Rhinovirus illnesses during infancy predict subsequent childhood wheezing

Robert F. Lemanske, Jr, MD,[a,c] Daniel J. Jackson, MD,[c] Ronald E. Gangnon, PhD,[b] Michael D. Evans, MS,[b] Zhanhai Li, PhD,[b] Peter A. Shult, PhD,[d] Carol J. Kirk, BS,[d] Erik Reisdorf, BS,[d] Kathy A. Roberg, RN, MS,[a] Elizabeth L. Anderson, BSN, MA,[a] Kirstin T. Carlson-Dakes, RN, Med,[a] Kiva J. Adler, RN, BSN,[a] Stephanie Gilbertson-White, MS, RN,[a] Tressa E. Pappas, BS,[a] Douglas F. DaSilva, BS,[a] Christopher J. Tisler, MT,[a] and James E. Gern, MD[a] *Madison, Wis*

Background: The contribution of viral respiratory infections during infancy to the development of subsequent wheezing and/or allergic diseases in early childhood is not established.
Objective: To evaluate these relationships prospectively from birth to 3 years of age in 285 children genetically at high risk for developing allergic respiratory diseases.
Methods: By using nasal lavage, the relationship of timing, severity, and etiology of viral respiratory infections during infancy to wheezing in the 3rd year of life was evaluated. In addition, genetic and environmental factors that could modify risk of infections and wheezing prevalence were analyzed.
Results: Risk factors for 3rd year wheezing were passive smoke exposure (odds ratio [OR] = 2.1), older siblings (OR = 2.5), allergic sensitization to foods at age 1 year (OR = 2.0), any moderate to severe respiratory illness without wheezing during infancy (OR = 3.6), and at least 1 wheezing illness with respiratory syncytial virus (RSV; OR = 3.0), rhinovirus (OR = 10) and/or non–rhinovirus/RSV pathogens (OR = 3.9) during infancy. When viral etiology was considered, 1st-year wheezing illnesses caused by rhinovirus infection were the strongest predictor of subsequent 3rd year wheezing (OR = 6.6; $P < .0001$). Moreover, 63% of infants who wheezed during rhinovirus seasons continued to wheeze in the 3rd year of life, compared with only 20% of all other infants (OR = 6.6; $P < .0001$).
Conclusion: In this population of children at increased risk of developing allergies and asthma, the most significant risk factor for the development of preschool childhood wheezing is the occurrence of symptomatic rhinovirus illnesses during infancy that are clinically and prognostically informative based on their seasonal nature. (J Allergy Clin Immunol 2005;116:571-7.)

Key words: *Rhinovirus, respiratory syncytial virus, virus, asthma, wheezing illnesses, allergic sensitization, atopy, infants, children, allergic disease*

Abbreviations used
COAST: Childhood Origins of Asthma
I−W: Moderate to severe respiratory illness without wheezing
I+W: Moderate to severe respiratory illness with wheezing
NRVP: Nonrhinovirus picornaviruses
OR: Odds ratio
RSV: Respiratory syncytial virus

Viral respiratory infections are the most common cause of acute illnesses and wheezing during infancy, and infections with respiratory syncytial virus (RSV) have been associated with a subsequent increased risk of recurrent wheezing and asthma.[1,2] Paradoxically, other studies have suggested that frequent viral infections during infancy could decrease subsequent rates of wheezing and atopy.[3] The precise role of viral illnesses in the pathogenesis of childhood wheezing, therefore, has yet to be comprehensively evaluated.

Although most children are infected with RSV by 2 years of age,[4] only a fraction of them go on to develop recurrent wheezing, suggesting a role for additional or interactive factors in this process, or that non-RSV pathogens may contribute as well. Recent reports documenting an increased asthma risk in infants hospitalized for rhinovirus-induced bronchiolitis[5,6] suggest that infections with this presumed upper respiratory tract pathogen during infancy may be contributing more to both short-term and long-term lower respiratory tract manifestations during early childhood than was previously appreciated.

To analyze more comprehensively these relationships in nonhospitalized infants and children, we used a birth cohort genetically at high risk of developing allergies and/or asthma to evaluate prospectively the relationship of timing, frequency, severity, and etiology of symptomatic viral infections during infancy to the subsequent development of early childhood wheezing.

