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# Rhinovirus Type in Severe Bronchiolitis and the Development of Asthma



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**What is already known about this topic?** Respiratory syncytial virus (RSV)- and rhinovirus (RV)-induced bronchiolitis are associated with an increased risk of asthma.

**What does this article add to our knowledge?** Compared with children with RSV-induced bronchiolitis, children with RV-A or RV-C-induced bronchiolitis start asthma control medication earlier and are more likely to use it 4 years later. The risk is especially high among patients with RV-C, atopic dermatitis, and fever.

**How does this study impact current management guidelines?** Secondary prevention strategies targeting rhinoviruses, especially RV-C, might help to prevent childhood asthma.

**BACKGROUND:** Respiratory syncytial virus (RSV)- and rhinovirus (RV)-induced bronchiolitis are associated with an increased risk of asthma, but more detailed information is needed on virus types.

**OBJECTIVE:** To study whether RSV or RV types are differentially associated with the future use of asthma control medication.

**METHODS:** Over 2 consecutive winter seasons (2008–2010), we enrolled 408 children hospitalized for bronchiolitis at age less than 24 months into a prospective, 3-center, 4-year follow-up study in Finland. Virus detection was performed by real-time

reverse transcription PCR from nasal wash samples. Four years later, we examined current use of asthma control medication.

**RESULTS:** A total of 349 (86%) children completed the 4-year follow-up. At study entry, the median age was 7.5 months, and 42% had RSV, 29% RV, 2% both RSV and RV, and 27% non-RSV/RV etiology. The children with RV-A (adjusted hazard ratio, 2.3;  $P = .01$ ), RV-C (adjusted hazard ratio, 3.5;  $P < .001$ ), and non-RSV/RV (adjusted hazard ratio, 2.0;  $P = .004$ ) bronchiolitis started the asthma control medication earlier than did children with RSV bronchiolitis. Four years later, 27% of patients used asthma control medication; both RV-A (adjusted odds ratio, 3.0;  $P = .03$ ) and RV-C (adjusted odds ratio, 3.7;  $P < .001$ ) etiology were associated with the current use of asthma medication. The highest risk was found among patients with RV-C, atopic dermatitis, and fever (adjusted odds ratio, 5.0;  $P = .03$ ).

**CONCLUSIONS:** Severe bronchiolitis caused by RV-A and RV-C was associated with earlier initiation and prolonged use of asthma control medication. The risk was especially high when bronchiolitis was associated with RV-C, atopic dermatitis, and fever. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;8:588-95)

**Key words:** Asthma development; Bronchiolitis; Respiratory syncytial virus; Rhinovirus; Wheeze; Wheezing

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*Abbreviations used*

*aHR*- Adjusted hazard ratio

*aOR*- Adjusted odds ratio

*HR*- Hazard ratio

*OR*- Odds ratio

*RSV*- Respiratory syncytial virus

*RV*- Rhinovirus

with the development of asthma.<sup>7-11</sup> Whether it is the RV infection itself or the immunologic responses of the child, which primarily enhance the development, is still partly unknown. Furthermore, it is unclear whether the RV types involved with bronchiolitis have different risks associated with the later development of asthma.

RVs cause 20% to 40% of bronchiolitis and 50% to 80% of wheezing episodes and asthma exacerbations in children.<sup>10,12,13</sup>

RV types are classified into 3 species: RV-A, RV-B, and RV-C.<sup>14</sup> RV-A and RV-C cause more severe respiratory illness than RV-B and are associated with wheezing in early childhood,<sup>14</sup> as well as exacerbations of asthma.<sup>15-19</sup> Cadherin-related family member 3 (a receptor for RV-C) and atopy have been shown to be risk factors for the development of early-onset asthma.<sup>20</sup> Cadherin-related family member 3 mediates RV-C binding and replication in airway epithelia, and polymorphism in gene encoding the protein has been linked with increased susceptibility to asthma.<sup>21,22</sup> We aimed to study whether RSV or RV types are differently associated with the use of long-term asthma control medication during the 4 years after severe bronchiolitis during infancy. Our study hypothesis was that RV-A or RV-C etiology of severe bronchiolitis is associated with increased need for the long-term asthma control medication.

## METHODS

### Study subjects

The study subjects consisted of the 408 participants of the 30th Multicenter Airway Research Collaboration (MARC-30) Finland study, which is a prospective, multicenter cohort study of the Emergency Medicine Network (EMNet, Boston, Mass). The children were recruited from the pediatric wards or intensive care units of Kuopio, Tampere, and Turku University Hospitals in Finland during the winter seasons 2008 to 2010 (from November 1 until March 31).<sup>23</sup> The children were hospitalized for bronchiolitis and were younger than 24 months on admission. The diagnosis of bronchiolitis was clinical and made according to the American Academy of Pediatrics guidelines including children with acute respiratory illness with some combination of rhinitis, cough, tachypnea, wheezing, crackles, and/or retractions.<sup>1</sup> No initial exclusions were made on the basis of history of wheezing or use of asthma medication before hospitalization. In addition, we identified a subgroup of 204 infants who were younger than 12 months with no history of wheezing (strict bronchiolitis criteria).<sup>24,25</sup> The exclusion criteria were previous enrollment or transfer to a participating hospital more than 48 hours after the original admission time. Because all the children were hospitalized, they were defined as having a severe bronchiolitis. The Institutional Ethical Board of Turku University Hospital approved the study. The institutional ethical boards of other participating hospitals confirmed this approval. The parents or guardians gave written informed consent to the study.

### Data collection

During hospitalization, the guardians were interviewed using a structured questionnaire, including demographic, environmental, and baseline medical data. Also, data on signs, symptoms, and management of the current infection were collected.<sup>23</sup> Four to 5 years after hospitalization, study questionnaires modified from the International Study of Asthma and Allergy in Childhood questionnaires were sent to all participants. The questionnaires consisted of inquiries on respiratory symptoms and need, prescription, and use of asthma medication during the follow-up period after the index hospitalization. If the parents did not respond within 6 months, participants were contacted by telephone and interviewed. If regular use of inhaled corticosteroids or leukotriene receptor antagonists ever was reported, the patient's files (ie, hospital records or inquiries sent to private sector pediatricians) of reported medical encounters were reviewed for the exact prescription time of medication.

