samples that identified more than one pathogen were excluded. Respiratory pathogens detected from babies in the neonatal unit ($N = 10$) were also excluded as bronchiolitis is more difficult to diagnose in this group, and they were more likely to have acquired infection nosocomially. NPA samples that were negative on PCR using an extended panel of respiratory viruses served as a control group.

The study was a service evaluation project, and patient consent was not required. Data were collected on median age at presentation, sex, associated risk factors (chronic lung disease, prematurity, congenital heart disease, genetic conditions), therapeutic interventions (intravenous fluids, intravenous antibiotics, chest X-ray), need for respiratory support (high flow oxygen, continuous positive airway pressure, ventilation), management in high-dependency unit (HDU)/paediatric intensive care unit (PICU) and outcome [length of stay (LOS) and any deaths]. LOS of seven days or less was defined as short, and LOS of eight to 21 days was defined as prolonged. Statistical analysis was performed using standard Chi-squared analysis, and $P < 0.05$ was considered to indicate significance.

Results

In total, 437 NPA samples were tested for children aged less than two years. One hundred and eighteen children were excluded from the study, either because they had a single respiratory pathogen other than RSV or RV ($N = 41$) or they had co-infection with two or more viruses ($N = 77$). Of the 41 children who had a single virus detected on extended PCR panel, the three most common viruses were: parainfluenza virus ($N = 14$), human metapneumovirus ($N = 10$) and coronavirus ($N = 7$). There was no single third predominant viral pathogen identified. The three most common viruses in the co-infection group ($N = 77$) were: rhinovirus ($N = 58$), RSV ($N = 19$) and human metapneumovirus ($N = 18$). Sixty-three patients had two pathogens, 13 patients had three pathogens, and one patient was co-infected with four pathogens.

The remaining 319 children were included in the study: 162 had RSV (114 antigen positive; 48 PCR positive), 65 had RV and 92 served as negative controls. The male:female ratio was 1.4:1 for RSV and 1.7:1 for RV. In the PCR-negative control group, the ratio was 1.3:1. The median age at presentation was 87 days (range 12–692 days) for the RSV group, 92 days (range nine to 693 days) for the RV group and 109 days (range 12–674 days) for the PCR-negative control group.

As expected, the occurrence of RSV infections was seasonal, with only 20/162 (12.3%) cases diagnosed between February and October (Figure 2). RV was much more evenly distributed all year round, with a peak in December [21/65 (32%)]. Forty-eight percent of cases ($N = 31$) of RV-associated bronchiolitis occurred outside the non-RSV season (February–October). This difference was significant when comparing the RV group with the RSV group ($P < 0.01$).

Figure 3 Highlights the distribution of risk factors amongst the three different groups. Children with RSV had significantly

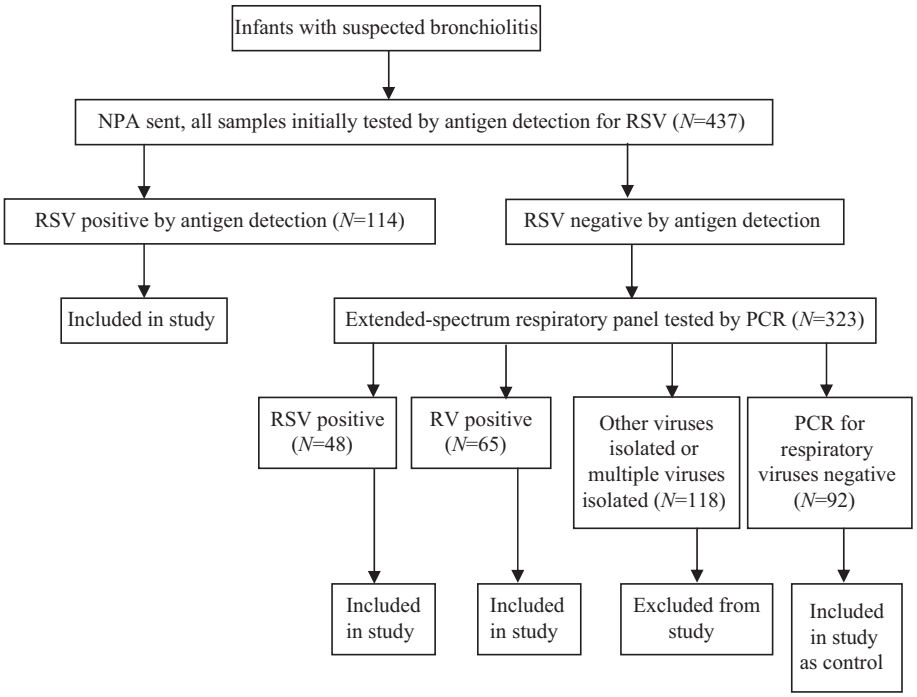

Figure 1. Pathway for nasopharyngeal aspirate sample testing and study inclusion/exclusion algorithm. NPA, nasopharyngeal aspirate; RSV, respiratory syncytial virus; RV, rhinovirus; PCR, polymerase chain reaction.