METHODS

Study subjects

A total of 289 newborns were enrolled from November 1998 through May 2000 in the Childhood Origins of ASThma (COAST)

From the Departments of [a]Pediatrics, [b]Biostatistics and Medical Informatics, and [c]Medicine, and [d]the Wisconsin State Laboratory of Hygiene, University of Wisconsin—Madison.

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Reprint requests: Robert F. Lemanske, Jr, MD, K4/916 University of Wisconsin Hospital, 600 Highland Avenue, Madison, WI 53792-9988. E-mail: rfl@medicine.wisc.edu.

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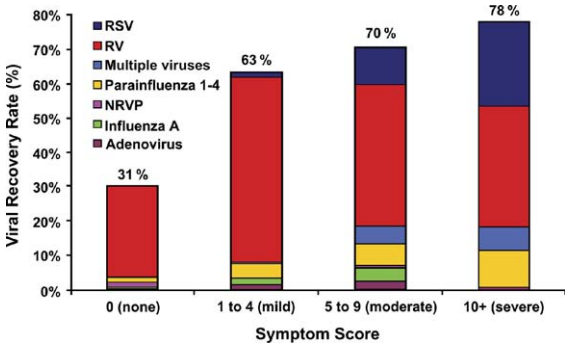

FIG 1. Viral recovery rates based on symptom severity scores. Symptom scores were obtained before all nasal washes when performed during protocol scheduled visits or during sick visits (symptom severity score was ≥ 5). *RV,* Rhinovirus.

study as previously described.[7-9] Of these children, 285 were followed prospectively for at least 1 year, and 275 were followed for 3 years.[7] To qualify, at least 1 parent was required to have respiratory allergies (defined as 1 or more positive aeroallergen skin tests) and/or a history of physician-diagnosed asthma. The Human Subjects Committee of the University of Wisconsin approved the study.

Nasal lavage samples

Nasopharyngeal mucus samples were collected during scheduled clinic visits (at 2, 4, 6, 9, and 12 months of age) and during times of acute respiratory illnesses. Parents notified a study coordinator when their child developed a respiratory tract infection and a respiratory symptom scorecard (maximum score, 31) was completed.[8] Symptoms were scored on the basis of the following scoring system: fever (≥100°F) = 1 point; cough, mild = 1 point, moderate = 2 points, severe = 3 points; rhinorrhea, mild (suction 0-4 times/d or wipe every 2 hours or less) = 1 point, moderate to severe (suction ≥ 5 times/d or wipe ≥ 1 time/h) = 2 points; hoarseness = 1 point; duration of illness > 4 days = 1 point; apnea = 3 points; wheezing = 5 points; retractions = 5 points; tachypnea = 5 points; cyanosis = 5 points. If the symptom score was ≥ 5, signifying a moderate to severe upper and/or lower respiratory infection, a sick visit was scheduled, and nasal lavage was performed and processed as described.[8]

Viral diagnostics

Nasal specimens were analyzed for respiratory viruses including RSV, rhinovirus, influenza types A and B, parainfluenza virus types 1 to 4, adenovirus, and nonrhinovirus picornaviruses (NRVPs) by using standard techniques.[8] Samples were also evaluated for rhinovirus RNA by seminested RT-PCR.[8,10] In addition, RSV serology was performed on plasma samples obtained at age 1 year.[11]

Allergen-specific IgE

Blood was collected and allergen-specific IgE was measured at age 1 year as described.[9]

Clinical definitions

Daycare attendance[11] and atopic dermatitis[9] were defined as described. A wheezing respiratory illness during infancy was defined as meeting 1 or more of the following criteria: (1) physician-diagnosed wheezing at an office visit; (2) an illness for which the child was prescribed short-acting or long-acting β-agonists and/or long-term controller medications; or (3) an illness given the following specific diagnoses: bronchiolitis, wheezing illness, reactive airway disease, asthma, or asthma exacerbation. Wheezing history in the 3rd year of life was documented by questionnaires at the 3rd year protocol-scheduled visit that asked the parent whether the child had ever wheezed during the past year.

