Prospective Multicenter Study of the Viral Etiology of Bronchiolitis in the Emergency Department

Jonathan M. Mansbach, MD, Alexander J. McAdam, MD, PhD, Sunday Clark, MPH, ScD, Paul D. Hain, MD, Robert G. Flood, MD, Uchechi Acholonu, BA, Carlos A. Camargo Jr., MD, DrPH

Abstract

Objectives: To determine the viral etiology of bronchiolitis and clinical characteristics of children age < 2 years presenting to the emergency department (ED) with bronchiolitis.

Methods: The authors conducted a 14-center prospective cohort study during 2005–2006 of ED patients age < 2 years with bronchiolitis. The study was conducted in 10 states as part of the Emergency Medicine Network. Researchers collected nasopharyngeal aspirates and conducted structured interviews, medical record reviews, and 2-week follow-up telephone calls. Samples were tested using reverse transcription polymerase chain reaction for respiratory syncytial virus (RSV), rhinovirus (RV), human metapneumovirus (hMPV), and influenza viruses (Flu).

Results: Testing of 277 samples revealed 176 (64%) positive for RSV, 44 (16%) for RV, 26 (9%) for hMPV, 17 (6%) for Flu A, and none for Flu B. When children were categorized as RSV only, RV only, RV and RSV, and all others (hMPV, Flu, no identified virus), children with RV only were more likely to be African American (19, 62, 14, and 40%, respectively; p < 0.001) and have a history of wheezing (23, 52, 21, and 15%, respectively; p = 0.01). In multivariate models, children with RV were more likely to receive corticosteroids (odds ratio [OR] 3.5; 95% confidence interval [CI] = 1.5 to 8.15). The duration of illness may be shorter for children with RV (Days 8, 3, 6, and 8; p = 0.07).

Conclusions: In this multicenter study, RSV was the most frequent cause of bronchiolitis (64%). RV was present in 16%, and these children have a distinct profile in terms of demographics, medical history, and ED treatment.

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B ronchiolitis is the leading cause of hospitalization for infants,^{1,2} and the associated hospitalization costs are more than \$500 million per year.³ This acute infection is caused by numerous viral pathogens,^{4–6}

From the Department of Medicine (JMM) and the Department of Laboratory Medicine (AJM), Children's Hospital Boston, Harvard Medical School, Boston, MA; the Department of Pediatrics, Vanderbilt Children's Hospital (PDH), Nashville, TN; the Department of Pediatrics, Temple University School of Medicine (RGF), Philadelphia, PA; and the Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School (SC, UA, CAC), Boston, MA.

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Address for correspondence and reprints: Jonathan M. Mansbach, MD; e-mail: jonathan.mansbach@childrens.harvard.edu.

and there have been several recent publications about the viral etiology of acute lower respiratory tract infections in hospitalized children.^{6–9} However, the clinical utility of identifying the specific infectious agent in children with bronchiolitis remains unclear.^{10,11} The 2006 American Academy of Pediatrics (AAP) bronchiolitis clinical practice guideline¹² states that knowing the infectious agent in a child with bronchiolitis in the acute setting rarely changes management decisions, except for the purposes of cohorting. However, over the past few years there has been a growing literature that bronchiolitis due to certain viruses, specifically rhinovirus (RV), may impact long-term outcomes.^{13–16}

To our knowledge, this study is the first prospective, multicenter emergency department (ED)-based sample with short-term follow-up investigating common viruses causing bronchiolitis. The virology samples were collected as complementary data at a subset of sites participating in a larger observational bronchiolitis study.¹⁷ Our objectives were to describe the

METHODS

Study Design

We conducted a prospective cohort study from December 14, 2005, through March 19, 2006, as part of the Multicenter Airway Research Collaboration (MARC). MARC is a division of the Emergency Medicine Network (EMNet) (http://www.emnet-usa.org/). All 14 hospitals had institutional review board approval for this study, and informed consent was obtained for all participants.