### Nasopharyngeal wash samples

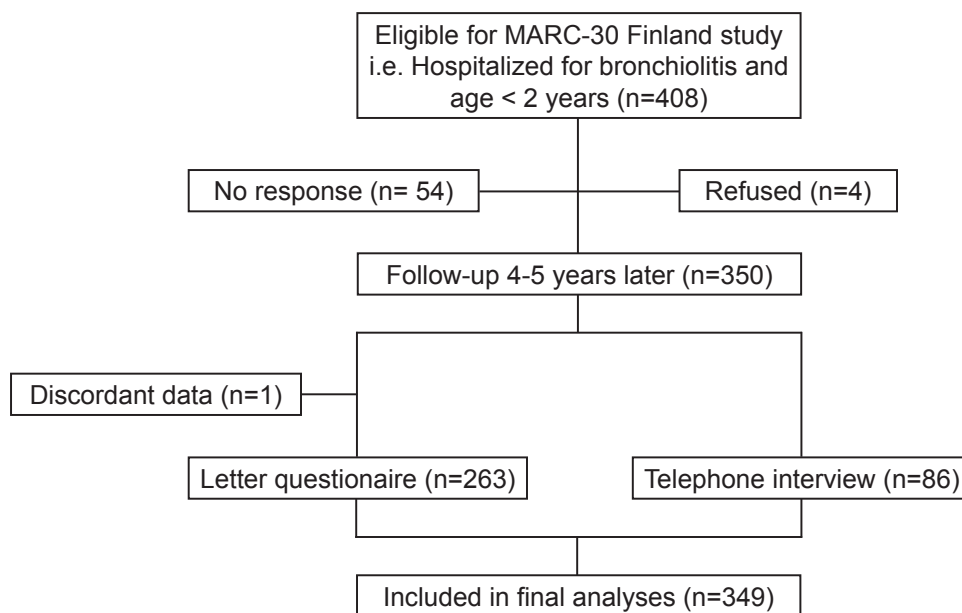
Nasopharyngeal wash samples were collected at the study entry using a standardized protocol.<sup>23,26</sup> The same collection equipment (Medline Industries, Mundelein, Ill) was used by all hospitals. The samples were collected within 24 hours after the child's arrival at the ward or in the intensive care unit by instilling 1 mL of normal saline into each naris and suctioned. Thereafter, the samples were immediately refrigerated and stored at  $-80^{\circ}\text{C}$  within 24 hours until further analyses.

### Virology testing

Viral detection was performed by using singleplex or duplex 2-step real-time PCR. Real-time reverse transcription PCR was used for the detection of RNA respiratory viruses (RSV types A and B; rhinovirus types A, B, and C; parainfluenza virus types 1, 2, and 3; influenza virus types A and B and 2009 novel H1N1; human metapneumovirus; coronaviruses NL-63, HKU1, OC43, and 229E; and enteroviruses) and real-time PCR for detection of DNA pathogens (adenovirus, *Mycoplasma pneumoniae*, and *Bordetella pertussis*). Details of the primers and probes have been described earlier.<sup>23</sup> All PCR assays were tested in duplicate, and samples with incongruent values (1 well positive) were retested. For the analyses, children were divided into 3 groups on the basis of virology testing: RSV (including coinfection with viruses other than RV), RV (including coinfection with viruses other than RSV), and non-RSV/-RV (including coinfection with viruses other than RSV or RV).<sup>27-30</sup>

### Main outcomes and clinical definitions

The time to initiation of long-term asthma control (inhaled corticosteroid or leukotriene receptor antagonist) medication was defined as time from the discharge of index hospitalization until the prescription of at least a 1-month period of asthma control medication. The children with reported use of asthma control medication before index hospitalization were excluded from the analyses. The current use of long-term asthma control medication was defined as the prescription of regular asthma control medication within the previous 12 months. If use or prescription of any asthma control medication was reported in the parental interview, the patient's medical files were reviewed for the exact beginning of medication use. Atopic dermatitis was defined as a parent-reported atopic dermatitis diagnosed by a physician. No IgE or other immunologic testing was done. Fever was defined as temperature higher than  $37.5^{\circ}\text{C}$  ( $99.5^{\circ}\text{F}$ ) during the severe bronchiolitis episode. In the case of missing data of initiation time of medication or some of the



**FIGURE 1.** Study flow chart. *MARC-30*, 30th Multicenter Airway Research Collaboration.

confounders used in multivariable analyses, the child in question was excluded from that particular analysis.

### Statistical methods

Unadjusted analyses for categorical data were done using Pearson  $\chi^2$  test, and for continuous data using Kruskal-Wallis test. Multivariable analyses were done using binary logistic and Cox regression and the results were presented as odds ratios (ORs) and hazard ratios (HRs), respectively, with 95% confidence intervals. The potential confounding factors were first tested in unadjusted analyses. The nonviral factors were then selected by the backwards stepwise method, and variables with  $P$  less than .05 were included in the final adjusted models. The tested variables were age at index hospitalization (<12 vs  $\geq$ 12 months), sex, parental history of asthma, gestational weeks at birth (<37 vs  $\geq$ 37 weeks), comorbid medical disorders, history of wheezing, history of atopic dermatitis, siblings, exposure to smoking during pregnancy or early childhood, breastfeeding, length of index hospitalization greater than or equal to 3 days, use of systemic corticosteroids during index hospitalization (yes vs no), and study center (Turku, Tampere vs Kuopio). Analyses were conducted with IBM SPSS Statistics for Windows version 24.0 (IBM Corp, Armonk, NY).

