Human Rhinovirus Species C Infection in Young Children with Acute Wheeze Is Associated with Increased Acute Respiratory Hospital Admissions

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Rationale: **Human rhinovirus species C (HRV-C) is the most common cause of acute wheezing exacerbations in young children presenting to hospital, but its impact on subsequent respiratory illnesses has not been defined.**

Objectives: **To determine whether acute wheezing exacerbations due to HRV-C are associated with increased hospital attendances due to acute respiratory illnesses (ARIs).**

Methods: **Clinical information and nasal samples were collected prospectively from 197 children less than 5 years of age, presenting to hospital with an acute wheezing episode. Information on hospital attendances with an ARI before and after recruitment was subsequently obtained.**

Measurements and Main Results: **HRV was the most common virus identified at recruitment (n = 135 [68.5%]). From the 120 (88.9%) samples that underwent typing, HRV-C was the most common HRV species identified, present in 81 (67.5%) samples. Children with an HRV-related wheezing illness had an increased risk of readmission with an ARI (relative risk, 3.44; 95% confidence interval, 1.17–10.17; $P = 0.03$) compared with those infected with any other virus. HRV-C, compared with any other virus, was associated with an increased risk of a respiratory hospital admission before (49.4% vs. 27.3%, respectively; $P = 0.004$) and within 12 months (34.6% vs. 17.0%; $P = 0.01$) of recruitment. Risk for subsequent ARI admissions was further increased in atopic subjects (relative risk, 6.82; 95% confidence interval, 2.16–21.55; $P = 0.001$). Admission risks were not increased for other HRV species.**

Conclusions: **HRV-C–related wheezing illnesses were associated with an increased risk of prior and subsequent hospital respiratory admissions. These associations are consistent with HRV-C causing recurrent severe wheezing illnesses in children who are more susceptible to ARIs.**

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Human rhinovirus (HRV)-related wheezing illnesses in early childhood are associated with an increased risk of subsequent wheezing.

What This Study Adds to the Field

HRV-C–related wheezing illnesses are associated with an increased risk of prior and subsequent hospital respiratory admissions.

Keywords: human rhinovirus; acute wheezing illnesses; hospital admissions; pediatrics

Numerous studies have demonstrated that wheezing associated with certain viruses in early childhood is an independent risk factor for subsequent wheezing illnesses and the development of asthma (1–7). Most earlier reports focused on respiratory syncytial virus (RSV) bronchiolitis in infancy and recurrent wheezing (1–3, 8, 9), but more recent research has shown that wheezing episodes due to human rhinovirus (HRV) have a stronger association than RSV with further wheezing episodes and asthma in early childhood (4, 5, 7, 9).

Previously, HRV-A and -B (10–12) were the only known HRV species, but improved virological detection methods using polymerase chain reaction (PCR) and sequencing (13–15) have revealed another species of rhinovirus, C (16, 17). A number of studies have shown that HRV-C is the most common HRV species associated with acute asthma attacks severe enough to result in children presenting to hospital (18–21), and further studies have shown that it also causes more severe asthma attacks than other rhinoviruses (22) and all other viruses (23).

These studies raise the issue of whether HRV-C also influences subsequent acute wheezing episodes in young children. Hence, the

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aim of this study was to examine whether there was an increase in respiratory presentations and/or admissions to hospital after an HRV-related wheezing illness and, in particular, to investigate whether there were differences in respiratory outcomes between respective HRV species. Some of the results of this study have been previously reported in the form of an abstract (24).

METHODS

Study Participants

To investigate the impact of early respiratory viral infections on the development of respiratory disease in young children, participants aged less than 5 years were prospectively recruited on presentation to the emergency department (ED) of a tertiary children's hospital (Princess Margaret Hospital [PMH], Perth, Western Australia, Australia) with an acute wheezing episode. Participants were drawn from two studies: the Perth Childhood Acute Asthma Study (PCAAS) and the Mechanisms of Acute Viral Respiratory Infections in Children (MAVRIC) study. Further details on the study participants can be found in the online supplement. The hospital's human ethics committee approved both studies, with parental/guardian written informed consent obtained before recruitment.