Study Setting and Population

Investigators at 14 EDs in 10 U.S. states from eight regions recruited patients 18-24 hours per day for 2 or 3 weeks. All but two sites enrolled patients for consecutive weeks. All patients were managed at the discretion of the treating physician. Inclusion criteria were final attending physician diagnosis of bronchiolitis, patient age less than 2 years, and parent/guardian informed consent. The diagnosis of bronchiolitis was considered for children younger than 2 years with acute tachypnea, retractions, and abnormal breath sounds who did not meet criteria for a diagnosis of pneumonia or another primary diagnosis. As defined by the AAP in its 2006 position statement, children with bronchiolitis typically have "rhinitis, tachypnea, wheezing, cough, crackles, use of accessory muscles, and/or nasal flaring."12 Retrospectively, the AAP definition was applied to the children in this cohort, and 98% met the definition. Those children who had a final attending diagnosis of pneumonia were excluded from the cohort. The exclusion criterion was previous enrollment.

Study Protocol

Virology Testing All sites were trained using a video, lecture, and written instructions to collect nasopharyngeal samples, and all used the same collection equipment (Cardinal Health, McGraw Park, IL). Once collected, the samples were placed on ice, refrigerated at 4° C within 1 hour, and frozen at -80° C within 24 hours.

Samples were tested for RSV, RV, human metapneumovirus (hMPV), and influenza viruses (Flu). RNA was purified using the QIAamp viral RNA mini kit (Qiagen, Valencia, CA) and amplified with the SuperScript III one-step reverse transcription polymerase chain reaction (RT-PCR) system (Invitrogen, Carlsbad, CA). Respiratory viruses were detected by RT followed by PCR. Positive controls (purified viral RNA) and negative control samples were included in each run of RT-PCR, and PCR products were detected by agarose gel electrophoresis with a molecular weight standard. Previously published primers were used to detect RSV,¹⁸ RV,¹⁹ hMPV,²⁰ and Flu A and B.²¹ Parainfluenza was not tested due to costs. All samples were tested in the same laboratory by the same person at Children's Hospital Boston.

Data Collection

The ED interview assessed patients' demographic characteristics, health history, and current illness. Wheezing was assessed by asking the parent, "Does [the child] have a history of wheezing?" Among the 29% of children who did have a history of wheezing, 65% had used β -agonists, inhaled corticosteroids, or systemic steroids during the past week. Data on ED presentation (including clinical assessment), management, and disposition were obtained by chart review. The reported vital signs were obtained at triage. Telephone interviews were conducted 2 weeks after the ED visit, and followup data were collected using a standard form. All forms were reviewed by site investigators before submission to the coordinating center, where they underwent further review by trained personnel and then double data entry.

Median household income was estimated using patients' home zip codes.²² Children were considered premature if they were born at less than 35 weeks' gestation. A comorbid condition was considered any past medical history of relevance as ascertained by the clinician (e.g., asthma, seizure disorder, spastic di-/quadriimmunodeficiency, chronic lung disease, plegia, congenital heart disease). The history of wheezing and eczema were obtained as part of the parent/quardian interview. A relapse event was defined as any urgent visit to an ED or clinic for worsening of bronchiolitis during the 2-week follow-up period. To examine the reproducibility of the relapse classification, two authors (JMM and CAC) independently reviewed the 2-week follow-up data for 100 randomly sampled cases $(\kappa = 0.98).$

Data Analysis

All analyses were performed using STATA 9.0 (Stata-Corp, College Station, TX). Data are presented as proportions (with 95% confidence intervals [CI]), means (with standard deviation [SD]), or medians (with interquartile range [IQR]). The association between viruses and other factors was examined using chi-square tests, Student's t-tests, and Kruskal-Wallis rank tests, as appropriate. All p-values are two-tailed, with p < 0.05considered statistically significant. Based on initial analyses and the emerging data on RV,^{14–16} the virology data are presented as RV, RSV, RV + RSV, and other. To be complete, the analyses were also performed excluding the "other" group and the results did not materially change. Therefore, all of the results include the other group (data not shown). Multivariate logistic regression was used to evaluate the association between presence of RV and ED treatment with corticosteroids. Our cohort had 83% power to detect a 30% difference in history of wheeze between virus groups (RSV and RV) at α = 0.05. Results are presented as odds ratios (OR) with 95% CIs.

