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Association of Rhinovirus C Bronchiolitis and Immunoglobulin E Sensitization During Infancy With Development of Recurrent Wheeze

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IMPORTANCE Rhinovirus infection in early life, particularly with allergic sensitization, is associated with higher risks of developing recurrent wheeze and asthma. While emerging evidence links different rhinovirus species (eg, rhinovirus C) to a higher severity of infection and asthma exacerbation, to our knowledge, little is known about longitudinal associations of rhinovirus C infection during infancy with subsequent morbidities.

OBJECTIVE To examine the association of different viruses (respiratory syncytial virus [RSV], rhinovirus species) in bronchiolitis with risks of developing recurrent wheeze.

DESIGN, SETTING, AND PARTICIPANTS This multicenter prospective cohort study of infants younger than 1 year who were hospitalized for bronchiolitis was conducted at 17 hospitals across 14 US states during 3 consecutive fall to winter seasons (2011-2014).

EXPOSURES Major causative viruses of bronchiolitis, including RSV (reference group) and 3 rhinovirus species (rhinovirus A, B, and C).

MAIN OUTCOMES AND MEASURES Development of recurrent wheeze (as defined in national asthma guidelines) by age 3 years.

RESULTS This analytic cohort comprised 716 infants who were hospitalized for RSV-only or rhinovirus bronchiolitis. The median age was 2.9 months (interquartile range, 1.6-3.8 months), 541 (76%) had bronchiolitis with RSV only, 85 (12%) had rhinovirus A, 12 (2%) had rhinovirus B, and 78 (11%) had rhinovirus C infection. Overall, 231 (32%) developed recurrent wheeze by age 3 years. In the multivariable Cox model, compared with infants with RSV-only infection, the risk of recurrent wheeze was not significantly different in those with rhinovirus A or B (rhinovirus A: hazard ratio [HR], 1.27; 95% CI, 0.86-1.88; rhinovirus B: HR, 1.39; 95% CI, 0.51-3.77; both $P > .10$). By contrast, infants with rhinovirus C had a significantly higher risk (HR, 1.58; 95% CI, 1.08-2.32). There was a significant interaction between virus groups and *IgE* sensitization on the risk of recurrent wheeze (P for interaction $< .01$). Only infants with both rhinovirus C infection and IgE sensitization (to food or aeroallergens) during infancy had significantly higher risks of recurrent wheeze (HR, 3.03; 95% CI, 1.20-7.61). Furthermore, compared with RSV-only, rhinovirus C infection with IgE sensitization was associated with significantly higher risks of recurrent wheeze with subsequent development of asthma at age 4 years (HR, 4.06; 95% CI, 1.17-14.1).

CONCLUSIONS AND RELEVANCE This multicenter cohort study of infants hospitalized for bronchiolitis demonstrated between-virus differences in the risk of developing recurrent wheeze. Infants with rhinovirus C infection, along with IgE sensitization, had the highest risk. This finding was driven by the association with a subtype of recurrent wheeze: children with subsequent development of asthma.

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Editorial
Supplemental content

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Bronchiolitis is the leading cause of hospitalizations in US infants, accounting for 130 000 hospitalizations annually.[1] In addition to the substantial acute morbidity, cohort studies have also demonstrated that 30% to 40% of infants hospitalized for bronchiolitis (severe bronchiolitis) subsequently develop recurrent wheeze and childhood asthma.[2-8] Among various causative pathogens, rhinovirus is the second most common pathogen following respiratory syncytial virus (RSV) and it contributes to 20% to 40% of severe bronchiolitis.[9] Epidemiological studies have reported that rhinovirus infection in early life, particularly with allergic sensitization, is associated with a higher risk of developing recurrent wheeze[10-14] and childhood asthma.[14-19]

The recent advent of sequencing technologies has led to the identification of approximately 170 rhinovirus genotypes that are classified into 3 species (rhinovirus A, B, and C).[20] Studies have demonstrated that rhinovirus C is associated with a higher severity of acute respiratory infection[21-26] and asthma exacerbation.[26-29] Additionally, a single-center study of 197 Australian children reported that children with atopic diseases with rhinovirus C wheezing illness had a higher risk of future respiratory hospitalizations.[30] However, to our knowledge, no longitudinal study has investigated the association of rhinovirus C infection with allergic sensitization in infants, let alone infants with bronchiolitis, with subsequent respiratory morbidities.

To address this knowledge gap, we conducted a multicenter prospective cohort study of racially/ethnically diverse infants with severe bronchiolitis to examine the association of infection by specific respiratory viruses (including rhinovirus species) with the development of recurrent wheeze. Specifically, we hypothesized that, compared with infants with RSV-only bronchiolitis, those with rhinovirus C bronchiolitis, particularly with early allergic sensitization, have a higher risk of developing recurrent wheezing.