Data Collection

Data and samples were obtained on each participant during the acute episode at the time of recruitment. A nasopharyngeal aspirate (NPA) was collected and a study questionnaire determined the patient's demographics and previous clinical history. Atopic status was determined by skin prick testing to 11 common allergens at recruitment (25).

We retrospectively obtained further information from the hospital database on each participant regarding the number of ED presentations and admissions to PMH with an acute respiratory illness (ARI) both before and after recruitment. The treating ED physician, independent of study staff, assigned all diagnoses. The length of time available for interrogation from the hospital records on each participant was also recorded. Definitions of ED presentations and hospital admissions are detailed in the online supplement.

The clinical outcomes of participants identified with HRV, the various HRV species, or other viruses detected at presentation were compared to assess the risk of subsequent hospital attendances. A hospital attendance was defined as either a presentation to the ED or an admission to hospital with an ARI.

Viral Detection

Detection of common respiratory viruses (HRV, RSV, adenovirus, influenza A and B, parainfluenza 1–4, human metapneumovirus, and enterovirus) was completed as previously described (23). Briefly, the NPA samples were divided into two aliquots for analysis. The first aliquot was assessed by the hospital's microbiology department, using direct immunofluorescence antibody testing, immunofluorescence after cell culture, and/or PCR using virus-specific primers. The second NPA aliquot was used to determine which HRV strains were present. HRV typing used specific primers for a 260-bp variable sequence in the 5′ noncoding region of the HRV genome as described in detail previously (16, 17, 23). HRV strains were assigned on the basis of comparisons of the 5′ noncoding region sequences with those of 101 classical serotypes as well as 52 newly identified genotypes, using ClustalX software (Conway Institute, University College Dublin, Dublin, Ireland) (26). HRV species was then confirmed by analyzing the 420-bp VP4/VP2 sequence for each HRV strain.

Statistical Analysis

Chi-squared testing compared viral detection at recruitment with subsequent hospital attendances. A Cox regression model was used to confirm the findings correcting for age, sex, atopy, family history of asthma, current parental smoking, and the number of months of hospital attendance data collected. Finally, Kaplan–Meier survival curves were employed to examine the relationship between HRV, different HRV species, and the time to subsequent hospital attendances.

RESULTS

Participant Demographics and Clinical Data at Recruitment

In total, 197 preschool participants with an acute wheezing episode were recruited prospectively between July 2002 and November 2010 and included in this analysis. Subjects were mostly male (n = 124, 62.9%) and had a mean age of 31.0 (SD, 16.6) months (Table 1). Skin prick testing was performed on 147 (74.6%) participants and of these 78 (53.1%) were atopic. More children (44.2%) were recruited during winter than in any other season. Acute asthma (53.8%) was the most common diagnosis assigned and 187 (94.9%) children were admitted to hospital, although of those admitted 84 (44.9%) were admitted to the overnight observation ward (Table 2). The majority of participants 130 (82.2%) had a severity score assigned at presentation (mean, 4.9; SD, 2.1). Most children had moderate asthma (n = 81 [62.3%]) and 31 (23.8%) had severe asthma.

The majority of participants 170 (86.3%) had a virus detected from the NPA at recruitment. HRV was the most common virus identified (n = 135 [68.5%]) (Figure 1), with RSV the next most common virus (n = 35 [17.7%]). Two or more viruses were identified in 27 (13.7%) samples, no virus was detected in 23 (11.7%), and data on viral detection were incomplete in four samples (2%).

From the 135 HRV-positive samples, 120 (88.9%) were successfully typed (Figure 2). HRV-C was the predominant HRV species identified, present in 81 (67.5%) samples. HRV-A and HRV-B were detected in 35 (29.2%) and 3 (2.5%) samples, respectively. One sample had both HRV-A and HRV-C identified.