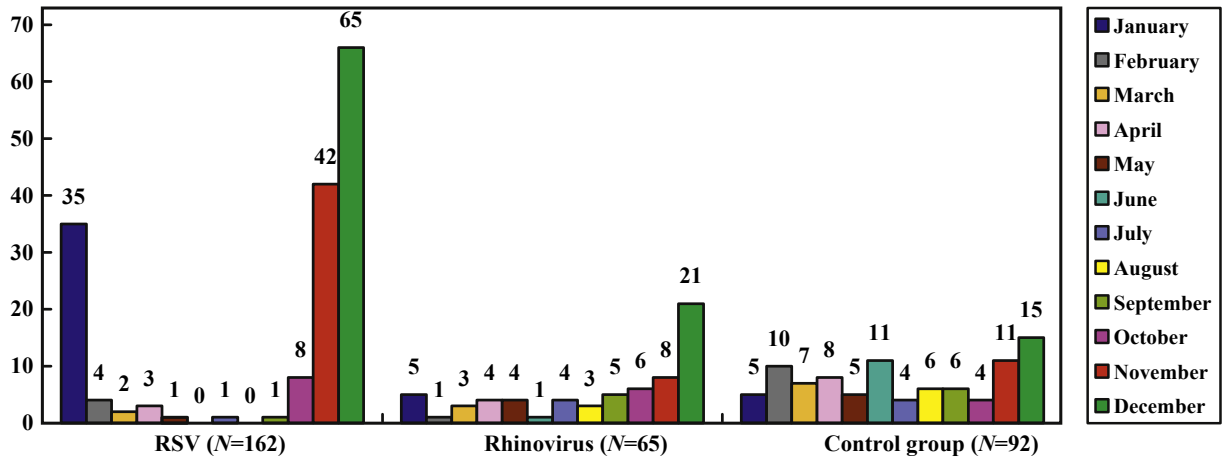

Figure 2. Seasonal trend for respiratory viral pathogens in comparison with control group. RSV, respiratory syncytial virus.

fewer risk factors (113/162; 70%) compared with the RV group (57/65; 88%) ($P = 0.004$).

Table I summarizes the elements of supportive management (intravenous fluids, intravenous antibiotics, chest X-ray, need for respiratory support) given to patients. Few children in any of the three groups needed HDU and PICU care for advanced respiratory management. Few significant differences between the groups were found, but this may reflect the relatively small number of cases and controls.

Infants with bronchiolitis will often have changes noted in their chest X-rays. Figure 4 compares the three groups when ordering a chest X-ray (if requested) and use of intravenous antibiotics. The study data did not show an increase in the use of antibiotics after a chest X-ray ($N = 39/227$; 17%) in the RSV or RV group when compared with cases in the RSV or RV group who were treated with antibiotics but did not have a chest X-ray ($N = 37/227$; 16%). However, patients with RV were more likely to have interventions (chest X-rays and/or antibiotics) than patients with RSV ($P = 0.034$).

There were no deaths amongst any of the patients. The mean LOS in the study group was: RSV group, 3.2 days (range 0–13 days), RV group, 4.6 days (range 0–21 days); and

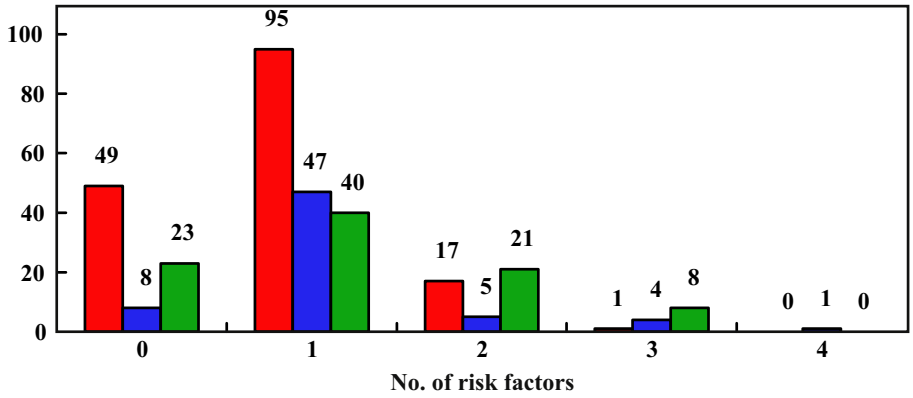

Figure 3. Distribution of risk factors amongst various groups. Red bars, respiratory syncytial virus ($N = 162$); blue bars, rhinovirus ($N = 65$); green bars, control group ($N = 92$).