Key Points

Question Is severe bronchiolitis by different rhinovirus species during infancy associated with distinct risks of developing recurrent wheeze?

Findings In this cohort study of 716 infants who were hospitalized for bronchiolitis, compared with respiratory syncytial virus infection, rhinovirus C infection was associated with a higher risk of developing recurrent wheeze by age 3 years. Furthermore, infants with rhinovirus C infection and IgE sensitization (to food or aeroallergen) in infancy had 3-fold higher risks of recurrent wheeze while those without sensitization had no significant differences.

Meaning The study identifies infants at higher risk of developing recurrent wheeze and informs strategies to develop targeted preventive therapies.

Methods

Study Design, Setting, and Participants

This is a preplanned analysis of data from an ongoing, multicenter prospective cohort study of infants (<12 months) hospitalized for bronchiolitis. This study, called the 35th Multicenter Airway Research Collaboration (MARC-35),[31-33] is coordinated by the Emergency Medicine Network,[34] which is a collaboration of 245 participating hospitals.

Using a standardized protocol,[31-33] the investigators at 17 sites across 14 US states (eTable 1 in the Supplement) enrolled infants hospitalized with an attending physician diagnosis of bronchiolitis during 3 consecutive bronchiolitis seasons from November 1, 2011, to April 30, 2014. Bronchiolitis was defined by the American Academy of Pediatrics guidelines as acute respiratory illness with some combination of rhinitis, cough, tachypnea, wheezing, crackles, and retractions.[35] We excluded infants who were transferred to a participating hospital more than 24 hours after the original hospitalization or those with known heart-lung disease, immunodeficiency, immunosuppression, or a gestational age younger than 32 weeks. All patients were treated at the discretion of the treating physician. Of 1016 infants initially enrolled into the MARC-35 cohort, 921 (91%) completed the run-in procedures (ie, contact at both 1 week after hospital discharge and 3 weeks after hospitalization) and comprised the longitudinal cohort. The institutional review board at each participating hospital approved the study. Written informed consent was obtained from the parent or guardian.

Data Collection

Investigators conducted a structured interview that assessed patients' demographic characteristics, family, medical, and environmental history, and details of the bronchiolitis course. After the index hospitalization for bronchiolitis (and run-in procedures), interviewers began interviewing parents/legal guardians by telephone at 6-month intervals in addition to medical record review by trained physicians. All data were reviewed at the Emergency Medicine Network Coordinating Center at Massachusetts General Hospital (Boston, Massachusetts), and site investigators were queried about missing data and discrepancies identified by manual data checks.

Nasopharyngeal aspirate samples were collected by trained site investigators using the standardized protocol that was used in a previous multicenter cohort study of children with bronchiolitis.[36,37] All sites used the same collection equipment (Medline Industries) and collected the samples within 24 hours of hospitalization. The nasopharyngeal sample was added to virus transport medium and stored at −80 °C.

Primary Exposure

The primary exposure was the infecting virus, with a focus on the 2 most common causative viruses of bronchiolitis: RSV and rhinovirus (A, B, and C species). Nasopharyngeal samples were first tested for 17 respiratory viruses (including RSV and rhinovirus) by using real-time polymerase chain reaction (PCR) assays.[36-38] Specifically, complementary DNA was generated using gene-specific primers for rhinovirus and singleplex real-time PCR was used. The details of the rhinovirus primers and probes have been described elsewhere.[39] Next, to identify the rhinovirus species (A, B, and C), rhinovirus-positive samples

were genotyped by using molecular typing assay using partial sequencing.[40]

IgE Measurement

Serum-specific IgE (sIgE) was measured at enrollment using 2 different assays (ImmunoCAP sIgE and ImmunoCAP ISAC; ThermoFisher Scientific) at the Phadia Immunology Reference Laboratory as previously described.[41] The sIgE allergen assays conducted were milk, egg white, peanut, cashew nut, and walnut; a positive test result was defined as 0.35 kU/L. The ImmunoCAP ISAC microarray immunoassay measures IgE antibodies to 112 components from 51 allergen sources, including foods and aeroallergens. A positive result was defined as 0.30 ISU-E or more (I; ISU-E provides an indication of IgE levels and is standardized to ImmunoCAP sIgE units. IgE sensitization was defined by having 1 or more positive values for serum allergen-specific IgE at the index hospitalization).