Statistical methods

Risk factors (maternal and paternal asthma, birth month and weight, dog and cat exposure, presence of older siblings, passive smoke exposure, daycare, exclusive breast-feeding, atopic dermatitis, and allergic sensitization to food protein [egg, milk, peanut] at age 1 year) for wheezing in the 3rd year of life were assessed individually and jointly by using logistic regression analyses. Relationships between 3rd year wheezing and the etiology, severity, and seasonality of 1st year illnesses were assessed by using logistic regression analyses, both in univariate models and in multivariable models including the risk factors given.

RESULTS

Viral isolates

A total of 1668 nasopharyngeal wash specimens were obtained during infancy. The likelihood of viral identification was related to the severity of illness, as measured by the symptom score (Fig 1; $P < .0001$). Viral identification occurred in 78% (95/122) of the severe (score ≥ 10), 70% (312/444) of the moderate (score = 5-9), and 63% (136/216) of the mild illnesses (score = 1-4; Fig 1). Virus was recovered from 66% (118/179) of the wheezing illnesses. Viral recovery from scheduled well (score = 0) visits was 31% on the basis of culture results of all well samples and RT-PCR for rhinovirus performed on randomly selected culture-negative well samples.

During infancy, a variety of respiratory viruses were recovered from children with each illness severity (Fig 1), with rhinovirus the most common. Of the 566 moderate to severe illnesses, only 7 (in 7 children) (1%) required hospitalization. The viruses identified during these illnesses included RSV (n = 3), rhinovirus (n = 1), rhinovirus + echovirus (n = 1), influenza A (H3N2; n = 1), and RSV + influenza A (H1N1). There were 99 moderate to severe RSV illnesses, 51 (51.5%) of which were wheezing respiratory illnesses. There were 258 moderate to severe rhinovirus illnesses, 60 (23.3%) of which were wheezing respiratory illnesses.

In the 3rd year of life, there were 180 wheezing illnesses among 76 children. Viruses recovered were rhinovirus (n = 76, 42%), RSV (n = 15, 8%), parainfluenza (n = 14, 8%), adenovirus (n = 2, 1%), influenza (n = 2, 1%), rhinovirus/influenza (n = 2, 0.5%), nonrhinovirus picornavirus (n = 1, 0.5%), and none (n = 69, 38%). Seventy-nine children were defined as wheezing in the 3rd year on the basis of parental questionnaires at the 3-year protocol-scheduled visit. Of these 79, 63 (80%) had a viral diagnostically confirmed wheezing respiratory illness during the 3rd year and 16 (20%) did not.

Risk factors for wheezing in the 3rd year of life

Nonviral factors. Various early life exposures and familial factors were associated with the development of wheezing in the 3rd year of life (Table I). Passive smoke

TABLE I. Risk factors for 3rd year wheezing

	Univariate			Multivariate		
Risk factor	**OR**	**(95% CI)**	***P* value**	**OR**	**(95% CI)**	***P* value**
Maternal asthma	1.1	(0.66, 1.9)	.66	0.94	(0.48, 1.8)	.85
Paternal asthma	1.2	(0.65, 2.1)	.60	1.2	(0.56, 2.5)	.66
Birth month	—	—	.54	—	—	.26
Birth weight (lb)	0.94	(0.75, 1.2)	.57	0.78	(0.58, 1.1)	.089
Cat in household at birth	1.1	(0.60, 1.9)	.83	1.2	(0.60, 2.5)	.60
Dog in household at birth	0.44	(0.24, 0.80)	.0067	0.59	(0.29, 1.2)	.14
Older siblings	2.5	(1.4, 4.4)	.0015	2.6	(1.3, 5.2)	.0074
Passive smoke exposure	2.1	(1.2, 3.8)	.0097	1.3	(0.61, 3.0)	.47
Daycare	1.3	(0.79, 2.2)	.29	1.8	(0.91, 3.7)	.093
Exclusive breast-feeding (6 mo)	1.4	(0.80, 2.4)	.24	1.7	(0.83, 3.5)	.15
Atopic dermatitis (1st year)	1.5	(0.90, 2.6)	.12	1.3	(0.64, 2.5)	.50
Positive egg RAST (1st year)	2.5	(1.3, 4.9)	.0059	3.0	(1.1, 7.8)	.0266
Positive milk RAST (1st year)	2.2	(1.0, 4.7)	.0428			
Positive peanut RAST (1st year)	2.7	(1.2, 6.0)	.0136			
Any positive food RAST (1st year)	2.0	(1.1, 3.6)	.0178			