Table I
Comparison of various interventions used in different groups

Interventions	RSV group ($N = 162$)	RV group ($N = 65$)	P-value (significant if $P < 0.05$)	RSV or RV group ($N = 227$)	Control group ($N = 92$)	P-value (significant if $P < 0.05$)
Chest X-ray	36	18	0.38	54	33	0.028
Intravenous fluids	26	9	0.67	35	23	0.044
Intravenous antibiotics	49	27	0.103	76	47	0.034
Respiratory support	36	9	0.37	47	9	0.02
High-dependency unit care	27	14	0.38	41	19	0.59
Paediatric intensive care unit management	3	2	0.59	5	3	0.58

control group, 3.9 days (range 0–21 days). The greater LOS in the RV group compared with the RSV group was significant ($P = 0.032$).

Children who had a chest X-ray and/or antibiotics had a longer LOS compared with children who did not need such interventions. For the RSV group, the mean LOS for those who needed interventions was 4.5 days, compared with 2.5 days for those who did not need interventions. In the RV group, the comparable figures were 6.3 and 3.1 days.

Discussion

RV is often considered to be a trivial infection as it is the most common viral pathogen causing common colds in adults and older children. This study has highlighted that RV is also an important cause of bronchiolitis in infancy and early childhood throughout the year. Until relatively recently, the role of RV may have been under-recognized in hospital settings due to the limited availability of routine RV diagnostic testing.

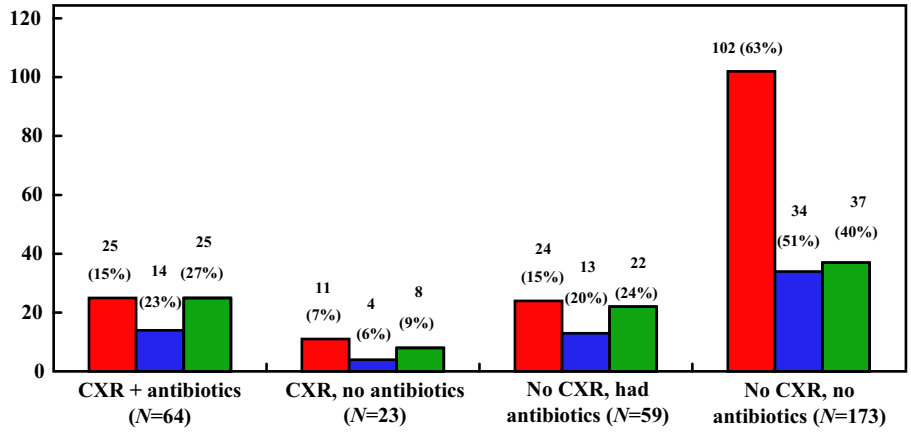

Figure 4. Comparison of use of antibiotics and ordering of chest X-rays (CXR) amongst various groups. Red bars, respiratory syncytial virus ($N = 162$); blue bars, rhinovirus ($N = 65$); green bars, control group ($N = 92$).

This study showed that RV is a year-round virus, and as such is the main cause of viral bronchiolitis outside the RSV season ($P < 0.01$). This study is a good example of pathway management in that only NPAs that were RSV antigen negative went on to have RV PCR testing as part of the extended PCR respiratory virus panel. This approach runs the risk of missing RSV-positive patients co-infected with RV or other pathogens. However, it is reassuring that only 2% of the children who had RSV detected by PCR also had RV detected. In a multi-centre US study with 2207 children with bronchiolitis, 72% had RSV and 25.6% had RV (ratio 2.8:1) [2]. A Greek study showed RSV in 72.4% of cases, compared with RV in 29% of cases (ratio 2.5:1) [4]. This was similar to the results of the present study (RSV:RV ratio of 2.5:1).

In a multi-centre US study of 1836 children with bronchiolitis, the median age at diagnosis was four months and 60% were males [5]. The present study also had a male predominance (59%), with a median age at diagnosis of three months. The US study reported that 48% of patients had sole RSV infection, 8% had sole RV infection, and 13% had RSV/RV co-infection [5]. In contrast, the present study showed that RSV/RV co-infection was far less frequent in those tested by PCR, with only 10 cases identified. In a Turkish study of 55 infants, RSV ($N = 25$) was identified as the major viral pathogen, although more than 50% of cases were associated with other respiratory viruses; the two most common were RV ($N = 9$) and human metapneumovirus ($N = 8$) [6].