Outcome Measures

The outcome measure of interest was development of recurrent wheeze by age 3 years. Recurrent wheeze was defined in the 2007 National Institutes of Health (NIH) asthma guidelines as having at least 2 corticosteroid-requiring exacerbations in 6 months or having at least 4 wheezing episodes in 1 year that last at least 1 day and affect sleep.[42]

Statistical Analyses

First, we categorized patients into 4 groups: RSV-only (reference) and 3 rhinovirus species (A, B, and C) infection groups, excluding 5 infants with coinfection of multiple rhinovirus species. We examined the between-group differences in the patient characteristics and clinical presentation by using Kruskal-Wallis, χ^2, and Fisher exact tests as appropriate. Next, to examine the association of viruses with the risk of outcome, we modeled the time to event (ie, the development of recurrent wheeze) by fitting Cox proportional hazards models. Patients who did not have an outcome were censored at their last follow-up interview or at the time of withdrawal during the 36-month follow-up period. In the multivariable model, we adjusted for 7 patient-level potential confounders (age, sex, race/ethnicity, parental history of asthma, household siblings, IgE sensitization, and bronchiolitis severity defined by the use of mechanical ventilation [continuous positive airway pressure and/or intubation] during the index hospitalization) and accounted for between-hospital differences by including the sites as random effects. We chose these covariates on the basis of a priori knowledge and clinical plausibility.[9] By using age strata, the evaluation of scaled Schoenfeld residuals was not statistically significant in the model. Additionally, based on an a priori-defined hypothesis,[43] we also tested for interactions between virology and IgE sensitization and stratified the analysis by IgE sensitization status.

We conducted several sensitivity analyses. First, we performed a subgroup analysis that excluded 101 infants with RSV/rhinovirus coinfection. Second, to address the potential heterogeneity of recurrent wheeze,[44,45] we also fit the models with stratifying the recurrent wheeze outcome (by age 3 years) by asthma status at age 4 years. Asthma was defined using a commonly used epidemiologic definition[46]: physician-diagnosis of asthma, with either asthma medication use (eg, albuterol inhaler or inhaled corticosteroids) or asthma-associated symptoms (eg, wheezing or nocturnal cough) in the preceding year. Lastly, we repeated the primary analysis, excluding the subset of children who did not have recurrent wheeze but who developed asthma. Analysis used R, version 3.4 (R Foundation). All P values were 2-tailed, with $P < .05$ considered statistically significant.

Results

Patient Characteristics

Of 921 infants in the longitudinal cohort, 716 (78%) had RSV-only or rhinovirus bronchiolitis and were eligible for this analysis. Among the analytic cohort, the median age was 2.9 months (interquartile range, 1.6-3.8 months), 430 (60%) were male; 321 (45%) were non-Hispanic white, 163 (23%) were non-Hispanic black, 204 (28%) were Hispanic, and 28 (4%) were other. Additionally, 138 (19%) had IgE sensitization at the enrollment (of whom 128 [93%] had IgE sensitization to food) and 107 (15%) underwent intensive care during the index hospitalization. Overall, 231 children (32%) developed recurrent wheeze by age 3 years. Of the 716 infants in the analytic cohort, 541 (76%) had bronchiolitis with RSV only (the reference group), 85 (12%) had rhinovirus A, 12 (2%) had rhinovirus B, and 78 (11%) had rhinovirus C infection; 101 (14%) had RSV/rhinovirus coinfection. **Table 1** and eTable 2 in the Supplement summarize the patient characteristics and clinical course of bronchiolitis. While most variables did not differ between the 4 virus groups, we noted significant differences in age, day care use, and having household siblings (Table 1).

Infants With Rhinovirus C Infection and Risk of Developing Recurrent Wheeze

The Kaplan-Meier curves for the recurrent wheeze outcome are shown in the **Figure**. Overall, the multivariable Cox proportional hazards model demonstrated that, compared with infants with RSV-only infection, the risk of developing recurrent wheeze was not significantly different in those with rhinovirus A or B infection. In contrast, infants with rhinovirus C had a significantly higher risk of recurrent wheeze (adjusted hazard ratio [HR], 1.58; 95% CI, 1.08-2.32; **Table 2** and Figure, A). In the sensitivity analysis excluding 101 infants with coinfection, the significant association persisted (adjusted HR, 3.76; 95% CI, 2.40-5.90; eTable 3 in the Supplement) while in the analysis excluding those with rhinovirus-only infection, there was no significant association (eTable 4 in the Supplement).