## RESULTS

### Study cohort

Among the 408 infants followed for 4 years after hospitalization, 264 returned the questionnaire and 86 underwent telephonic interviews (Figure 1). However, 1 child had discordant data; thus, taken together, 349 children (86%) had sufficient follow-up data to be included in this cohort study.

### Virus etiology

At the time of hospitalization 145 (42%) patients had RSV, 101 (29%) had RV, 8 (2%) had both RSV and RV, and 95 (27%) were negative for both viruses (non-RSV/-RV) (Table I). Of all patients, 73 (21%) had RV-C, 24 (7%) had RV-A, 3 (1%) had RV-B, and 1 (0%) had both RV-B and RV-C (Table I).

### Patient characteristics

The median age at study entry was 7.5 months, 64% were males, 23% had parental asthma, 13% were born preterm, 12% had some comorbid medical disorder, 37% had a history of wheezing, and 30% had a history of atopic dermatitis (Table I). The baseline characteristics were similar in the dropout group, except for including less males (48%) and more children with early childhood smoking exposure (25%).

When children were compared in relation to the virus type (Table II), some between-group differences were seen. Children with RSV were younger and had less comorbid medical disorders, but needed longer hospitalizations and more often intensive care unit care, whereas history of wheezing or atopic dermatitis and use of systemic corticosteroids during initial hospitalization were more common among the other children. Patient characteristics of children with RV-A and RV-C were similar.

### Time to initiation of asthma control medication

Of the 319 patients with data adequate for analyses of initiation time of medication, 145 (45%) reported prescription of asthma control medication within 48 months after hospitalization (Table III). Asthma control medication was started a mean of 4.6 months after hospitalization in patients with RV, 6.1 months in patients with non-RSV/-RV, and 15.4 months in patients with RSV bronchiolitis (see Figure E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). Patients with RV (adjusted  $P < .001$ ) and non-RSV/-RV (adjusted  $P = .003$ ) bronchiolitis started asthma control medication significantly earlier than did those with RSV bronchiolitis (Table III and Figure E1). When RV types were analyzed separately, asthma control medication was started significantly earlier after RV-C (3.7 months, adjusted  $P < .001$ ) and RV-A bronchiolitis (8.7 months, adjusted  $P = .01$ ) (Table III and Figure 2).

All 68 children with detailed data on medication use during the 48-month follow-up (45% of the children) had been using inhaled corticosteroids. Furthermore, 37% of children with RSV, 50% of children with RV, and 31% of children with non-RSV/-

**TABLE I.** Patient characteristics of the 349 study children at study entry

Characteristic	No. of children (%)
Age at study entry (mo), median (range)	7.5 (23.7)
Sex: male	223 (64)
Parental history of asthma	81 of 346 (23)
Prematurity	46 of 343 (13)
Comorbid medical disorder	40 (12)
History of wheezing	128 (37)
History of atopic dermatitis	103 (30)
Siblings	243 (70)
Exposure to smoking during pregnancy or early childhood	51 of 346 (15)
Breast-feeding	321 of 348 (92)
Hospitalization $\geq 3$ d	108 (31)
ICU stay	12 (3)
Systemic corticosteroid	73 of 348 (21)
Virus positive	302 (87)
RSV*	145 (42)
RV†	101 (29)
RV-A	24 (7)
RV-B	3 (1)
RV-C	73 (21)
RV-B + RV-C	1 (0)
RV + RSV‡	8 (2)
Non-RSV/-RV	95 (27)
Human metapneumovirus	17 (5)
Parainfluenzavirus 1	12 (3)
Parainfluenzavirus 3	7 (2)
Coronavirus	5 (1)
Adenovirus	2 (1)
Influenzavirus A	3 (1)
H1N1-virus	3 (1)
Enterovirus	1 (0)
Parainfluenzavirus 2	1 (0)
Negative for tested viruses	44 (13)

ICU, Intensive care unit.

\*Including coinfection with viruses other than RV.

†Including coinfection with viruses other than RSV.

‡Including coinfection with viruses other than RV or RSV.

RV bronchiolitis had used a leukotriene receptor antagonist at some point during the follow-up ( $P = .42$ ). No difference ( $P = .94$ ) was found in the use of leukotriene receptor antagonist between RV-A (50% of the children) and RV-C (52% of the children).

### Use of asthma control medication 4 years after severe bronchiolitis

Four years after bronchiolitis, 47 (47%) patients with RV, 24 (26%) patients with non-RSV/-RV, and 21 (15%) patients with RSV bronchiolitis had used asthma control medication during the past 12 months (Table IV). Patients with RV infection were more likely to use asthma control medication compared with those with RSV infection (adjusted  $P < .001$ ) (Table IV). When RV types were compared separately, both RV-A (42%, adjusted  $P = .03$ ) and RV-C (48%, adjusted  $P < .001$ ) were associated with current use of asthma control medication (Table IV and Figure 3). In unadjusted analyses, patients negative for both

viruses used asthma control medication more than did patients with RSV ( $P = .04$ ), but the difference was no longer significant after adjustment ( $P = .22$ ) (Table IV and Figure 3).

### Other risk factors for the use of asthma control medication

We also analyzed nonviral risk factors at the study entry for the initiation and the current use of asthma control medication (see Table E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). History of wheezing (adjusted HR [aHR], 1.7;  $P = .01$ ), atopic dermatitis (aHR, 1.8;  $P = .002$ ), and use of systemic corticosteroid during the index hospitalization (aHR, 1.8;  $P = .005$ ) were independent risk factors in multivariable analysis for initiation of asthma control medication in addition to bronchiolitis caused by RV-A (aHR, 2.1;  $P = .04$ ), RV-C (aHR, 3.3;  $P < .001$ ), or non-RSV/-RV (aHR, 1.8;  $P = .02$ ), whereas the length of hospital stay of more than 3 days was not (aHR, 0.7;  $P = .04$ ) (Table E1). Respectively, for the current use of asthma medication 4 years after bronchiolitis, only history of atopic dermatitis (adjusted OR [aOR], 2.1;  $P = .01$ ) in addition to bronchiolitis caused by RV-A (aOR, 2.8;  $P = .048$ ) or RV-C (aOR, 3.6;  $P = .001$ ) were significant risk factors (Table E1). When children with RV-C infection were analyzed separately, those with both history of atopic dermatitis and fever at the time of hospitalization were more likely to use asthma medication 4 years after bronchiolitis (65%; aOR, 5.0;  $P = .03$ ) compared with children with only a history of atopic dermatitis (50%; aOR, 2.7;  $P = .19$ ), with fever (54%; aOR, 2.5;  $P = .16$ ), or neither (33%) (Figure 4).