Hospital Attendance Data

Information on hospital attendances was collected on all 197 participants between December 2000 and November 2010. The mean number of months of data collected on each participant was 35.7 (SD, 36.2; range, 1.1–108). In total, 132 children represented to the ED with a respiratory illness within 12 months and the mean time from recruitment to the next respiratory ED presentation was 4.9 (SD, 2.5; range, 0.2–11) months. Regarding hospital admissions, 126 children were readmitted to hospital with a respiratory illness within the first 12 months and the mean time from recruitment to the next respiratory hospital admission was 5.1 (SD, 2.7; range, 0.1–11) months.

TABLE 1. PATIENT DEMOGRAPHICS

Demographic	Value
n	197
Age, mo	31.0 ± 16.6 (1.1–58.4)
Sex (male), %	124 (62.9)
Atopic (n = 147)	78 (53.1)
Cumulative mean SPT wheal size, mm (n = 147)	8.29 ± 9.65 (0–41.5)
Number of positive SPT reactions (n = 147)	1.34 ± 1.64 (0–7)
Family history of asthma (n = 183)	144 (78.7)
Parental smoking at recruitment (n = 183)	34 (18.6)
History of day-care attendance (n = 183)	77 (42.1)
Previous admission with a wheezing illness (n = 182)	92 (50.5)
Season recruited	
Spring (September to November)	43 (21.8)
Summer (December to February)	21 (10.7)
Autumn (March to May)	46 (23.3)
Winter (June to August)	87 (44.2)

Definition of abbreviation: SPT = skin prick testing.

Data are presented as n (%) or mean ± SD (range) and generated from n = 197, unless otherwise indicated in parentheses.

TABLE 2. CLINICAL DATA OF SUBJECTS AT RECRUITMENT

Clinical Information	Value
Diagnosis assigned*	
Acute asthma	106 (53.8)
Virus-induced wheezing	60 (30.5)
Bronchiolitis	31 (15.7)
Admitted	187 (94.9)
Overnight observation ward	84 (44.9)
Hospital ward	101 (54.0)
Pediatric intensive care unit	2 (1.1)
Time to discharge, h	37.8 ± 31.2 (0.9–242.1)
Severity group (n = 130)†	
Mild (score, 0–3)	18 (13.8)
Moderate (score, 4–7)	81 (62.3)
Severe (score, 8–10)	31 (23.8)
Severity score (n = 130)†	4.9 ± 2.07 (0–10)
On preventive treatment at recruitment (n = 166)	57 (34.3)
Received oral steroids at recruitment (n = 186)	144 (77.4)
URTI symptoms at recruitment (n = 190)	175 (92.1)

Definition of abbreviation: URTI = upper respiratory tract infection.

Data are presented as n (%) or mean ± SD (range) and generated from n = 197, unless otherwise indicated in parentheses.

*Diagnosis was determined by the treating emergency department physician and recorded at recruitment.

† Severity score assigned using a modified National Institutes of Health (NIH) score (23, 33, 34).

HRV and ED Presentations

Regarding ED presentations with respiratory illnesses, 107 (54.3%) participants had a prior presentation to the ED and 72 (36.5%) subsequently re-presented to the ED, of which 53 (26.9%) re-presented to the ED within 12 months of recruitment (Table 3). The mean number of ED presentations before recruitment was 1.2 (SD, 2.05), within 12 months of recruitment the mean number was 0.4 (SD, 0.9), and at any time after recruitment it was 0.8 (SD, 1.6).

Children with HRV detected at recruitment, compared with other viruses, were not more likely to have an ED presentation with a respiratory illness at any time point studied (Table 3).

We compared children with each of the different HRV species to children with other viruses in terms of the proportion that had either prior or subsequent ED presentations for a respiratory illness. When compared with participants with other viruses, those participants who had either HRV-A or HRV-B (Table 3) detected at recruitment did not have a significantly higher proportion of respiratory ED presentations. However, there was a significant association between having HRV-C detected at recruitment and respiratory presentations to the ED before recruitment (54.3% vs. 38.6%; $P = 0.04$) (Table 3).

Infection with any one particular virus did not result in a participant having a higher risk of subsequent respiratory ED presentations (Tables 3 and 4).