Differences in Virus-Recurrent Wheeze Association by IgE Sensitization Status During Infancy

Further, there was a significant interaction between virus groups and IgE sensitization during infancy on the risk of recurrent wheeze (P for interaction < .01), suggesting that the magnitude of virus-outcome association differed by IgE sen-

Table 1. Baseline Characteristics and Clinical Presentation of 716 Infants Hospitalized for Bronchiolitis by Virus Group[a]

Variables	RSV	Rhinovirus A	Rhinovirus B	Rhinovirus C	*P* Value[b]
No. (%)	541 (76)	85 (12)[c]	12 (2)[c]	78 (11)[c]	
Characteristics					
Age, median (IQR), mo	2.8 (1.5-4.9)	3.1 (1.9-5.7)	3.0 (2.1-4.7)	4.7 (2.4-7.9)	<.01
Male sex	313 (58)	58 (68)	6 (50)	53 (68)	.11
Race/ethnicity					
Non-Hispanic white	254 (47)	32 (38)	5 (42)	30 (38)	.46
Non-Hispanic black	117 (22)	19 (22)	4 (33)	23 (29)	
Hispanic	147 (27)	32 (38)	3 (25)	22 (28)	
Other	23 (4)	2 (2)	0 (0)	3 (4)	
Parental history of asthma	173 (32)	31 (36)	4 (33)	29 (37)	.95
Parental history of eczema	99 (18)	12 (14)	2 (17)	18 (23)	.87
Maternal smoking during pregnancy	76 (14)	11 (13)	1 (8)	10 (13)	.32
Mode of birth (caesarean delivery)	198 (37)	24 (28)	3 (25)	26 (33)	.11
Prematurity (32-37 wk)	101 (19)	15 (18)	1 (8)	21 (27)	.25
History of eczema	75 (14)	9 (11)	0 (0)	15 (19)	.21
Previous breathing problems before index hospitalization	74 (14)	19 (22)	2 (17)	27 (35)	<.01
Ever attended day care	97 (18)	23 (27)	3 (25)	28 (36)	<.01
Household sibling	423 (78)	75 (88)	12 (100)	57 (73)	.02
Breastfed	245 (45)	37 (44)	7 (58)	31 (40)	.87
Smoke exposure at home	87 (16)	9 (11)	3 (25)	7 (9)	.17
Presentation and course at hospitalization for bronchiolitis					
Weight at presentation, median (IQR), kg	5.7 (4.6-7.2)	5.9 (4.7-7.6)	5.9 (5.2-6.9)	7.3 (5.6-8.5)	<.01
Respiratory rate at presentation, median (IQR), per minute	48 (40-60)	48 (40-60)	50 (38-60)	48 (40-56)	.42
Oxygen saturation at presentation, %					
<90	51 (10)	8 (10)	1 (8)	6 (7)	.86
90-93	83 (15)	9 (11)	3 (25)	9 (12)	
≥94	393 (73)	64 (75)	8 (67)	62 (79)	
Received corticosteroids during pre-hospitalization visit	35 (6)	11 (13)	2 (17)	10 (13)	.17
Laboratory testing					
Coinfection with RSV	n/c	49 (58)	10 (83)	42 (54)	n/c
Nasopharyngeal CCL5, median (IQR), pg/mL	36 (16-93)	61 (30-149)	33 (28-48)	35 (9-85)	<.01
Blood eosinophilia (≥4%)	52 (10)	7 (8)	0 (0)	9 (12)	.64
Serum total 25OHD, median (IQR), ng/mL	26 (17-33)	25 (18-33)	31 (18-36)	26 (17-33)	.74
Serum LL-37, median (IQR), ng/mL	46 (32-58)	50 (34-64)	51 (32-68)	58 (42-74)	<.01
sIgE sensitization[d]	106 (20)	14 (16)	3 (25)	15 (19)	.87
Food sensitization	96 (18)	14 (16)	3 (25)	15 (19)	.89
Aeroallergen sensitization	12 (2)	0 (0)	0 (0)	1 (1)	.49
Clinical course					
Intensive care use[e]	82 (15)	11 (13)	3 (25)	11 (14)	.73
Use of mechanical ventilation	29 (5)	3 (4)	0 (0)	3 (4)	.71
Hospital length of stay, median (IQR), d	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	.09

Abbreviations: CCL5, chemokine ligand 5; IQR, interquartile range; n/c, not computed; RSV, respiratory syncytial virus; sIgE, specific immunoglobulin E; 25OHD, 25-hydroxyvitamin D.

[a] Data are number (percentage) of children unless otherwise indicated. Percentages may not equal 100 because of rounding and missingness.

[b] Between-group differences were tested by using Kruskal-Wallis, χ^2, and Fisher exact tests as appropriate.