exposure (odds ratio [OR] = 2.1; 95% CI, 1.2, 3.8); older siblings (OR = 2.5; 95% CI, 1.4, 4.4); and allergic sensitization to egg (OR = 2.5; 95% CI, 1.3, 4.9), milk (OR = 2.2; 95% CI, 1.0, 4.7), peanut (OR = 2.7; 95% CI, 1.2, 6.0), or any positive food RAST (OR = 2.0; 95% CI, 1.1, 3.6) at 1 year were all associated with the development of persistent wheezing by age 3 years by univariate analyses. In multivariate models, only the associations with older siblings and allergic sensitization to egg remained significant (Table I).

Viral-related events. The types and severity of respiratory illnesses children had during infancy significantly influenced wheezing in the 3rd year of life (Table II). The occurrence of at least 1 moderate to severe respiratory illness without wheezing (I−W) associated with rhinovirus (univariate OR = 2.3; 95% CI, 1.2, 4.4) or of at least 1 moderate to severe respiratory illness with wheezing (I+W) associated with rhinovirus (univariate OR = 10; 95% CI, 4.7, 23) was related to an increased incidence of wheezing during year 3 of life. Weaker relationships were observed for illnesses associated with RSV (I−W: OR = 1.3; 95% CI, 0.64, 2.8; I+W: OR = 3.0; 95% CI, 1.6, 5.8) and for illnesses associated with viruses other than rhinovirus or RSV, or no viral recovery (I−W: OR = 1.8; 95% CI, 0.96, 3.2; I+W illness: OR = 3.9; 95% CI, 1.9, 8.1). For all etiologies combined, there was a significant relationship between symptomatic illnesses in infancy and wheezing in year 3 (I−W: OR = 3.6; 95% CI, 1.2, 11; I+W: OR = 10; 95% CI, 3.3, 30). The relationships were not significantly altered by adjustment for other potential risk factors listed in Table I or stratification by month of birth. Finally, there was no difference in the frequency of viral isolation measured at scheduled visits during infancy between those children who wheezed versus children who did not during the 3rd year of life (any virus, $P = .96$; RSV, $P = .72$; rhinovirus, $P = .85$; non-RSV/rhinovirus, $P = .85$). Thus, the incidence of 3rd year wheezing was significantly associated with illness severity but not with the frequency of infections during infancy.

To assess further the relationship between the occurrence of and the response to rhinovirus, RSV, and other viruses, the rates of 3rd year wheezing were compared on the basis of the most severe illness (none or mild, moderate to severe without wheezing, wheezing) associated with each virus during the 1st year of life (Fig 2). The severity of the rhinovirus illnesses was strongly associated with wheezing in the 3rd year of life after stratifying by the severity of RSV (Fig 2, A) or non-RSV/nonrhinovirus (Fig 2, B) illnesses ($P < .0001$ for both). Conversely, after stratifying by the severity of rhinovirus illnesses, neither the severity of RSV illnesses nor the severity of non-RSV, nonrhinovirus illnesses was significantly associated with wheezing in the 3rd year of life ($P = .53$ and .10, respectively). Although the occurrence of a single I+W rhinovirus infection at any time during infancy was strongly associated with 3rd year wheezing, the point during the 1st year of life that a moderate to severe or wheezing rhinovirus infection occurred did not further modify the risk of wheezing in the 3rd year of life ($P = .74$).