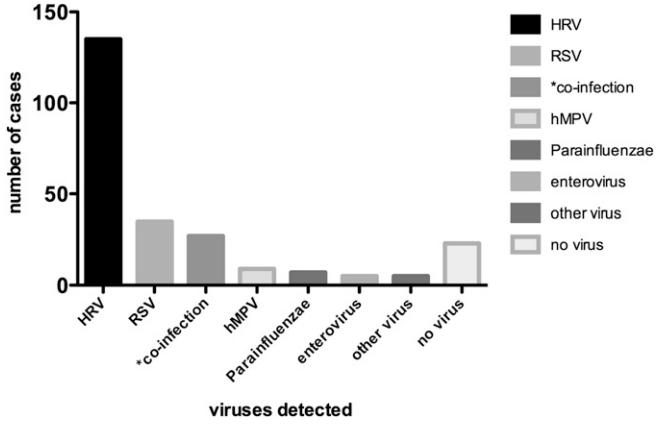

Figure 1. Frequency of the various viruses detected at recruitment. *Coinfection indicates two or more viruses detected.

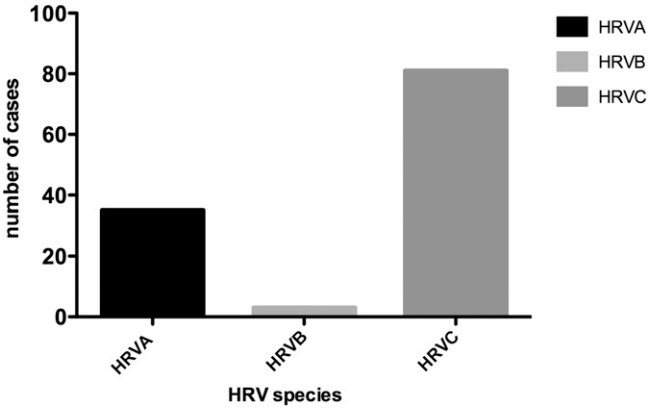

Figure 2. Frequency of the human rhinovirus (HRV) species detected at recruitment.

HRV and Hospital Admissions

Regarding hospital admissions with respiratory illnesses, 74 (37.6%) participants had a prior hospital admission and 64 (32.5%) were subsequently admitted to hospital, of which 48 (24.4%) were admitted to hospital with a respiratory illness within 12 months of recruitment (Table 3). The mean number of hospital admissions before recruitment was 0.9 (SD, 2.06), within 12 months of recruitment was 0.4 (SD, 1.0), and any time after recruitment was 0.7 (SD, 1.6).

Children with HRV detected at recruitment, compared with children infected with other viruses, had a significantly greater proportion of hospital admissions with respiratory illnesses before recruitment (43.0% vs. 17.1%; $P = 0.005$), within 12 months of recruitment (30.4% vs. 5.7%; $P = 0.003$), and any time after recruitment (38.5% vs. 17.1%; $P = 0.018$) (Table 3). Individuals with an HRV-related wheezing illness compared with those with any other virus had a threefold higher risk of being readmitted with a respiratory illness (relative risk [RR], 3.44; 95% confidence interval [CI], 1.17–10.17; $P = 0.03$) (Table 4) and a shorter time from recruitment to readmission (Kaplan–Meier survival analysis, $P = 0.02$) (Figure 3).

Children with either HRV-A or HRV-B at recruitment, when compared with other viruses, did not have a significantly greater proportion of hospital admissions at any time point studied (Table 3). Participants with HRV-C, when compared with participants with other viruses, had a significantly higher proportion of hospital admissions with a respiratory illness both before (49.4% vs. 27.3%; $P = 0.004$) and within 12 months of recruitment (34.6% vs. 17.0%; $P = 0.01$) but not at any time after recruitment (40.7% vs. 28.4%; $P = 0.10$) (Table 3). However, HRV-C detection at recruitment was associated with a twofold increase in the risk of subsequent respiratory admissions to hospital (RR, 2.36; 95% CI, 1.19–4.71; $P = 0.02$) compared with any other virus. No other HRV species demonstrated a significant association with an increase in respiratory admissions (Table 4). We found that the risk of subsequent respiratory admissions was considerably reduced for RSV compared with any other virus (RR, 0.05; 95% CI, 0.06–0.38; $P = 0.004$). On examining the time to next respiratory admission, using Kaplan–Meier survival analysis (Figure 4), participants who had HRV-C