### Study outcomes using strict bronchiolitis criteria

Characteristics of the 175 children with bronchiolitis defined by strict criteria (age  $< 12$  months and the first wheeze) are presented in Table E2 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org). Of them, 111 had bronchiolitis induced by RSV, 17 had RV-C infection, and 2 tested positive for RV-A (Table E2). Both RV-C (adjusted  $P < .001$ ) and non-RSV/-RV (adjusted  $P = .001$ ) bronchiolitis were associated with earlier prescription of asthma control medication compared with RSV bronchiolitis (see Table E3 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). RV-C bronchiolitis also increased the use of asthma medication 4 years later after the hospitalization compared with RSV (adjusted  $P = .009$ ) (see Table E4 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)).

## DISCUSSION

Our study has 4 clinically interesting findings. First, among children hospitalized for bronchiolitis before age 2 years, bronchiolitis caused by RV-A or RV-C was associated with an earlier initiation of asthma control medication. Second, 4 years after RV-A or RV-C bronchiolitis, 40% to 50% of patients were still using asthma control medication compared with 15% of patients after RSV and 26% of patients after non-RSV/-RV bronchiolitis. Third, patients with RV-C bronchiolitis, atopic dermatitis, and fever had the highest risk for the development of asthma. Fourth, bronchiolitis caused by RV-C was also associated with an earlier initiation of asthma control medication in children with their initial wheezing episode in the first year of life.

Several factors can contribute to the linkage of RV-induced wheezing in infancy with the risk of childhood asthma. The



**TABLE II.** Patient characteristics at study entry according to virus type

Characteristic	No. of children (%)				P value
	RSV* (n = 145)	RV-A† (n = 24)	RV-C‡ (n = 73)	Non-RSV/-RV‡ (n = 95)	
Age at study entry (mo), median (range)	3.7 (23.2)	13.2 (17.3)	13.6 (23.5)	9.8 (23.5)	<.001
Sex: male	86 (59)	16 (67)	46 (63)	64 (67)	.62
Parental history of asthma	38 (27)	3 (13)	13 (18)	26 (27)	.22
Prematurity	19 (14)	4 (17)	8 (11)	14 (15)	.87
Comorbid medical disorder	8 (6)	4 (17)	14 (19)	12 (13)	.02
History of wheezing	27 (19)	14 (58)	42 (58)	40 (42)	<.001
History of atopic dermatitis	30 (21)	10 (42)	27 (37)	33 (35)	.02
Siblings	67 (81)	16 (67)	35 (48)	118 (71)	<.001
Exposure to smoking during pregnancy or early childhood	24 (17)	5 (21)	6 (9)	15 (16)	.34
Breast-feeding	132 (92)	23 (96)	67 (92)	87 (92)	.91
Hospitalization ≥3 d	60 (41)	6 (25)	14 (19)	24 (25)	.003
ICU stay	11 (9)	0 (0)	0 (0)	1 (1)	.02
Systemic corticosteroid	10 (7)	8 (33)	27 (37)	25 (26)	<.001

ICU, Intensive care unit.

P values are from Pearson  $\chi^2$  or Kruskal-Wallis test.Bold indicates statistical significance ( $P < .05$ ).

\*Including coinfection with viruses other than RV.

†Including coinfection with viruses other than RSV.

‡Including coinfection with viruses other than RV or RSV.

**TABLE III.** Viral risk factors for the time to initiation of asthma control medication

Viral risk factor	No. of children in analyses* (n = 319)	No. of children who have started medication† (n = 145)	Unadjusted analysis			Multivariable analysis‡		
			HR	95% CI	P value	aHR	95% CI	P value
RSV	142/141	36 (25%/26%)	1			1		
RV	88	65 (74%)	<b>5.14</b>	<b>3.41-7.75</b>	<b>&lt;.001</b>	<b>3.19</b>	<b>2.03-5.01</b>	<b>&lt;.001</b>
Non-RSV/-RV	89	44 (49%)	<b>2.51</b>	<b>1.62-3.90</b>	<b>&lt;.001</b>	<b>2.02</b>	<b>1.27-3.20</b>	<b>.003</b>
RSV	142/141	36 (25%/26%)	1			1		
RV-A	19	14 (74%)	<b>4.16</b>	<b>2.24-7.74</b>	<b>&lt;.001</b>	<b>2.30</b>	<b>1.19-4.44</b>	<b>.01</b>
RV-C	65	48 (74%)	<b>5.45</b>	<b>3.52-8.43</b>	<b>&lt;.001</b>	<b>3.48</b>	<b>2.17-5.59</b>	<b>&lt;.001</b>
Non-RSV/-RV	89	44 (49%)	<b>2.52</b>	<b>1.62-3.92</b>	<b>&lt;.001</b>	<b>1.99</b>	<b>1.25-3.17</b>	<b>.004</b>

CI, Confidence interval.

HRs and 95% CIs are from Cox regression.

Bold indicates statistical significance ( $P < .05$ ).

\*Numbers apply to both analyses, unless 2 figures are presented, whereupon they apply to unadjusted and multivariable analysis, respectively.

†Percentages apply to both analyses, unless 2 figures are presented, whereupon they apply to unadjusted and multivariable analysis, respectively.