RESULTS

Among the 277 samples tested, 155 (56%) were positive for RSV only, 27 (10%) for RV only, 19 (7%) for hMPV only, 11 (4%) for Flu A only, and 25 (9%) for multiple viruses, and 40 (14%) samples were negative for any tested viruses (Figure 1). No children tested positive for Flu B. When the single and multiple pathogen infections are combined, 176 (64%) of the children were positive for RSV and 44 (16%) were positive for RV. The majority of patients were recruited in January (35%) and February (43%), with 3% being recruited in December and 19% in March. Each site enrolled between 5 and 33 children, with 12 (86%) sites enrolling

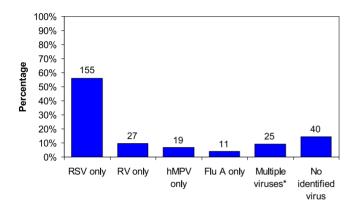


Figure 1. The identified viruses from children age < 2 years presenting to an ED with bronchiolitis. The *X*-axis represents the percentage of children with the identified virus. The number of children with each virus is indicated above the bar. *Multiple virus combinations included all possible combinations of two viruses and one patient with RSV + RV + Flu A. ED = emergency department; RSV = respiratory syncytial virus; RV = rhinovirus; hMPV = human metapneumovirus; Flu A = influenza A.

Table 1

Virology Results by MARC-25 Virology Site

15 or more children. Overall these 277 children had a median age of 6.3 months (IQR 3.1 to 10.2) and most were male (61%). One-third of children were white, 29% were African American, and 39% were Hispanic. Nearly all children (96%) had a primary care provider; 31% had private insurance, 56% Medicaid, 9% other public insurance, and 5% no insurance. Compared to the other children in the larger observational study,¹⁷ those who agreed to have a nasopharyngeal sample were more likely to be admitted to the hospital (data not shown).

The results are presented as RSV only (n = 155; 56%). RV only (n = 27; 10%), RSV + RV (n = 14; 5%), and other viruses (n = 81; 29%). The other virus category includes hMPV, Flu, other combination infections, and no identified virus. Viral infections and month of enrollment by participating site are shown in Table 1. Demographic factors and medical history are shown in Table 2. Children with RSV only were younger than children with RV only, children with RSV + RV, or children with other viruses or combinations of viruses. Children with RV only were more likely to be African American. The groups were similarly likely to be male and did not differ according to other demographic characteristics. While medical history was similar across the virus groups, some differences were noted (Table 2). Children with RV only were more likely to have a concomitant medical disorder and have a history of wheezing.

ED presentation and clinical course are shown in Table 3. Children with RV only tended to have a shorter duration of symptoms prior to presentation to the ED. While children with RSV + RV had a higher temperature at ED presentation, the virus groups were similar with respect to initial heart rate, respiratory rate, retractions, and oxygen saturation. The groups also did not differ according to presence of cough or wheeze at ED presentation.

		RSV Only (<i>n</i> = 155)	RV Only (<i>n</i> = 27)	RSV and RV (<i>n</i> = 14)	All others* (<i>n</i> = 81)
Massachusetts	Dec, Jan–Feb	13 (59)	1 (5)	1 (5)	7 (32)
Ohio	Mar	6 (40)	2 (10)	1 (5)	8 (40)
Ohio	Feb–Mar	8 (73)	0 (0)	3 (27)	0 (0)
New York	Jan–Feb	8 (42)	4 (21)	1 (5)	6 (32)
New York	Jan–Feb	9 (45)	2 (10)	1 (5)	8 (40)
New Jersey	Jan	16 (80)	1 (5)	0 (0)	3 (15)
Pennsylvania	Feb	7 (25)	8 (29)	0 (0)	13 (46)
Kansas	Feb–Mar	10 (53)	1 (5)	1 (5)	7 (37)
California	Jan	12 (57)	2 (10)	0 (0)	7 (33)
Tennessee	Jan–Feb	28 (85)	1 (3)	0 (0)	4 (12)
California	Mar	13 (68)	1 (5)	1 (5)	4 (21)
California	Feb	11 (52)	1 (5)	6 (29)	3 (14)
Arizona	Jan–Feb	13 (54)	0 (0)	0 (0)	11 (46)
Texas	Mar	1 (20)	2 (40)	0 (0)	2 (40)