TABLE 3. HOSPITAL ATTENDANCE DATA OF PARTICIPANTS, COMPARING THOSE WITH HUMAN RHINOVIRUS SPECIES WITH THOSE WITH ANOTHER VIRUS AT RECRUITMENT

	n = 197*			HRV vs. Other Virus (*n = 170*)†		HRV-A vs. Other Virus (*n = 169*)‡		HRV-B vs. Other Virus (*n = 169*)		HRV-C vs. Other Virus (*n = 169*)	
Hospital Attendances	Number of Cases	Number of Attendances	Number of Months of Follow-up Data	+ (*n = 135*)	− (*n = 35*)	+ (*n = 36*)	− (*n = 133*)	+ (*n = 3*)	− (*n = 166*)	+ (*n = 81*)	− (*n = 88*)
ED presentations											
Before recruitment	107 (54.3)	1.2 ± 2.0 (0–14)	43.7 ± 36.7	67 (49.6)	11 (31.4)	16 (44.4)	62 (46.6)	0 (0)	78 (47.0)	**44 (54.3)**§	**34 (38.6)**
After recruitment	72 (36.5)	0.8 ± 1.6 (0–12)	51.2 ± 36.2	47 (34.8)	14 (40.0)	14 (38.9)	47 (35.3)	1 (33.3)	60 (36.1)	28 (34.6)	33 (37.5)
Within 12 mo of recruitment	53 (26.9)	0.4 ± 0.9 (0–5)	44.4 ± 36.2	36 (26.7)	12 (34.3)	12 (33.3)	36 (27.1)	1 (33.3)	47 (28.3)	21 (25.9)	27 (30.7)
Hospital admissions											
Before recruitment	74 (37.6)	0.9 ± 2.0 (0–16)	40.8 ± 35.7	**58 (43.0)**§	**6 (17.1)**	14 (38.9)	50 (37.6)	0 (0)	64 (38.6)	**40 (49.4)**§	**24 (27.3)**
After recruitment	64 (32.5)	0.7 ± 1.6 (0–13)	49.6 ± 38.1	**52 (38.5)**§	**6 (17.1)**	12 (33.3)	46 (34.6)	1 (33.3)	57 (34.3)	33 (40.7)	25 (28.4)
Within 12 mo of recruitment	48 (24.4)	0.4 ± 1.0 (0–8)	38.0 ± 35.7	**41 (30.4)**§	**2 (5.7)**	10 (27.8)	33 (24.8)	1 (33.3)	42 (25.3)	**28 (34.6)**§	**15 (17.0)**

Definition of abbreviations: ED = emergency department; HRV = human rhinovirus.

Data are presented as number of cases, n (%); number of attendances, mean ± SD (range); number of months of follow-up data, mean ± SD; HRV and HRV species versus other virus, n (%); +, named virus detected, −, other viruses detected.

* Total number of participants.

† Number of participants who had a virus detected at recruitment.

‡ One participant had a coinfection with both HRV-A and -C and was removed from this analysis.

§ Boldface values indicate $P < 0.05$.

at recruitment had a shorter time to readmission compared with children infected with any other virus ($P = 0.02$).

HRV, Atopy, and Hospital Attendances

We performed a further analysis on atopic individuals (n = 78). Once again, having a particular virus at recruitment was not significantly associated with a greater proportion of subsequent ED presentations (Table 5).

HRV detected in atopic subjects at recruitment was not associated with the risk of subsequent respiratory admissions compared with other viruses (RR, 4.21; 95% CI, 0.55–32.01; $P = 0.17$). However, within atopic subjects, HRV-C was associated with a sixfold increased risk in subsequent respiratory admissions (RR, 6.82; 95% CI, 2.16–21.55; $P = 0.001$) compared with other viruses (Table 5). Further examination of the readmission data revealed a significant interaction ($P = 0.027$) between atopy and HRV-C infections. The risk of subsequent respiratory admissions was lower for HRV-A than for other viruses (RR, 0.09; 95% CI, 0.01–0.68; $P = 0.02$). There were not sufficient numbers of atopic subjects with HRV-B or RSV at recruitment to perform the same analyses.