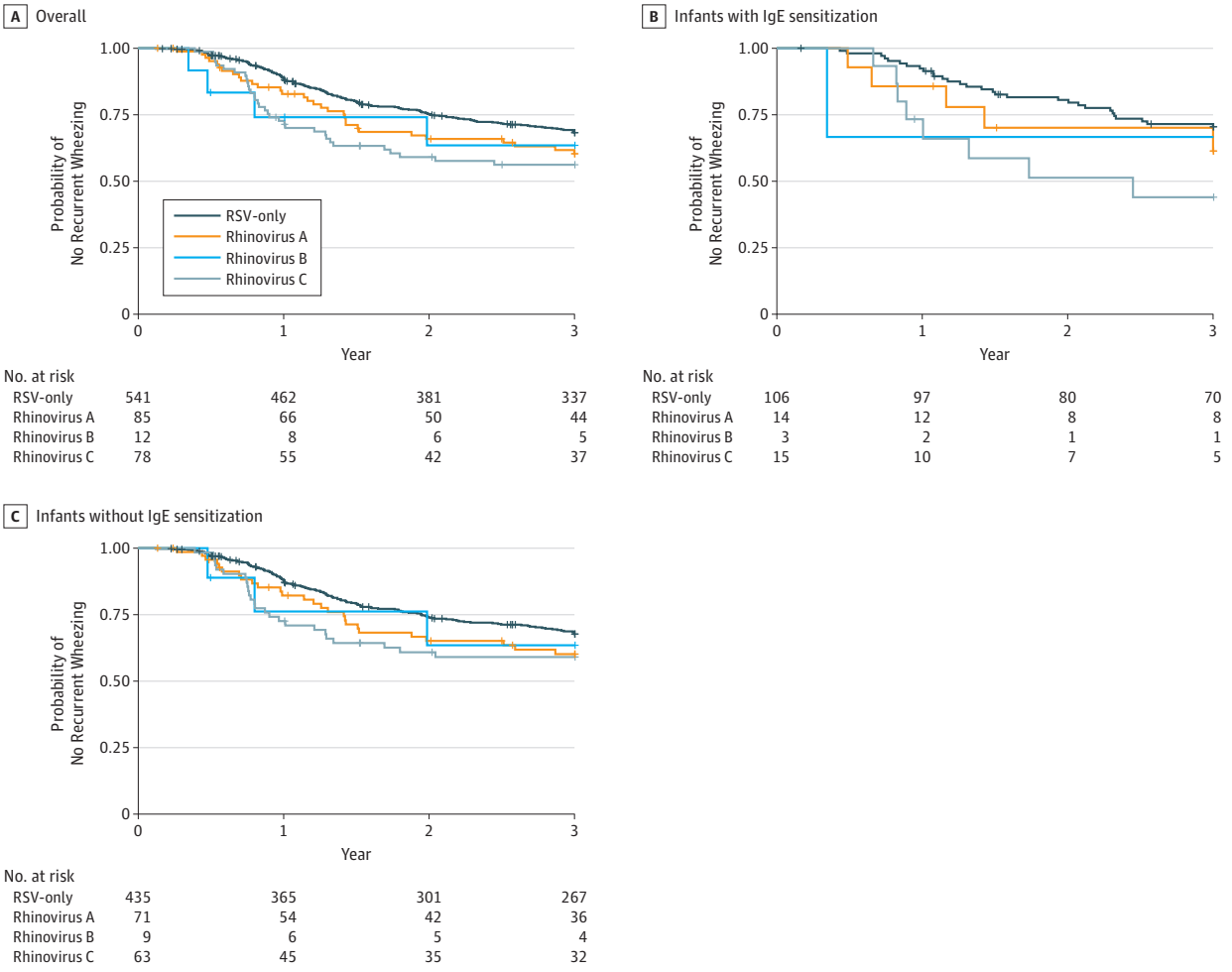
[c] Excluded 5 infants with multiple rhinovirus species.

[d] Defined by having 1 or more positive values for serum allergen-specific IgE at the index hospitalization.

[e] Defined as admission to the intensive care unit and/or use of mechanical ventilation (continuous positive airway pressure and/or intubation during inpatient stay, regardless of location) at any time during the index hospitalization.

sitization status. Indeed, among infants who had IgE sensitization at enrollment, the magnitude of the association between rhinovirus C infection and outcomes was larger, with a corresponding adjusted HR of 3.03 (95% CI, 1.20-7.61; Table 2 and Figure, B). In contrast, among infants who did not have IgE sensitization at enrollment, there was no significant difference in the risk of recurrent wheeze between the virus groups (Table 2 and Figure, C).