Data are reported as n (%). Number in each cell represents the number of children at each site who tested positive for the specified virus. The percentage in each cell represents the percentage of children at each site who tested positive for the specified virus.

MARC = Multicenter Airway Research Collaboration; RSV = respiratory syncytial virus; RV = rhinovirus; Flu A = influenza A; hMPV = human metapneumovirus.

* Flu A, hMPV, or no virus.

Table 2

Demographic Characteristics and Medical History among Children with Bronchiolitis, According to Viral Infection

	RSV Only (<i>n</i> = 155)	RV Only (<i>n</i> = 27)	RSV and RV (n = 14)	All Others* (n = 81)	p-Value
Demographic characteristics					
Age (months), median (IQR)	4.9 (2.4–9.4)	7.5 (3.4–10.8)	7.3 (5.1–11.7)	7.3 (4.2–10.5)	0.04
Male (%)	59	78	64	58	0.29
Race/ethnicity (%)					
White	39	15	50	21	<0.001
African American	19	62	14	40	
Hispanic	42	23	36	39	
Estimated median household	43,633	34,538	37,712	42,333	0.12
income (U.S.\$), median (IQR)	(33,889–56,122)	(26,469–48,075)	(26,981–43,898)	(30,379–55,394)	
Insurance (%)		., , .	. , , .	., , .	
Private HMO/commercial	34	26	36	26	0.72
Medicaid	52	63	64	59	
Other public	9	4	0	11	
None	9 5	7	0	4	
Has primary care provider (%)	95	93	100	98	0.57
Medical history					
Concomitant medical	12	33	21	17	0.03
disorder (%)					
Premature (%)†	10	15	21	15	0.42
Breast-fed (%)	59	48	64	59	0.69
History of wheezing (%)	23	52	21	33	0.01
History of eczema (%)	13	11	7	11	0.92
Attends daycare (%)	21	19	43	20	0.26
Has siblings in home (%)	97	89	93	95	0.22
Any parental history of asthma (%)	28	52	31	32	0.12

RSV = respiratory syncytial virus; RV = rhinovirus; IQR = interquartile range; HMO = health maintenance organization; Flu A = influenza A; hMPV = human metapneumovirus.

* Flu A, hMPV, or no virus.

† Premature defined as gestation < 35 weeks.</p>

The four groups also were similar in terms of ED course. β -Agonist and epinephrine treatments during the first hour and over the entire ED stay did not differ across groups. However, children with RV or RV + RSV were more likely to receive corticosteroid treatment in the ED. In a multivariate model controlling for age, gender, race/ethnicity, concomitant medical disorder, history of wheeze, and presence of wheeze, children with RV were more likely to receive corticosteroids (OR 3.5; 95% CI = 1.5 to 8.2). When site of care was investigated as a potential confounder, the results did not materially change, but the sample sizes were small (data not shown). When region of care was controlled for in the logistic regression model, the association between RV and ED steroids use was potentially stronger (OR 9.5; 95% CI = 2.3 to 39.3). No differences were observed for antibiotic treatment in the ED. Median length of stay in the ED was 186 minutes for the children in this cohort, and this did not differ across groups. Hospital admission also was similar across the groups. When RSV was compared directly to RV, the results remained similar (data not shown).

Two-week follow-up also is shown in Table 3. Relapse events and activity limitations during the 2 weeks following the ED visit did not differ across the virus groups. While not statistically significant (p = 0.07), there is a suggestion that children with RV only had a shorter duration of symptoms from symptom onset through 2 weeks after the ED visit.