DISCUSSION

This study found that infection with HRV, in particular HRV-C, was associated with an increased risk of prior and subsequent hospital admissions with respiratory illnesses. To our knowledge, this is the first study to examine the relationship between the various HRV species and respiratory illnesses that require specialist medical treatment. We found that, compared with other viruses, an HRV-C–related wheezing illness resulted in a twofold increase in the risk of subsequent respiratory admissions to a tertiary referral pediatric hospital, and the risk was further increased if the child was atopic. In contrast, other HRV species and RSV were not associated with an increased risk of subsequent wheezing illness requiring hospital admission.

Our findings are consistent with other studies on the relationship between HRV infection and the risk of further wheezing illnesses (4–7, 9). One study prospectively monitored a group of children after a wheezing illness in infancy and found that those who wheezed with HRV were four times more likely to develop asthma in early childhood compared with those infants with other viruses (4). The Childhood Origins of Asthma (COAST) study demonstrated that wheezing in the first 3 years of life with rhinovirus was the most significant predictor of asthma at 6 years in a cohort of high-risk children (5).

The findings of our study provide significant insight into the role of infection with various HRV species in wheezing illnesses in young children. Previously, we have shown that HRV-C is the most common virus detected in children with acute asthma exacerbations and is associated with more severe episodes compared with other viruses (23). Yet, other studies have found variable results on HRV in young children with ARIs (21, 26–30). This could be due to the inclusion of milder cases, as HRV-C appears to be most common in children with more severe wheezing exacerbations. Variability of subject age and diagnoses included may also contribute to these differences. A major strength of the current study is that we focused on preschool children presenting to a tertiary referral pediatric hospital with an acute wheezing illness, reducing the likely impact of age and diagnostic bias on our findings and so improving the robustness of the results. Furthermore, given that almost 90% of participants were classified into either the moderate or severe wheezing category, our results highlight the importance of HRV-C infection in more severe wheezing illnesses. The lack of a significant correlation between HRV and subsequent respiratory ED presentations in our study would support this. Children presenting

TABLE 4. RISK OF FURTHER HOSPITAL ATTENDANCES ACCORDING TO VIRUS DETECTED AT RECRUITMENT, ADJUSTING FOR POTENTIAL CONFOUNDERS*

		ED Presentations			Hospital Admissions		
Virus	n	RR	95% CI	*P* Value	RR	95% CI	*P* Value†
HRV	128	1.13	0.49–2.66	0.77	3.44	1.17–10.17	**0.03**
HRV-A	127	0.90	0.46–1.78	0.76	0.85	0.40–1.82	0.68
HRV-B‡	127	3.16	0.37–26.69	0.29	—	—	—
HRV-C	127	1.18	0.63–2.22	0.61	2.36	1.19–4.71	**0.02**
RSV	178	0.70	0.28–1.76	0.45	0.05	0.06–0.38	**0.004**

Definition of abbreviations: CI = confidence interval; ED = emergency department; HRV = human rhinovirus; RR = relative risk; RSV = respiratory syncytial virus.

n = number of participants included in the analysis.

* Age, sex, family history of asthma, current parental smoking, and number of months of respiratory admission data collected.

† Boldface values indicate $P < 0.05$.

‡ Insufficient n.