Season of illness and risk of 3rd year wheezing. Rhinovirus and RSV infections have different seasonal patterns: RSV infections occur mainly from December to February, whereas rhinovirus infections predominate the rest of the year, with significant peaks in the spring and fall. Therefore, the relationship between the season in which I+Ws occurred during infancy and 3rd year wheezing was evaluated to assess the usefulness of seasonality of illness as a surrogate for I+W rhinovirus illnesses (Table III). The risk of wheezing during the 3rd year was greatly increased for children who had 1st-year wheezing illnesses during both rhinovirus and RSV seasons (OR = 7.5; 95% CI, 3.3, 17), and for children who wheezed only during rhinovirus season (OR = 5.5; 95% CI, 2.3, 13). In contrast, children who wheezed only during their 1st RSV season were not at increased risk for wheezing in year 3 (OR = 0.95; 95% CI, 0.36, 2.5). Moreover, the 3rd year wheezing rate (19%; 6/31) in children who wheezed only during RSV season is

TABLE II. Third year wheezing

			Univariate					Multivariate				
					P value					*P* value		
First year illnesses	N	%	OR	(95% CI)	Overall	Vs (none)	Vs (I−W)	OR	(95% CI)	Overall	Vs (none)	Vs (I−W)
Any etiology					<.0001					.0001		
No moderate-severe illness (none)	49	8%	1.0					1.0				
Moderate-severe illness without wheeze (I−W)	139	24%	3.6	(1.2, 11)		.0205		3.9	(1.1, 15)		.0422	
Moderate-severe wheezing illness (I+W)	87	47%	10	(3.3, 30)		<.0001	.0005	12	(3.0, 44)		.0003	.0013
RSV					.0039					.0042		
No moderate-severe illness (none)	180	23%	1.0					1.0				
Moderate-severe illness without wheeze (I−W)	45	29%	1.3	(0.64, 2.8)		.44		1.4	(0.61, 3.3)		.42	
Moderate-severe wheezing illness (I+W)	50	48%	3.0	(1.6, 5.8)		.0009	.059	3.5	(1.7, 7.5)		.0010	.062
RV					<.0001					<.0001		
No moderate-severe illness (none)	119	15%	1.0					1.0				
Moderate-severe illness without wheeze (I−W)	113	29%	2.3	(1.2, 4.4)		.0108		1.8	(0.86, 3.8)		.12	
Moderate-severe wheezing illness (I+W)	43	65%	10	(4.7, 23)		<.0001	<.0001	10	(4.1, 26)		<.0001	<.0001
Other (virus other than RV or RSV, or no virus recovered)					.0011					.0019		
No moderate-severe illness (none)	122	20%	1.0					1.0				
Moderate-severe illness without wheeze (I−W)	106	30%	1.8	(0.96, 3.2)		.067		2.2	(1.1, 4.5)		.0347	
Moderate-severe wheezing illness (I+W)	47	49%	3.9	(1.9, 8.1)		.0002	.0273	4.6	(2.0, 11)		.0005	.073

RV, Rhinovirus.

significantly lower than the rates in children who wheezed in rhinovirus season only (58%; 14/24; $P = .004$) or in both seasons (66%; 21/32; $P = .0004$). These relationships were unchanged after controlling for other risk factors for wheezing (Table I). Similar results were observed when rhinovirus season was divided into peak rhinovirus season (the spring and fall months) and summer (June through August). These data strongly indicate that, even without culture confirmation, infantile wheezing illnesses during rhinovirus, but not RSV, seasons are important predictors of persistent wheezing later in childhood.

DISCUSSION

We have used a birth cohort at high risk of developing allergic diseases and/or asthma to define more comprehensively the relationships between specific viral respiratory infections during infancy and the subsequent development of early childhood wheezing. A major advance of our findings is the documentation throughout early childhood of the specific viral pathogens involved in both asymptomatic (ie, at scheduled protocol visits) and symptomatic infections. By using this approach, we established that 3rd year wheezers were not infected more often during the 1st year of life, but clearly developed more severe symptoms of illness. Most importantly, we were able to ascertain that outpatient infections with the common respiratory pathogen, rhinovirus, played a significant role in the developments of both infantile and early childhood wheezing that, to our knowledge, has been unrecognized previously.