Another US study showed that bronchiolitis-related hospitalizations in children aged less than two years (N = 4800) increased significantly from 536 (3.3%) in 2002 to 1241 (5.5%) in 2007, and that RSV-positive cases had a lower percentage of underlying medical conditions than children hospitalized with non-RSV bronchiolitis (27% vs 37.5%; $P < 0.001$) [7]. The present study also found that comorbidities were more common in the RV-associated bronchiolitis group ($P = 0.004$). Following analysis by a logistic regression model controlling for age, sex, birth weight, presence of fever, and day of disease on admission, a Greek study found that the presence of RV was associated with more severe disease, and that this risk was approximately five-fold greater [4]. The present study found a higher morbidity rate for RV infection compared with RSV, especially for prolonged LOS ($P < 0.05$), as well as the need for chest X-rays and/or antibiotics ($P < 0.05$). This trend was noted for other parameters such as need for intravenous fluids and respiratory support, although these differences did not reach statistical significance. It is hypothesized that younger children with RV-related bronchiolitis behave differently to those with RSV-related bronchiolitis, and may need longer to recover due to a longer period of oxygen dependency and the requirement for feeding support.

Interestingly, use of chest X-rays, antibiotics and intravenous fluids (Table I) was lower in the RSV and RV groups than in the PCR-negative group which served as a control. This may reflect the possibility of primary or secondary bacterial infection in the control group.

Neither the AAP (2014) nor the NICE (2015) guidelines recommend routine NPA testing in bronchiolitis, as it primarily remains a clinical diagnosis and tends to be self-limiting, requiring symptomatic management [1,3]. However, it may still be a useful adjunct in infants and young children with additional risk factors, as this and other studies have suggested an association with prolonged LOS where children are less likely to need antibiotic intervention. Also, lower respiratory tract infections caused by viral pathogens including RSV have been implicated in numerous nosocomial outbreaks, which could be missed easily, particularly if routine testing is no longer recommended and diagnosis is based on clinical presentation alone. Therefore, it remains essential that there is rapid access to screening, followed by extended PCR testing including RV should secondary cases occur in a hospital setting.

As children are expected to recover from an acute episode of respiratory illness within three weeks, those ($N = 8$) whose LOS extended beyond three weeks were not included in the data analysis. Cross-infection may be more likely to occur in neonates who are already inpatients in the neonatal units [8]. Of note, three of 10 neonates were already being managed as inpatients in the neonatal unit when they developed bronchiolitis, and required an extended LOS because of their prematurity. The remaining five children who had LOS exceeding three weeks had ongoing health issues, including four children who developed a bronchiolitis-like illness during their inpatient stay. This suggests that cross-infection may occur readily in the hospital setting [9]. Only one case could be correlated directly with significant complications from his original bronchiolitis infection on admission.

Following this study, and taking into account the AAP and NICE guidelines, the authors now follow a revised policy in their centre by only performing targeted extended respiratory PCR testing of NPA samples in children needing HDU care or in children with two or more risk factors (e.g. prematurity, chronic lung disease on supplemental home oxygen, congenital heart disease). Children are also tested if there is any suspicion of secondary spread or outbreak occurring in an inpatient setting, or if cohorting is being considered due to lack of suitable isolation facilities. These approaches help to avoid unnecessary investigations or antibiotic treatment in this group, while minimizing the risk of further spread. However, for infants and children where NPAs are negative by the extended respiratory panel PCR, serious consideration of other primary causes of infection, including bacteria, needs to be sought and treated appropriately in keeping with managing sepsis while supporting antimicrobial stewardship.

In conclusion, this single-centre study of 437 cases of bronchiolitis showed that RSV and RV are the two main viral pathogens associated with bronchiolitis in children. The study highlights the importance of considering RV as an important respiratory pathogen in infants and young children who present with bronchiolitis, particularly during the non-RSV season, which can necessitate hospitalization and therapeutic interventions, and lead to prolonged LOS. RV was found to be more common in children with pre-existing risk factors, and targeted NPA testing may be useful in selective settings. The study data further support the limited existing literature that RV may be an important causative viral pathogen in bronchiolitis. Larger multi-centre studies are required to further categorize clinicopathological outcomes in bronchiolitis caused by RSV and RV, as well as other viral pathogens.

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Conflict of interest statement
None declared.

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