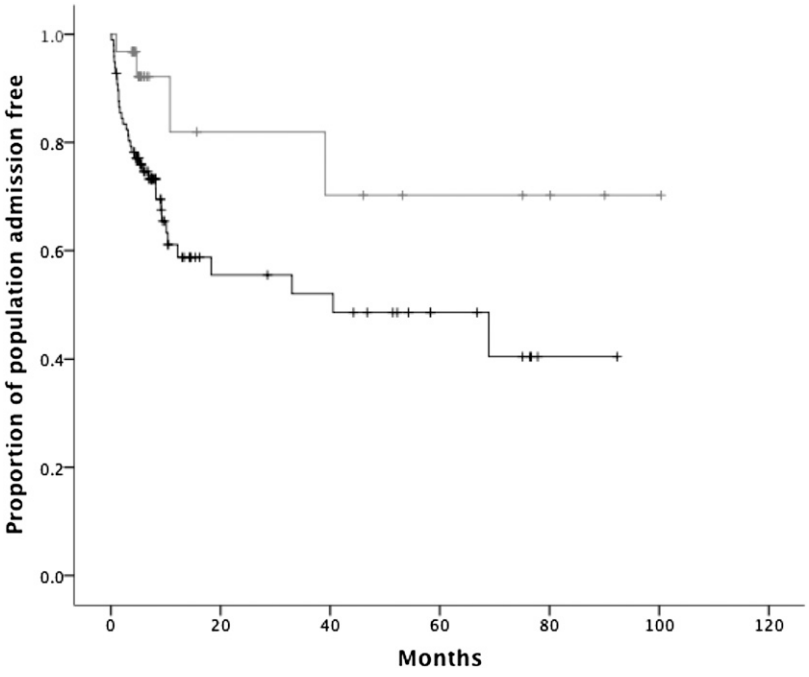

Figure 3. Kaplan–Meier survival analysis comparing human rhinovirus (HRV) with any other virus with respect to the number of months from the time of recruitment to the next hospital admission ($P = 0.02$). *Black line* = HRV; *gray line* = other virus.

to a hospital ED have quite variable severity of ARI compared with hospital admissions as they include milder cases that may initiate attendance to the ED but not require admission. Our results underline the role of HRV, and particularly HRV-C, in more severe wheezing illnesses because the recurrence was predominantly associated with hospital admission.

Participants identified with an HRV-C infection when compared with participants infected with other viruses were more likely to be admitted to hospital with a respiratory illness both before and after recruitment. This finding suggests that HRV-C causes recurrent severe wheezing illnesses in children who are more susceptible to acute respiratory infections, rather than the HRV-C virus itself altering susceptibility to repeated respiratory infections or illnesses. Participants with HRV infections, in particular HRV-C infections, were more likely to have a subsequent respiratory admission and also be readmitted within a shorter timeframe when compared with participants infected with other viruses. These findings were consistent with both univariate and multivariate analyses, thus confirming the robustness of the data.

In this study, RSV was not associated with subsequent wheezing illnesses as demonstrated in previous studies (3, 8, 9, 31). RSV infections are common in infants (32). Yet the mean age of our study participants was 31 ± 16.6 months and, thus, the number of infants recruited, as well as the number of RSV infections, was low. The association between RSV detections and subsequent respiratory admissions may have been replicated if infancy had been the focus of this study.

Other strengths of this study include the prospective design and the use of sensitive molecular viral detection methods leading to our high rate of HRV species identification (88.9%).