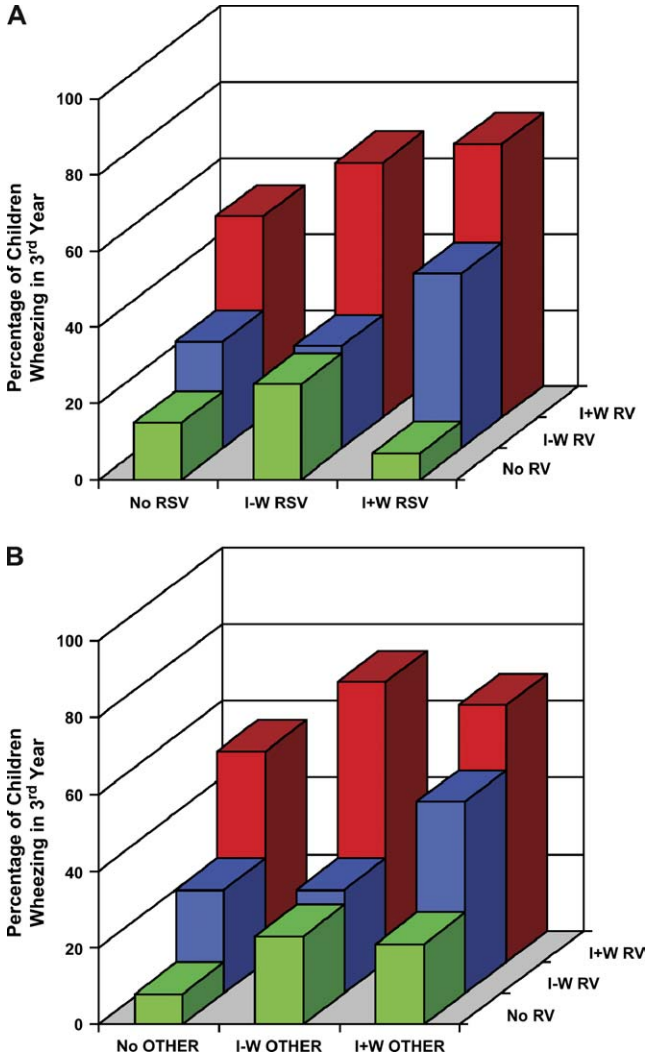

FIG 2. A, Prevalence of 3rd year wheezing by the severity of RSV-related illnesses and rhinovirus (RV)-related illnesses during infancy. **B,** Prevalence of 3rd year wheezing by the severity of RV-related illnesses and non-RSV, non-RV–related illnesses during infancy. *I−W,* moderate to severe illness without wheezing (score $\geq$ 5); *I+W,* moderate to severe infection with wheezing (score $\geq$ 5); *OTHER,* non-RV, non-RSV, or no virus identified.

Although the use of wheezing as an outcome measure has been used in several epidemiologic studies,[1,2,12,13] its use in children has been criticized because of its inconsistency and subjectivity.[14-16] Parental and clinician use of the term often does not agree.[14,15] However, when physician assessment of wheezing has been compared with objective measures of lung function in early childhood, children with physician-confirmed wheeze have significantly poorer lung function compared with those with parentally reported but unconfirmed wheezing and children who have never wheezed.[16] Importantly, the definition of a wheezing illnesses during infancy was based entirely on 3 levels of physician, not parental, assessment.

We confirmed previous observations linking infantile RSV infections with long-term wheezing outcomes. A novel finding, however, was that infantile rhinovirus illnesses were the ones most significantly associated with the prevalence of wheezing in the 3rd year of life. Despite having more frequent rhinovirus-confirmed than RSV-confirmed illnesses during infancy, only about 25% of children wheezed with rhinovirus, as opposed to 50% with RSV illnesses. However, the clinical implications of wheezing with rhinovirus infections during this period were quite remarkable. Indeed, infants with moderate to severe rhinovirus illnesses with wheezing were 2 to 3 times more likely to wheeze in year 3 compared with infants who wheezed with RSV infections. In addition to wheezing illnesses, I−W with rhinovirus infections significantly enhanced 3rd year wheezing rates as well.