The univariate results and the multivariate model for use of corticosteroids did not change when the analysis was restricted to the 98% of children who met the AAP definition (data not shown). Moreover, because it can be difficult to distinguish those children with reactive airways disease (RAD)/asthma, and those with bronchiolitis, we created a different subset by removing the 19 children with the diagnosis of RAD and asthma. The results from this subgroup also were similar to those of the entire cohort (data not shown). In our final sensitivity analysis, we assessed the results in the subset of children < 12 months of age, again finding similar results (data not shown).

DISCUSSION

In this prospective, multicenter cohort study of children age < 2 years presenting to the ED with bronchiolitis, we found that the two most common viral etiologies were RSV (64%) and RV (16%). In addition, we found that those children infected with RV alone (or RV in combination with RSV) have a different clinical profile compared to children infected with RSV, hMPV, Flu, multiple pathogen infections, or no identified virus. The clinical characteristics of the children infected with RV in this cohort resemble older children who present to the ED with an asthma exacerbation²³ in terms of demographics (African American), medical history (wheezing), ED treatment (systemic corticosteroids), and possibly duration of illness (shorter course).

Table 3

ED Presentation, Clinical Course, and Two-week Follow-up among Children with Bronchiolitis, According to Viral Infection

	RSV Only (<i>n</i> = 155)	RV Only (<i>n</i> = 27)	RSV and RV (<i>n</i> = 14)	All Others* (<i>n</i> = 81)	p-Valu
Presentation	· · ·				•
Duration of symptoms (%)					
<24 hours	7	33	0	10	0.006
1–3 days	36	37	38	36	0.000
4–7 days	37	19	46	28	
>7 days	20	11	15	26	
Pulse (beats/min),	156 ± 21	149 ± 22	162 ± 29	154 ± 21	0.22
mean ± SD	100 1 21	140 ± 22	102 ± 20	104 ± 21	0.22
Temperature (°F),	100.0 ± 1.5	100.0 ± 1.3	101.2 ± 1.6	100.4 ± 2.0	0.01
mean \pm SD	100.0 ± 1.0	100.0 ± 1.0	10112 ± 110	100.4 ± 2.0	0.01
Respiratory rate,	48 (36–60)	44 (32–60)	40 (32–48)	43 (34–56)	0.15
median (IQR)	40 (30-00)	44 (32-00)	40 (32-40)	43 (34-30)	0.15
Retractions (%)					
None/mild	80	69	64	85	0 17
Moderate/severe	20	31	36	15	0.17
Oxygen saturation on	20 96 ± 3	96 ± 2	95 ± 4	96 ± 4	0.63
room air, mean ± SD	90 ± 3	90 ± 2	95 ± 4	90 ± 4	0.05
	00	02	02	91	0.05
Presence of cough (%)	90 70	92	93		0.95
Presence of wheeze (%)	73	73	79	63	0.37
D course		00 . 0	00 7		0.10
Lowest room air oxygen	95 ± 4	96 ± 3	92 ± 7	95 ± 5	0.18
saturation, mean \pm SD	1 (0 A)				
No. inhaled β -agonist	1 (0–1)	1 (0–1)	0 (0–1)	1 (0–1)	0.28
treatments in first hour,					
median (IQR)					
No. inhaled β -agonist	1 (1–2)	1 (1–2)	2 (1–3)	1 (1–2)	0.30
treatments over entire					
ED stay, median (IQR)					
No. epinephrine	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.21
treatments in first hour,					
median (IQR)					
No. epinephrine	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)	0.15
treatments over					
entire ED stay,					
median (IQR)					
Given corticosteroids (%)	16	35	46	16	0.01
Given antibiotics (%)	14	11	14	15	0.97
Oral intake (%)					
Adequate oral intake	72	89	57	72	0.33
Inadequate oral intake	19	4	29	22	
Unknown	8	7	14	6	
Any laboratory test	81	89	86	77	0.52
performed in ED (%)					
ED length of stay	189 (85–327)	156 (129–273)	218 (134–435)	172 (101–304)	0.86
(minutes), median (IQR)					
Admitted (%)	49	33	36	43	0.38
Two-week follow-up					
Relapse within 2 weeks (%)*	12	8	15	13	0.93
Days of activity limitation	2 (0–6)	1 (0–3)	0 (0–3)	0 (0–7)	0.45
during 2 weeks after	- (0 0)				0.10
ED visit, median (IQR)					
Duration (in days) of	8 (4–10)	3 (2–8)	6 (2–9)	8 (2–9)	0.07
symptoms from symptom	0 (7-10)	0 12 0/	0 (2 -0)	0 12 01	0.07
onset through 2 weeks after					
ED visit, median (IQR)					