Figure. Between-Virus Differences in the Proportion of Patients Who Remained Recurrent Wheeze–Free Over 36 Months According to Immunoglobulin E(IgE) Sensitization Status in Infancy



A, Kaplan-Meier curve in the overall analytic cohort (n = 716). Compared with infants with respiratory syncytial virus (RSV)–only bronchiolitis, the risk of developing recurrent wheeze by age 3 years was not significantly different in those with rhinovirus A or rhinovirus B infection (both log-rank $P > .10$). In contrast, the risk was significantly higher in infants with rhinovirus C bronchiolitis (log-rank $P = .006$). B, Kaplan-Meier curve among the positive IgE sensitization strata (n = 138). Similar to the analysis in the overall cohort, compared with infants with RSV-only bronchiolitis, the risk of developing recurrent wheeze was significantly higher only in those with rhinovirus C infection (log-rank $P = .01$). C, Kaplan-Meier curve in the negative IgE sensitization strata (n = 578). The risk of developing recurrent wheeze did not differ between the virus groups (log-rank $P > .05$). Corresponding hazard ratios are presented in Table 2.

Persistence of Significant Association Among Children With Recurrent Wheeze Who Developed Asthma

To address potential heterogeneity of recurrent wheeze, we further stratified the outcome by subsequent asthma status and found that rhinovirus C infection was significantly associated with a higher risk of recurrent wheeze that resulted in asthma at age 4 years (**Table 3**). For example, among infants who had IgE sensitization, the rhinovirus C infection group had a higher risk (adjusted HR, 4.06; 95% CI, 1.17-14.1). In contrast, there was no significant association between the virus and risks of developing recurrent wheeze that did not result in asthma. In the sensitivity analysis that excluded children without recurrent wheeze but who developed asthma, the results did not materially change (eTable 5 in the Supplement).

Discussion

In this prospective multicenter cohort of 716 infants with severe bronchiolitis, we found that the risk of developing recurrent wheeze differed by the causative virus of the bronchiolitis. Specifically, compared with infants with RSV-only infection, those with rhinovirus C infection had a higher risk of recurrent wheeze. We also found that the association remained significant only in infants who had IgE sensitization during infancy. For example, infants with rhinovirus C infection and IgE sensitization had a 3-fold increased risk of recurrent wheeze while those without IgE sensitization had no significant differences. Furthermore, the data also suggest that

Table 2. Associations of Respiratory Viruses With Risks of Developing Recurrent Wheeze by Age 3 Years According to IgE Sensitization Status at the Enrollment

Virus Group and IgE Sensitization Status	HR (95% CI)	
	Unadjusted Model[a]	Adjusted Model[a]
Overall	n = 716	n = 716
RSV-only	1 [Reference]	1 [Reference][b,c]
Rhinovirus A	1.37 (0.93-2.02)	1.27 (0.86-1.88)
Rhinovirus B	1.43 (0.53-3.87)	1.39 (0.51-3.77)
Rhinovirus C	1.69 (1.16-2.47)	1.58 (1.08-2.32)
IgE sensitization	n = 138	n = 138
RSV-only	1 [Reference]	1 [Reference][d]
Rhinovirus A	1.49 (0.56-3.97)	1.21 (0.41-3.60)
Rhinovirus B	1.60 (0.20-13.0)	1.90 (0.20-18.1)
Rhinovirus C	2.61 (1.17-5.83)	3.03 (1.20-7.61)
No IgE sensitization	n = 578	n = 578
RSV-only	1 [Reference]	1 [Reference][d]
Rhinovirus A	1.33 (0.88-2.03)	1.27 (0.83-1.95)
Rhinovirus B	1.29 (0.41-4.05)	1.23 (0.39-3.87)
Rhinovirus C	1.51 (0.98-2.31)	1.42 (0.92-2.20)

Abbreviations: HR, hazard ratio; RSV, respiratory syncytial virus.

[a] Cox proportional hazards model accounting for patient clustering within the sites as random effects.

[b] Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, use of mechanical ventilation during the index hospitalization, and IgE sensitization (aeroallergen and/or food) at the enrollment.

[c] *P* value for interaction between virus groups and IgE sensitization, <.01.

[d] Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, and use of mechanical ventilation during the index hospitalization.

the observed findings are driven by the associations with a subtype of recurrent wheeze, recurrent wheeze with subsequent development of asthma. To our knowledge, this is the first study that has investigated the longitudinal association of rhinovirus C bronchiolitis in infancy with the risk of chronic respiratory morbidities in later childhood.