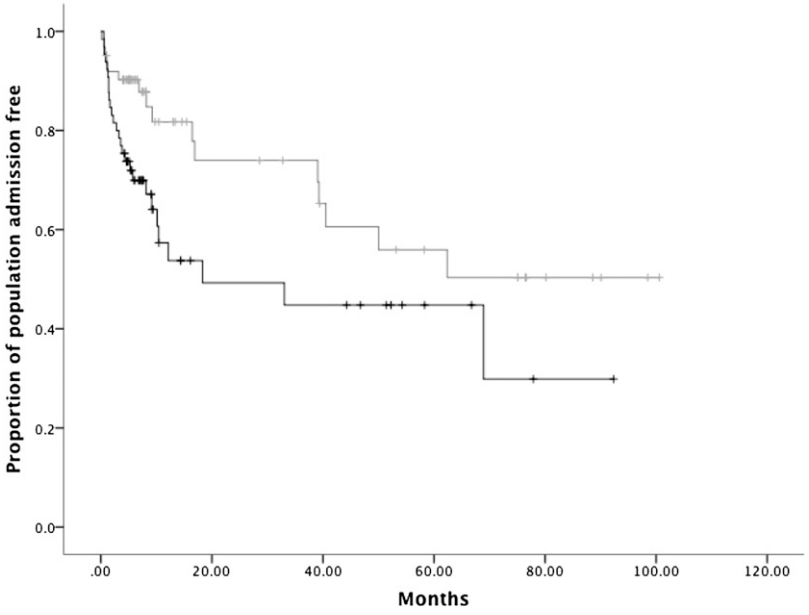

Figure 4. Kaplan–Meier survival analysis comparing human rhinovirus (HRV)-C with any other virus with respect to the number of months from the time of recruitment to the next hospital admission ($P = 0.02$). *Black line* = HRV; *gray line* = other virus.

TABLE 5. RISK OF FURTHER HOSPITAL ATTENDANCES ACCORDING TO VIRUS DETECTED AT RECRUITMENT IN ATOPIC INDIVIDUALS, CORRECTING FOR CONFOUNDERS*

		ED Presentations			Hospital Admissions		
Virus	n	RR	95% CI	*P* Value	RR	95% CI	*P* Value†
HRV	68	0.37	0.12–1.15	0.09	4.21	0.55–32.01	0.17
HRV-A	67	0.45	0.12–1.68	0.24	0.09	0.01–0.68	**0.02**
HRV-B‡	67	—	—	—	—	—	—
HRV-C	67	0.85	0.31–2.39	0.76	6.82	2.16–21.55	**0.001**
RSV‡	73	2.11	0.46–9.76	0.34	—	—	—

Definition of abbreviations: CI = confidence interval; ED = emergency department; HRV = human rhinovirus; RR = relative risk; RSV = respiratory syncytial virus.

n = number of participants included in the analysis.

*Age, sex, family history of asthma, current parental smoking and number of months of respiratory admission data collected.

† Boldface values indicate $P < 0.05$.

‡ Insufficient n.

Our finding of a strong association between HRV-C and subsequent respiratory admissions in atopic subjects is unique and of substantial interest. No other HRV species (or RSV) was associated with a worse outcome in atopic children. To date, the mechanisms of infection used by HRV-C have not been determined and this limits insight into why HRV-C has a strong association with wheezing illnesses in atopic children. How the virus attaches itself to a host cell and replicates has not been determined, and attempts are being made to discover the HRV-C receptor. We postulate that atopic children may have a predisposition to wheezing with HRV-C infection as a result of underlying immune pathway defects that fail to protect children when infected with a virus of significant pathogenicity.

One of the limitations of this study was the length of time during which the participants were followed up. Those recruited more recently would have had a shorter follow-up time compared with those recruited earlier in the study. However, this was addressed in the statistical analysis by adjustment for the time period studied on each participant. Another limitation was the lack of data on viruses detected during subsequent hospital attendances. This study was initially designed as a cross-sectional analysis of wheezing children presenting to the ED, and the clinical information on subsequent hospital attendances was only collected from the hospital database retrospectively. Therefore, we cannot comment on which viruses were responsible for these respiratory illnesses. We acknowledge that this was a single-center study with small numbers of preschool children recruited with acute wheezing illnesses. However, the data presented here were collected over a number of seasons during an 8-year period and the mean number of months of follow-up data collected on participants was almost 3 years, all of which strengthens our findings. Also, our study used data from hospital attendances rather than study follow-up and is therefore not likely to be affected by systematic bias from subject loss to follow-up. We acknowledge that participants may have presented to other health care facilities after recruitment. However, Princess Margaret Hospital is the sole tertiary pediatric referral center for the state of Western Australia. Therefore most children with severe wheezing illnesses would present or be referred to this hospital

In summary, HRV-C infection in children with an acute wheezing episode was associated with a twofold increased risk of respiratory admissions to hospital. This risk was much higher (sixfold) in young children with atopy. This study highlights the importance of HRV-C in acute wheezing illnesses in young children. In conclusion, the strong association of HRV-C infection with admissions to hospital with respiratory illnesses supports the likelihood that it is more pathogenic than other HRV species in children with more severe wheezing illnesses.

Author disclosures are available with the text of this article at www.atsjournals.org.

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