* See Methods for details.

Bronchiolitis is a clinical diagnosis^{24,25} with considerable variation in care and testing.^{10,11,26} The current consensus is that knowing the viral etiology, among those viruses with established rapid testing, does not affect treatment of the individual patient.¹² One of the viruses with rapid testing is Flu, and among the viruses tested, we found that Flu A and B were the least common

viruses detected. Although we did not test for parainfluenza virus (PIV), one recent study noted that among children born into asthmatic/ atopic families, infection with PIV in the first year of life was associated with possible asthma at 2 years.²⁷ Children with lower respiratory tract infections due to viruses that do not have rapid testing, however, may have slightly different clinical presentations and courses.⁹ In addition to further characterizing newly discovered coronaviruses,^{28–30} one inpatient study noted that hMPV, in comparison to RSV and Flu A, occurred more frequently in older children and in those diagnosed with pneumonia and asthma.⁹

Bronchiolitis due to RV may also be different from bronchiolitis caused by other viruses. RV has historically been considered an upper respiratory virus,³¹ but RV has been reported to infect the lower airways^{5,14} and causes bronchiolitis.⁵ Results from single-center studies of hospitalized infants³²⁻³⁴ are similar to our multicenter ED data and suggest a different clinical profile for children with RV bronchiolitis. When compared to infants with RSV bronchiolitis, infants with RV bronchiolitis are older and present for medical care earlier in the course of infection.^{32–35} Some data have demonstrated an association between infection with RV and infants with atopic dermatitis,^{32,34} but our data did not demonstrate this association. Unlike results observed from a single-center study of hospitalized children,³⁴ we found that children with a history of wheezing are more likely to have RV infection compared to RSV infection or other viral infection. Moreover, the other reports have not included race/ethnicity. Our data suggest that African American infants were significantly more likely to have RV infection. This racial/ethnic preponderance is similar to that among U.S. children with asthma.36 It appears that these results are not being driven by one dominant site, because we had a good distribution of the number of samples and viruses among the sites.

Previous work describes RV as a distinct pathogen. These studies were from a single ED,³⁷ the outpatient setting,^{13,14} and the inpatient setting.^{32,38,39} Our data are from 14 EDs across the United States and both confirm and extend previous work suggesting that RV may have a distinct role. Specifically, several recent single-center studies have linked RV infection to asthma exacerbations in children and adults,^{40,41} to infant wheezing,^{15,37} and to infants with recurrent respiratory symptoms and abnormal lung function.¹⁴ Recent evidence also links lower respiratory tract illnesses with RV-related wheezing in infancy to childhood wheezing at age 3 years¹³ and to children with asthma at age 6 years.^{16,38} For example, in the Childhood Origins of ASThma (COAST) birth cohort study of children at high risk of developing asthma conducted in Madison, Wisconsin, the most significant predictor in multivariate analysis of wheezing at age 3 years was a moderate-to-severe RV illness with wheezing during infancy.13

In addition to the different clinical profile of infants with RV, the medications prescribed to the infants in our cohort suggest a different clinical assessment by physicians. Although the treating physicians in our study could not have been aware of the RV infection, they were significantly more likely to treat these children with corticosteroids, even after controlling for other factors in a multivariate model. It is not clear if the corticosteroids shortened the course of the illness, but our data suggest a shorter duration of illness for children with RV infection. One trial of prednisolone for 3 days versus placebo for children hospitalized with their first or second episode of wheezing due to RV demonstrated reduced relapses during a 2-month period after the hospitalization³⁴ and reduced recurrent wheezing at 1 year.⁴² These data are in contrast to other recent corticosteroid treatment results in children with undefined viral illnesses.^{43–45} The children who develop wheezing due to RV seem to have a high likelihood of developing asthma and, therefore, may merit further investigation for clarifying the pathogenesis of asthma and possibly as a target population for the primary prevention of asthma.