Although RSV is the most common pathogen associated with bronchiolitis and has been effectively used to define bronchiolitis cohorts,[46] emerging evidence suggests that rhinovirus infection during early life has strong associations with the development of chronic respiratory morbidities, such as recurrent wheeze[10-14] and childhood asthma.[14-19] Additionally, several epidemiological studies have also reported interrelations of rhinovirus infection and allergic sensitization with the risk of chronic outcomes. For example, in the Childhood Origins of Asthma cohort of 259 predominantly white children at high risk of asthma, children with rhinovirus infection and IgE sensitization to aeroallergens at age 1 year had an increased risk of asthma at ages 6 and 13 years.[16,17] Likewise, in an Australian cohort of 198 white children at high risk for allergic diseases, those with rhinovirus infection during infancy and a positive skin prick test result to food or aeroallergen by age 2 years had a higher risk of recurrent wheeze at age 5 years[10]; those with rhinovirus infection during infancy and a positive skin prick test result only after age 2 years had an increased risk of asthma at age 10 years.[15] These findings are consistent with our observations in a larger, racially/ethnically diverse sample of US children. Moreover, the larger cohort provided the opportunity to examine the potentially different role of rhinovirus species.

Since the identification of rhinovirus C in 2006,[20] studies have reported that this specific species is associated with a higher severity of acute respiratory infection[21-26] and asthma exacerbation.[26-29] Yet, little has been known about the role of rhinovirus C infection during early life on the development of chronic respiratory morbidities. Within the sparse literature, in a single-center study of 197 Australian children (mean age, 3 years) who presented to the emergency department with an acute wheezing episode, children with rhinovirus C infection had an increased risk of future respiratory hospitalizations compared with those with other viruses.[30] Our multicenter study corroborates these earlier reports and extends them by demonstrating the longitudinal associations between rhinovirus C infection during infancy in conjunction with early IgE sensitization and the risk of chronic respiratory morbidities.

The mechanisms underlying the observed associations between rhinovirus C bronchiolitis, IgE sensitization, and the development of recurrent wheeze warrant clarification. First, it is possible that there is a causal relationship (ie, severe rhinovirus C infection modulates host immune response and damages the airways during early infancy, which is a crucial period of lung development).[9] Indeed, studies have shown that acute rhinovirus respiratory infection induces various cellular factors regulating airway inflammation, repair, and remodeling,[20] and that rhinovirus-C infection, in particular, leads to increased proinflammatory cytokine and chemokine production (eg, interleukin [IL] 6, chemokine ligand 8, and chemokine ligand 10) and higher cytotoxicity compared with rhinovirus B infection.[47] Additionally, rhinovirus infection and allergen exposures increase airway epithelial cell production of IL-25 and IL-33, promoting type 2 airway inflammation and remodeling.[48-50] Second, severe rhinovirus infection could simply be an early marker of impaired antiviral response (eg, diminished types I and III interferon production) in the setting of an abnormal host response (eg, an enhanced expression of a high-affinity IgE receptor and cross-linking).[51] Third, the results may reflect the "2-hit hypothesis"[52] (ie, that genetic predisposition to asthma in conjunction with severe respiratory infection in early life leads to recurrent wheeze and childhood asthma). Indeed, recent studies have shown that *cadherin-related family member 3* (*CDHR3*) gene, an asthma susceptibility gene,[53] encodes a protein that mediates the binding and entry of rhinovirus C[54] and that its genetic variant increases the cell surface expression of CDHR3 protein in the airway epithelium,[54] thereby leading to enhanced rhinovirus C binding, replication, and airway injury.[55] Finally, these mechanisms are not mutually exclusive. Notwithstanding the complexity, identifying the association of rhinovirus C bron-

Table 3. Associations of Respiratory Viruses With Risks of Developing Recurrent Wheeze, With or Without Asthma at Age 4 Years According to IgE Sensitization at the Enrollment