Although epidemiologic studies have mainly focused on the association of RSV infections in early life with the subsequent development of wheezing and/or asthma, more sensitive molecular diagnostic techniques have highlighted the contribution of rhinovirus infections to these same outcomes. In children hospitalized with

TABLE III. Third year wheezing

			Univariate						Multivariate					
					P value						*P* value			
	N	%	OR	(95% CI)	Overall	Vs (none)	Vs (RSV)	Vs (RV)	OR	(95% CI)	Overall	Vs (none)	Vs (RSV)	Vs (RV)
First year wheezing illnesses					<.0001						<.0001			
None (none)	188	20%	1.0						1.0					
During Dec-Feb only (RSV)	31	19%	0.95	(0.36, 2.5)		.91			0.89	(0.29, 2.7)		.84		
During Mar-Nov only (RV)	24	58%	5.5	(2.3, 13)		.0002	.0041		6.0	(2.2, 17)		.0006	.0076	
During both Dec-Feb and Mar-Nov (both)	32	66%	7.5	(3.3, 17)		<.0001	.0004	.58	9.1	(3.4, 24)		<.0001	.0009	.52

RV, Rhinovirus.

bronchiolitis, rhinovirus was the causative agent in about 1/3 of the cases evaluated,[5,17] and children who were infected with rhinovirus were more likely to develop asthma subsequently than children who were not.[5] In comparison with children with RSV-induced bronchiolitis, children with rhinovirus-induced bronchiolitis tended to be older and more atopic[18] and have a more severe disease course during their acute infection.[19]

Our findings uniquely extend these inpatient observations into the outpatient setting. Although we chose a priori not to ascertain definitively whether the COAST children have physician-diagnosed asthma until age 6 years, the fact that they are still wheezing in year 3 of life places them at a significantly increased risk for subsequent asthma on the basis of previously published observations.[13]

Clinically, this strongly suggests that diagnosing rhinovirus-induced infantile I+W is informative in predicting which children are at increased risk of developing preschool childhood wheezing and, subsequently, childhood asthma. Such early recognition would be essential if ongoing therapeutic intervention trials aimed at prevention demonstrate efficacy.[20] Documentation of specific viral etiologies responsible for infantile wheezing would be an important initial step in this process. Although such diagnostic tools are available, their convenience and cost limit their use to research settings. Our data demonstrate, however, that the seasonal pattern of wheezing episodes during infancy provides important diagnostic and prognostic information for the practicing physician. Indeed, 63% of infants who wheezed during rhinovirus season continued to wheeze in the 3rd year of life, compared with 20% of infants who wheezed during RSV season only or did not wheeze during infancy. These relationships provide novel and clinically relevant information to primary care physicians who treat wheezing infants during rhinovirus seasons, because they underscore the importance of close prospective monitoring of these children on the basis of their increased risk of developing early childhood wheezing and asthma.

Although the nature of the associations between rhinovirus and these short-term and long-term consequences remains to be determined, several published observations provide some insight. Rhinovirus infections can invade the lower airway,[21,22] increase lower airway inflammatory responses to allergen,[23] enhance airway responsiveness,[24] and promote the development of late asthmatic reactions.[24] Variations in host immune response may also contribute. COAST children with decreased mitogen-induced cord blood mononuclear cell IFN-γ responses had an increased number of viral infections during infancy,[11] and mitogen-induced mononuclear cell IL-13 responses are differentially regulated in children who wheeze with these infections during infancy (Gern et al, unpublished data, July 2005). Others have demonstrated distinct cytokine response patterns both during (reduced IFN-γ production)[25] and after (increased IL-10 production)[26] RSV infections associated with wheezing. Moreover, polymorphisms for genes encoding for CCR5, IL-4, IL-4RA, IL-8, IL-10, surfactant protein D, and TGF-β1 have also been associated with more severe RSV infections.[27-33]

Our findings suggest at least 2 potential mechanisms for the development of recurrent wheezing in early childhood. First, healthy infants who undergo repetitive severe viral respiratory infections could develop recurrent wheezing as a consequence of lung damage and/or airway remodeling. Second, infants who are born with poor antiviral responses and/or airway hyperresponsiveness are prone to repetitive severe illnesses, and these same abnormalities may increase the risk of recurrent wheezing and possibly asthma. Our results demonstrating that even 1 moderate-severe rhinovirus infection during infancy drastically increases the risk for recurrent wheezing through 3 years of age seem to support the latter explanation. The findings reported herein will provide a solid foundation to investigate further the relationship of these early life events with the subsequent development of asthma and allergic diseases in this high-risk birth cohort as the children mature into later childhood and beyond.

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