LIMITATIONS

Despite our relatively large sample from multiple institutions, few children tested positive for hMPV, Flu, and combination infections, limiting our power to detect meaningful differences between these groups. In addition, due to the 2- to 3-week sampling time frame at the 14 sites, the results do not represent the viral epidemiology of an entire bronchiolitis season at the site or regional level. Another potential limitation of this study is that some of the historical items (specifically wheezing and eczema) may not be accurate, because they were determined via parent interview, as opposed to evaluation by health professionals. There is, however, a similar potential for inaccurate reporting from study participants, and the differences between the children infected with RV compared to the other viruses are quite clear and often statistically significant. We did not collect other measures of atopy (e.g., nasal eosinophilia, radioallergosorbent test) from this cohort but will pursue this issue in future research. Although these findings are in children presenting to the ED for bronchiolitis and not necessarily generalizable to other clinical settings, it is possible that the children in our study are similar to those children with moderate-tosevere wheezing RV illnesses who do not present to the ED.13

CONCLUSIONS

These prospective multicenter data of children age < 2 years presenting to the ED with bronchiolitis demonstrate that RSV is clearly the most common etiology, but RV is the etiology in almost one of every six children. Moreover, children with RV bronchiolitis have an interesting clinical profile when compared to other children with bronchiolitis; children with RV bronchiolitis have demographics, medical histories, and ED treatments similar to those of older children with an asthma exacerbation. Future studies of children with RV bronchiolitis are needed to determine if identification of this virus is critical to guiding short- and long-term treatment decisions (e.g., the initiation of oral and/or inhaled corticosteroids) to improve bronchiolitis outcomes.

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APPENDIX A

Emergency Medicine Network (EMNet) Steering Committee

Michelle P. Blanda, MD Edwin D. Boudreaux, PhD Carlos A. Camargo Jr., MD (Chair) Theodore J. Gaeta, DO, MPH Susan Key, RN, MS, CEN Jonathan Mansbach, MD Steven Polevoi, MD Michael S. Radeos, MD, MPH Benjamin C. Sun, MD, MPP

EMNet Coordinating Center

Christina Ahn Carlos A. Camargo Jr., MD (Director) Kate E. Delaney Lisa A. Dubois Adit Ginde, MD Andrea J. Pelletier, MS, MPH Ashley F. Sullivan, MS, MPH Chu-Lin Tsai, MD, MPH All at Massachusetts General Hospital, Boston, MA

Participating Sites

- C. Baker, Children's Hospital Oakland, Oakland, CA
- B. Barcega, Loma Linda Medical Center, Loma Linda, CA
- N. Christopher, Children's Hospital Medical Center-
- Akron, Akron, OH
- J. Colvin, Stormont-Vail Regional Medical Center, Topeka, KS
- D. Damore, New York Presbyterian Hospital–Weill Cornell Medical Center, New York, NY
- R. Flood, Temple University Children's Medical Center, Philadelphia, PA
- T. Gaeta, New York Methodist Hospital, Brooklyn, NY
- H. Haddad, Rainbow Babies & Children's Hospital, Cleveland, OH
- P. Hain, Vanderbilt Children's Hospital, Nashville, TN
- F. LoVecchio, Maricopa Medical Center, Phoenix, AZ
- C. Macias, Texas Children's Hospital, Houston, TX
- J. Mansbach, Children's Hospital Boston, Boston, MA
- R. Ragothaman, Virtua West Jersey Hospital, Voorhees, NJ
- V. Wang, Children's Hospital of Los Angeles, Los Angeles, CA