Virus Group and IgE Sensitization Status	HR (95% CI)			
	Recurrent Wheeze With Subsequent Development of Asthma[a]		Recurrent Wheeze Without Subsequent Development of Asthma[b]	
	Unadjusted Model)	Adjusted Model[c]	Unadjusted Model)	Adjusted Model
Overall	n = 590	n = 590	n = 604	n = 604
RSV-only	1 [Reference]	1 [Reference][c]	1 [Reference]	1 [Reference][c]
Rhinovirus A	1.60 (0.91-2.81)	1.40 (0.79-2.49)	1.25 (0.72-2.16)	1.21 (0.69-2.10)
Rhinovirus B	2.63 (0.82-8.41)	2.41 (0.75-7.78)	0.63 (0.09-4.50)	0.60 (0.08-4.34)
Rhinovirus C	2.23 (1.33-3.76)	2.04 (1.19-3.49)	1.38 (0.80-2.39)	1.31 (0.75-2.30)
IgE sensitization	n = 118	n = 118	n = 113	n = 113
RSV-only	1 [Reference]	1 [Reference][d]	1 [Reference]	1 [Reference][d]
Rhinovirus A	2.24 (0.74-6.76)	1.19 (0.33-4.33)	0.78 (0.10-6.34)	0.85 (0.10-7.51)
Rhinovirus B	3.88 (0.51-29.6)	3.94 (0.41-37.7)	n/c	n/c
Rhinovirus C	3.09 (1.02-9.34)	4.06 (1.17-14.1)	2.48 (0.78-7.85)	2.63 (0.66-10.6)
No IgE sensitization	n = 472	n = 472	n = 491	n = 491
RSV-only	1 [Reference]	1 [Reference][d]	1 [Reference]	1 [Reference][d]
Rhinovirus A	1.44 (0.75-2.76)	1.41 (0.73-2.74)	1.31 (0.74-2.32)	1.27 (0.71-2.26)
Rhinovirus B	2.23 (0.54-9.23)	1.96 (0.47-8.20)	0.74 (0.10-5.30)	0.72 (0.10-5.23)
Rhinovirus C	2.12 (1.17-3.83)	1.88 (1.03-3.45)	1.17 (0.62-2.20)	1.15 (0.61-2.19)

Abbreviations: CHR, hazard ratio; n/c, not computed given that there were no outcomes in this virus group; RSV, respiratory syncytial virus.

[a] The outcome is recurrent wheeze by age 3 years with epidemiological definition of asthma at age 4 years (n = 105); the analysis excludes children who developed recurrent wheeze without subsequent development of asthma. *P* value for interaction between virus groups and IgE sensitization, <.01.

[b] The outcome is recurrent wheeze by age 3 years without epidemiological definition of asthma at age 4 years (n = 119); the analysis excludes children who developed recurrent wheeze with subsequent development of asthma. *P* value for interaction between virus groups and IgE sensitization <.01.

[c] Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, use of mechanical ventilation during the index hospitalization, and IgE sensitization (aeroallergen and/or food) at the enrollment, and accounted for patient clustering within the sites as random effects.

[d] Adjusted for patient-level confounders, including age, sex, race/ethnicity, parental history of asthma, household sibling, and use of mechanical ventilation during the index hospitalization, and accounted for patient clustering within the sites as random effects.

chiolitis and IgE sensitization during infancy with the development of recurrent wheeze (and asthma) is an important finding. Our data, in conjunction with the earlier studies, provide an evidence base for the early identification of children at high risk for chronic respiratory morbidities as well as the development of targeted prevention strategies (eg, anti-IgE therapy, vaccines, and antiviral agents).[27,56,57]

Limitations

Our study has potential limitations. First, the study did not have information from "healthy controls." However, the objective was to investigate the role of respiratory virus infection in early infancy on the development of recurrent wheeze among infants with severe bronchiolitis, of whom 30% to 40% will develop asthma.[2-8] Second, this analysis examined the association of different respiratory viruses with the risk of recurrent wheeze rather than incident asthma at older age. However, the presence of recurrent wheeze carries a 5.5-fold increased risk of developing asthma by age 6 years.[58] Additionally, our data also demonstrated significant associations between rhinovirus C infection and recurrent wheeze with the subsequent development of asthma. Regardless, to better address this important question, the study participants are currently being followed up longitudinally up to age 6 years and older. Third, as with any observational study, causal inferences could be confounded by unmeasured factors, such as cocirculating viruses and practice patterns within hospitals or regions. Yet, the observed association between bronchiolitis viruses and recurrent wheeze remained significant after accounting for between-hospital differences using mixed-effects models. Lastly, even with our racially/ethnically and geographically diverse US sample, we must generalize the inferences cautiously beyond infants with severe bronchiolitis. Still, the data remain highly relevant for 130 000 hospitalized US children each year.[1] A further understanding of hospitalized infants at the highest risk (eg, those with rhinovirus C bronchiolitis and early IgE sensitization) could better delineate the mechanism linking early respiratory virus infections to asthma in larger populations of children.

Conclusions

In this prospective multicenter cohort of 716 infants with severe bronchiolitis, we found significant between-virus differences in the risk of developing recurrent wheeze by age 3 years. Infants with rhinovirus C infection, particularly with IgE sensitization during infancy, had the highest risk. Additionally, the data also suggest that the findings were driven by the associations with recurrent wheeze that resulted in asthma at age 4 years. Our data facilitate further investigations into the mechanisms underlying the association between distinct respira-

tory viruses, host immunity, and respiratory health in children. Furthermore, the study identifies infants at higher risk of developing recurrent wheeze and asthma and informs strategies to develop targeted preventive therapies.

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