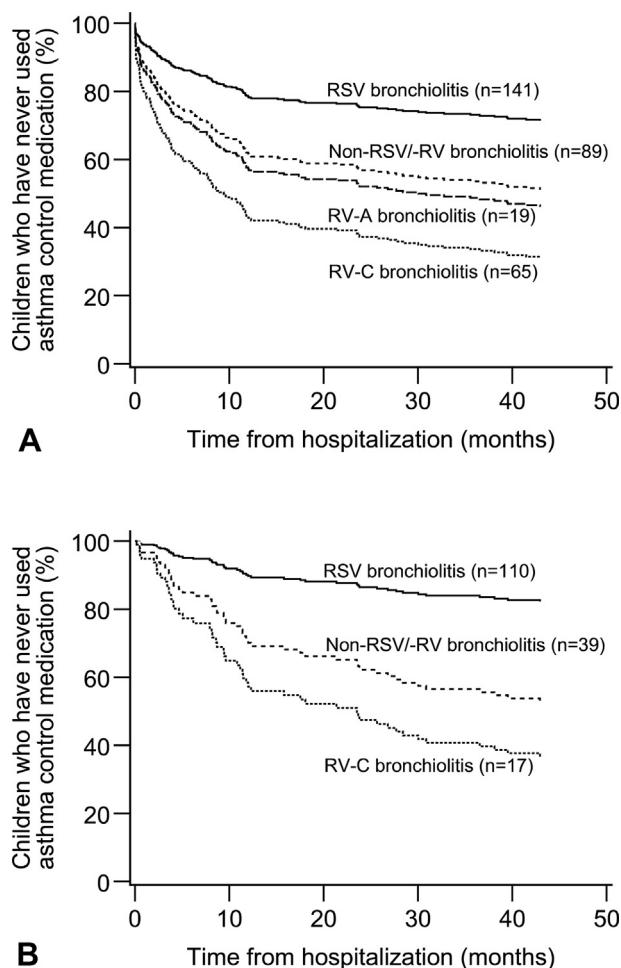
‡Analyses are adjusted for history of wheezing, history of atopic dermatitis, siblings, length of hospital stay, use of systemic corticosteroids, and study center.

inflammatory response caused by different RVs might damage the airways, although RSV could cause even more structural damage to airway epithelium than RV.<sup>11</sup> However, changes in epithelial barrier function even before the infection can increase the risk of severe RV bronchiolitis, and host factors such as atopy and low IFN responses could have additive effects. In addition, risk genes such as *cadherin-related family member 3* (encoding a receptor for RV-C) and 17q21 can predispose children to more severe RV-C infections and development of asthma.<sup>8,11,21,22,31</sup> Finally, RV infection can inhibit IFN responses and potentiate T<sub>H</sub>2-cell-driven inflammation and production of cytokines, which promote airway obstruction and wheeze.<sup>10</sup> Atopic characteristics are not seen as a risk factor for RSV-induced wheezing and asthma, which is more linked to young age and low lung function, indicating that the timing of RSV infection may be important for the future development of respiratory illnesses.<sup>11</sup>

Similarly, genetic factors can modify the risk of RSV bronchiolitis and development of asthma.<sup>10</sup>

Our finding of strong association of both RV-A- and RV-C-induced bronchiolitis with the use of asthma control medication 4 years later is consistent with previous RV studies. In a recent meta-analysis including 15 original articles, the association between RV-induced wheezing and later development of asthma was confirmed.<sup>32</sup> In our previous report, the link between RV-A or RV-C and recurrences of wheezing was already evident at 12-month follow-up.<sup>27</sup> Interestingly, in our study and others, the need for long-term asthma control medication typically develops within 2 years after RV-induced bronchiolitis.<sup>28,33,34</sup>

Early-life RV wheezing illnesses and aeroallergen sensitization increase the risk of asthma.<sup>10,11</sup> In a high-risk birth cohort, the persistence of asthma at age 13 years has been shown to be strongly and additively associated with RV wheezing illness and



**FIGURE 2.** Use of asthma control medication during 4-year follow-up after bronchiolitis: effect of viral etiology. (A) All children. RSV vs RV-A, RV-C, or non-RSV/-RV (all  $P \leq .001$ ). (B) Children with bronchiolitis by strict criteria. RV-A excluded ( $n = 2$ ). RSV vs RV-C or non-RSV/-RV (both  $P \leq .001$ ). The figures are from Cox regression.

initiation and the current use of asthma control medications 4 years later. Data from these studies suggest that atopic airways are more likely to develop obstructive changes after RV-related wheeze. Also, severe febrile viral respiratory infections in infancy and early atopy are known risk factors for persistent wheeze and asthma.<sup>35</sup> Similarly, in our study, the occurrence of RV-C bronchiolitis, atopic dermatitis, and fever together was an especially important marker of risk for wheeze and asthma later in childhood.

Because bronchiolitis is defined differently in the United States and in Europe, we also analyzed the data using strict (European) criteria for bronchiolitis, for example, age less than 12 months and the first wheezing episode.<sup>1,24,25</sup> Using these strict criteria for bronchiolitis, RV-C bronchiolitis in the first year of life was strongly associated with increased use of asthma medication 4 years later, whereas RV-A bronchiolitis was very rare in this age group. This is in agreement with our previous report on recurrence of wheezing within 12-month follow-up.<sup>27</sup>

The strengths of the study are the prospective design and longitudinal follow-up with high follow-up rates (86%). In this real-life study, only hospitalized patients with bronchiolitis who were younger than 2 years were included. We also conducted analyses separately for children with bronchiolitis by strict criteria, making the population more uniform and considering the possible effect of previous wheezing illnesses. In addition, the different viruses were evaluated at the time of bronchiolitis, and the later use of asthma medication was carefully characterized using registry data in addition to parental reporting. However, no further specific tests to confirm allergic sensitization were performed. One limitation is that the cohort includes only patients with severe bronchiolitis cases hospitalized before age 2 years. The role of viral infections may differ in children with milder forms of bronchiolitis.

## CONCLUSIONS

It will be a challenge to prevent the development of asthma. To achieve that, we should reevaluate the diagnosis of bronchiolitis, which is generally considered to be a uniform entity. However, our data suggest that bronchiolitis is instead a disease with subgroups that have different risk factors and genetic and pathogenetic etiologies that lead to dissimilar responses to treatment and distinct prognosis.<sup>10</sup> Our previous trials have

**TABLE IV.** Viral risk factors for the use of asthma control medication 4 y after severe bronchiolitis

Viral risk factor	No. of children in analyses	No. of children using medication (%)	Unadjusted analysis			Multivariable analysis*		
			OR	95% CI	P value	aOR	95% CI	P value
RSV	145	21 (15%)	1			1		
RV	101	47 (47%)	<b>5.14</b>	<b>2.81-9.42</b>	<b>&lt;.001</b>	<b>3.67</b>	<b>1.88-7.19</b>	<b>&lt;.001</b>
Non-RSV/-RV	94	24 (26%)	<b>2.02</b>	<b>1.05-3.90</b>	<b>.04</b>	1.53	0.77-3.05	.22
RSV	145	21 (15%)	1			1		
RV-A	24	10 (42%)	<b>4.22</b>	<b>1.66-10.73</b>	<b>.003</b>	<b>3.02</b>	<b>1.12-8.17</b>	<b>.03</b>
RV-C	73	35 (48%)	<b>5.44</b>	<b>2.83-10.44</b>	<b>&lt;.001</b>	<b>3.72</b>	<b>1.80-7.66</b>	<b>&lt;.001</b>
Non-RSV/-RV	94	24 (26%)	<b>2.02</b>	<b>1.05-3.90</b>	<b>.04</b>	1.50	0.75-2.99	.22

CI, Confidence interval.

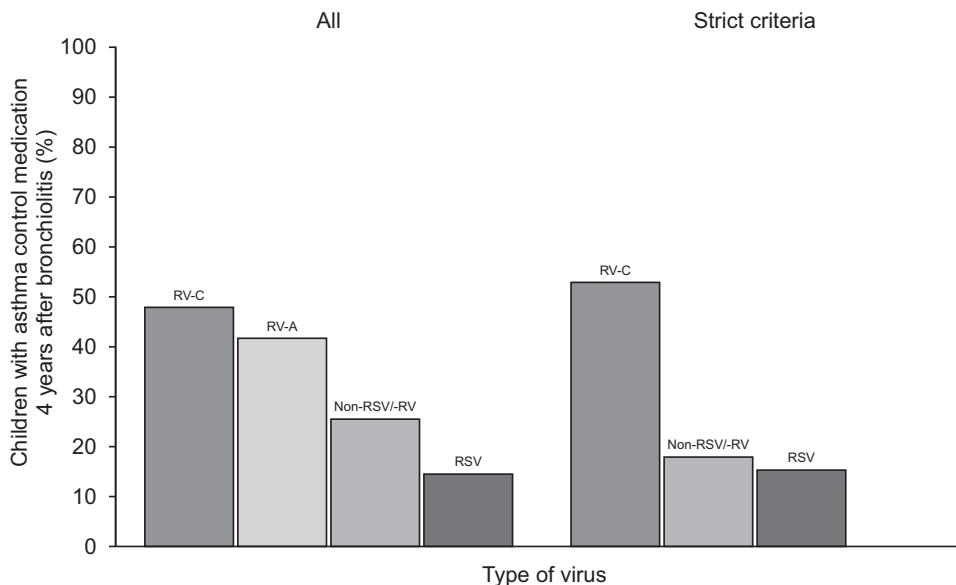
ORs and 95% CIs are from logistic regression.

Bold indicates statistical significance ( $P < .05$ ).

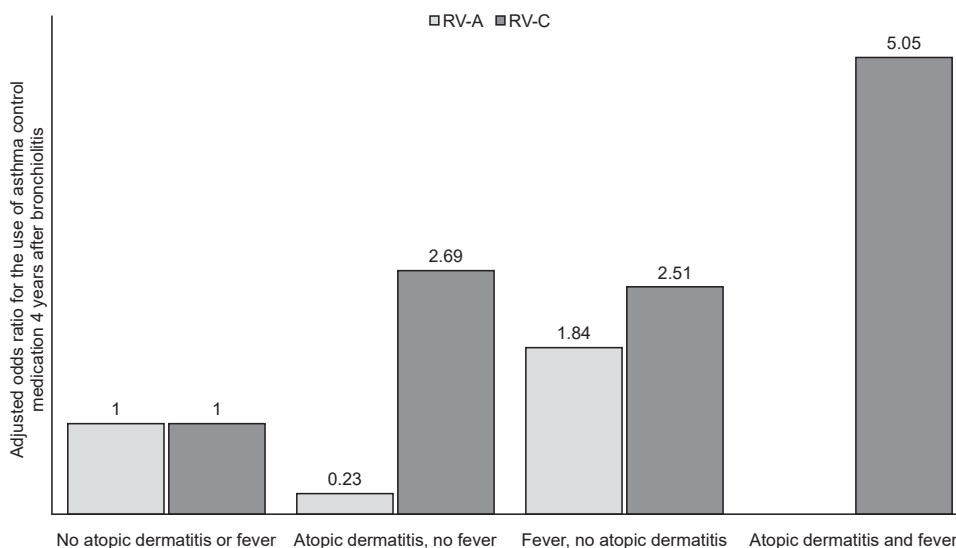
\*Analyses are adjusted for age, history of atopic dermatitis, siblings, and study center.

aeroallergen sensitization in early life.<sup>8</sup> In accordance, we show that histories of wheezing, atopic dermatitis, and RV-A- and RV-C-induced bronchiolitis were independently associated with the

shown that systemic corticosteroid during the first RV-induced wheezing episode reduced recurrences and need for asthma control medication although in those trials RVs were not



**FIGURE 3.** Children who had used asthma control medication during past 12 months at the time of 4-year follow-up after bronchiolitis: effect of viral etiology. Figure presents separately the outcome for all children with bronchiolitis and children with bronchiolitis by strict criteria. The cases with RV-A infection were excluded from the latter (n = 2).



**FIGURE 4.** Current use of asthma control medication 4 years after hospitalization for bronchiolitis: the effect of history of atopic dermatitis and fever on the current use of asthma control medication 4 years after hospitalization for bronchiolitis. Figures are aORs from logistic regression and presented separately for patients with RV-A and patients with RV-C.

subtyped.<sup>29,33,36</sup> If these results are confirmed in further trials, testing for viral etiology of bronchiolitis could be recommended in forthcoming treatment guidelines to better estimate the future risk for developing asthma. This study also suggests that a preventive strategy targeting either RV-A or especially RV-C, and the inflammatory response associated with these viruses, might help to prevent at least some types of childhood asthma.

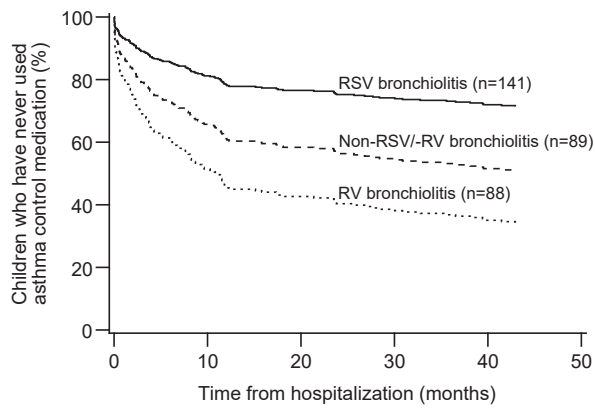
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## ONLINE REPOSITORY



**FIGURE E1.** Children who never used asthma control medication during the 4-year follow-up period after hospitalization for bronchiolitis: effect of viral etiology. Analysis of the main study population.  $P < .001$  for RSV vs RV and  $P = .003$  for RSV vs non-RSV/-RV. The figure and  $P$  value are from adjusted Cox regression analysis.

**TABLE E1.** Risk factors at study entry for the initiation and use of asthma control medication 4 y after bronchiolitis

Risk factor	Time to initiation of asthma control medication					
	Unadjusted analysis			Multivariable analysis		
	HR	95% CI	P value	aHR	95% CI	P value
Age at admission >12 mo	<b>2.41</b>	<b>1.75-3.33</b>	<b>&lt;.001</b>	1.00	0.64-1.56	.98
Male	<b>1.70</b>	<b>1.19-2.43</b>	<b>.004</b>	1.33	0.91-1.95	.14
Parental history of asthma	0.79	0.53-1.19	.27	0.94	0.60-1.47	.77
Prematurity	1.05	0.66-1.66	.84	1.24	0.75-2.05	.41
Comorbid medical disorder	<b>1.75</b>	<b>1.08-2.83</b>	<b>.02</b>	1.08	0.61-1.91	.80
History of wheezing	<b>2.96</b>	<b>2.14-4.08</b>	<b>&lt;.001</b>	<b>1.66</b>	<b>1.13-2.44</b>	<b>.01</b>
History of atopic dermatitis	<b>2.38</b>	<b>1.72-3.30</b>	<b>&lt;.001</b>	<b>1.77</b>	<b>1.24-2.56</b>	<b>.002</b>
Siblings	<b>0.58</b>	<b>0.42-0.80</b>	<b>.001</b>	0.82	0.57-1.19	.30
Exposure to smoking during pregnancy or early childhood	0.69	0.42-1.12	.13	0.67	0.38-1.16	.15
Breast-feeding	0.64	0.38-1.08	.09	0.58	0.33-1.02	.06
Hospitalization ≥3 d	<b>0.63</b>	<b>0.43-0.91</b>	<b>.02</b>	<b>0.65</b>	<b>0.42-0.99</b>	<b>.04</b>
Systemic corticosteroid	<b>3.06</b>	<b>2.17-4.32</b>	<b>&lt;.001</b>	<b>1.84</b>	<b>1.20-2.82</b>	<b>.005</b>
RV-A compared with RSV	<b>4.16</b>	<b>2.24-7.74</b>	<b>&lt;.001</b>	<b>2.08</b>	<b>1.04-4.17</b>	<b>.04</b>
RV-C compared with RSV	<b>5.45</b>	<b>3.52-8.43</b>	<b>&lt;.001</b>	<b>3.34</b>	<b>2.03-5.47</b>	<b>&lt;.001</b>
Non-RSV/-RV compared with RSV	<b>2.51</b>	<b>1.62-3.90</b>	<b>&lt;.001</b>	<b>1.77</b>	<b>1.11-2.84</b>	<b>.02</b>

Risk factor	Use of asthma control medication 4 y after bronchiolitis					
	Unadjusted analysis			Multivariable analysis		
	OR	95% CI	P value	aOR	95% CI	P value
Age at admission >12 mo	<b>2.49</b>	<b>1.53-4.05</b>	<b>&lt;.001</b>	1.25	0.66-2.36	.50
Male	1.46	0.88-2.42	.15	1.37	0.77-2.45	.28
Parental history of asthma	1.47	0.86-2.52	.16	1.74	0.92-3.28	.09
Prematurity	1.08	0.54-2.17	.82	1.26	0.57-2.82	.57
Comorbid medical disorder	1.54	0.76-3.08	.23	0.94	0.42-2.13	.89
History of wheezing	<b>2.31</b>	<b>1.43-3.75</b>	<b>.001</b>	1.11	0.59-2.07	.75
History of atopic dermatitis	<b>2.40</b>	<b>1.46-3.94</b>	<b>.001</b>	<b>2.13</b>	<b>1.20-3.78</b>	<b>.01</b>
Siblings	<b>0.45</b>	<b>0.27-0.73</b>	<b>.001</b>	0.62	0.35-1.11	.11
Exposure to smoking during pregnancy or early childhood	1.03	0.53-2.01	.93	1.10	0.49-2.47	.82
Breast-feeding	0.61	0.27-1.37	.23	0.59	0.22-1.59	.30
Hospitalization ≥3 d	0.82	0.48-1.38	.45	0.99	0.54-1.83	.97
Systemic corticosteroid	<b>2.29</b>	<b>1.33-3.94</b>	<b>.003</b>	1.48	0.75-2.91	.26
RV-A compared with RSV	<b>4.22</b>	<b>1.66-10.73</b>	<b>.003</b>	<b>2.84</b>	<b>1.01-7.99</b>	<b>.048</b>
RV-C compared with RSV	<b>5.44</b>	<b>2.83-10.44</b>	<b>&lt;.001</b>	<b>3.56</b>	<b>1.63-7.77</b>	<b>.001</b>
Non-RSV/-RV compared with RSV	<b>2.02</b>	<b>1.05-3.90</b>	<b>.04</b>	1.36	0.66-2.80	.41

CI, Confidence interval.  
HRs and their 95% CIs are from Cox regression; ORs and their 95% CIs are from logistic regression.  
Bold indicates statistical significance ( $P < .05$ ).

**TABLE E2.** Patient characteristics of the 175 study children with bronchiolitis defined by strict criteria at study entry

Characteristic	No. of children (%)
Age at study entry (mo), median (range)	3.7 (11.7)
Sex: male	106 (61)
Parental history of asthma	36 of 173 (21)
Prematurity	23 of 172 (13)
Comorbid medical disorder	11 (6)
History of atopic dermatitis	30 (17)
Siblings	133 (76)
Exposure to smoking during pregnancy or early childhood	28 (16)
Breast-feeding	155 of 174 (89)
Hospitalization $\geq 3$ d	64 (37)
ICU stay	12 (7)
Systemic corticosteroid	12 of 174 (7)
Virus positive	157 (90)
RSV*	111 (63)
RV†	19 (11)
RV-A	2 (1)
RV-B	0 (0)
RV-C	17 (10)
RV-B + RV-C	0 (0)
RV + RSV‡	6 (3)
Non-RSV/-RV	39 (22)
Human metapneumovirus	10 (6)
Parainfluenzavirus 1	4 (2)
Parainfluenzavirus 3	3 (2)
Adenovirus	1 (1)
Coronavirus HKU1	1 (1)
Coronavirus NL63	1 (1)
Influenza virus A	1 (1)
Negative for tested viruses	18 (10)

ICU, Intensive care unit.

\*Including coinfection with viruses other than RV.

†Including coinfection with viruses other than RSV.

‡Including coinfection with viruses other than RV or RSV.

**TABLE E3.** Viral risk factors for the time to initiation of asthma control medication among children with bronchiolitis defined by strict criteria

Viral risk factor	No. of children in analyses*	No. of children who have started medication	Unadjusted analysis			Multivariable analysis†		
			HR	95% CI	P value	aHR	95% CI	P value
RSV	111/110	24 (22%)	1			1		
RV	19	12 (63%)	<b>5.34</b>	<b>2.66-10.72</b>	<b>&lt;.001</b>	<b>4.29</b>	<b>2.01-9.16</b>	<b>&lt;.001</b>
Non-RSV/-RV	39	16 (41%)	<b>2.35</b>	<b>1.25-4.42</b>	<b>.008</b>	<b>3.19</b>	<b>1.58-6.41</b>	<b>.001</b>
RSV	111/110	24 (22%)	1			1		
RV-A	2	1 (50%)	2.78	0.38-20.60	.32	1.67	0.21-12.99	.63
RV-C	17	11 (65%)	<b>5.83</b>	<b>2.84-11.95</b>	<b>&lt;.001</b>	<b>5.13</b>	<b>2.31-11.41</b>	<b>&lt;.001</b>
Non-RSV/-RV	39	16 (41%)	<b>2.35</b>	<b>1.25-4.42</b>	<b>.008</b>	<b>3.26</b>	<b>1.62-6.57</b>	<b>.001</b>

CI, Confidence interval.

HRs and 95% CI are from Cox regression.

Bold indicates statistical significance ( $P < .05$ ).

\*Numbers apply to both analyses, unless 2 figures are presented, whereupon they apply to unadjusted and multivariable analysis, respectively.

†Analyses are adjusted for history of atopic dermatitis, siblings, use of systemic corticosteroids, and study center.

**TABLE E4.** Viral risk factors for the use of asthma control medication 4 y after severe bronchiolitis among children with bronchiolitis defined by strict criteria

Viral risk factor	No. of children in analyses*	No. of children using medication† (%)	Unadjusted analysis			Multivariable analysis‡		
			OR	95% CI	P value	aOR	95% CI	P value
RSV	111/109	17 (15%/16%)	1			1		
RV	19	9 (47%)	<b>4.98</b>	<b>1.76-14.05</b>	<b>.002</b>	<b>4.07</b>	<b>1.30-12.76</b>	<b>.02</b>
Non-RSV/-RV	39	7 (18%)	1.21	0.46-3.18	.70	0.99	0.34-2.92	.99
RSV	111/109	17 (15%/16%)	1			1		
RV-A	2	0 (0%)	—	—	—	—	—	—
RV-C	17	9 (53%)	<b>6.22</b>	<b>2.11-18.38</b>	<b>.001</b>	<b>4.93</b>	<b>1.49-16.30</b>	<b>.009</b>
Non-RSV/-RV	39	7 (18%)	1.21	0.46-3.18	.70	1.00	0.34-2.92	.99

CI, Confidence interval.

ORs and 95% CIs are from logistic regression.

Bold indicates statistical significance ( $P < .05$ ).

\*Numbers apply to both analyses, unless 2 figures are presented, whereupon they apply to unadjusted and multivariable analysis, respectively.

†Percentages apply to both analyses, unless 2 figures are presented, whereupon they apply to unadjusted and multivariable analysis, respectively.

‡Analyses are adjusted for parental history of asthma, history of atopic dermatitis, siblings, and study center.