Bronchiolitis in young infants: is it a risk factor for recurrent wheezing in childhood?

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Background: **Acute bronchiolitis in infancy is considered a risk factor for recurrent wheezing episodes in childhood. The present study assessed prevalence, clinical manifestations and risk factors for recurrent wheezing events during the first 3 years of life and persistent wheezing events beyond this age in children hospitalized as young infants with acute bronchiolitis.**

Methods: **Two groups of children aged 6 years were included. The study group comprised 150 children with a history of hospitalization for bronchiolitis, with the first event at <6 months of age. The control group comprised 66 age- and sex-matched children with no history of bronchiolitis before 6 months of age. Children in both groups had been followed until 6 years of age by their pediatricians; data were obtained retrospectively by reviewing ambulatory records during children's visits in pediatricians' clinics. The data included epidemiological parameters, prevalence, age at onset, number of and treatments given for episodes of wheezing events prior to 6 years of age, pathogens detected, and severity of acute bronchiolitis in the study group.**

Results: **Overall, 58% and 27% of children in the study and control groups, respectively (*P*=0.001) had recurrent wheezing episodes prior to the age of 3 years. Children in the study group had earlier onset of recurrent wheezing, had more episodes of wheezing, and required more bronchodilator and systemic steroids treatments compared to the control group.**

Conclusion: **Hospitalization within the first six months of life for acute bronchiolitis is an independent risk factor for recurrent wheezing episodes during the first 3 years of life.**

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Key words: **acute bronchiolitis; recurrent wheezing; young infants**

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Introduction

Recurrent wheezing events are common and among the main causes of morbidity in children younger than 3 years. Many factors contribute to the development of recurrent wheezing events in children, including genetic factors (e.g., familial history of atopic diseases), environmental factors (e.g., air pollution, passive smoking, respiratory infections) and immunogenic factors.[1,2]

Acute bronchiolitis is a common illness in infancy. In children hospitalized with acute bronchiolitis, respiratory syncytial virus (RSV) with or without another organism is the most frequently identified pathogen.[2,3] Other organisms such as rhinovirus, influenza virus, parainfluenzavirus types 1-3, human metapneumovirus, human adenovirus, human bocavirus, and bordetella pertussis are also detected to a lesser extent, primarily with RSV or other organisms.[4,5]

Previous reports suggest a possible association between recurrent wheezing events in children aged less than 3 years and acute bronchiolitis during infancy.[6-8] The pathogenesis of this phenomenon is still unknown, but there is evidence suggesting that both genetic and environmental factors contribute to the host immune response to RSV and that this immune response may adversely affect lung development and lower airway control mechanisms.[9-11] Most studies have included children diagnosed with acute bronchiolitis in infancy, but not all of the children were hospitalized in these studies. Several confounding factors could influence conclusions regarding future recurrent wheezing events in these studies: detection studies for RSV only, recurrent acute bronchiolitis, varying severity of

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the disease, and a short follow-up.[3,8,12] The inclusion of infants admitted with the first episode of acute bronchiolitis at less than 6 months of age and a follow-up duration of at least 6 years more clearly defines the study population. However, few studies that had included infants less than 6 month of age followed up the patients for a short duration.[2,8,13]

Unlike recurrent wheezing events, the pathogenesis of persistent wheezing events seems to be different and related to familial tendency of atopic diseases and other genetic factors rather than previous hospitalization due to acute bronchiolitis. Data regarding the association between acute bronchiolitis and persistent recurrent wheezing events are controversial.[9,10]

The present study assessed prevalence and clinical manifestations of recurrent wheezing events during the first 6 years of life in children hospitalized with acute bronchiolitis as young infants. The primary outcomes were prevalence of recurrent wheezing events within the first 3 years of life, and at 6 years of life.

Methods

Study population

Two groups of children aged 6 years were included: The study group consisted of children hospitalized with the first event of acute bronchiolitis at <6 months in 3 pediatric departments in northern Israel between December 2005 and March 2006, and the control group consisted of children matched for age (±1 month), sex, and residence who had neither been hospitalized nor suffered acute bronchiolitis at less than 6 months of age. Acute bronchiolitis was defined as a clinical syndrome that occurs in upper respiratory symptoms followed by lower respiratory infection wheezing and/or crackles.[14] Children who had prematurity, chronic pulmonary disease, congenital heart anomalies, immunodeficiency, metabolic diseases or other chronic medical problems were excluded. All children in the study and the control groups belonged to one Health Medical Organization (HMO), Clalit Health Services, in a county in northern Israel; the children were patients at 15 different ambulatory clinics. Children in both groups were followed in the same ambulatory clinics and by the same physicians. The enrolment of the children in the control group was performed randomly and based on matching of several factors including sex, age and ethnicity.

Based on the literature,[2,3] the expected prevalence of wheezing following RSV-associated lower respiratory infection in young children was 40% *vs.* 10% in the control group;[3] and a sample of about 65 children in each study group was necessary for 80% power with $P<0.05$ (using WinPepi software ver. 9.9 by J.H. Abramson©). For further analysis of the risk factors for recurrent wheezing events, the number of children in the study group had to be increased to 150, in order of the study subgroups to be representative of the original study, and also to allow 90% power with $P<0.05$ between groups.

Data collection

In all study group patients, sputum specimens were tested during hospitalization for 11 possible pathogens (RSV, rhino virus, influenza A&B, parainfluenza virus I-III, adenovirus, human metapneumovirus, human bocavirus, and bordetella pertussis) by antigen detection assays and/or polymerase chain reaction, as previously reported.[15]

Following the admission, children had been followed up by HMO pediatricians who prospectively recorded details regarding disease severity, treatment during every visit. During that period of time pediatricians also prospectively recorded the control group visits which take place in the same clinics at similar time intervals.

Data were collected from ambulatory children's records in both groups. The data recorded included history of recurrent wheezing events (defined as 2 or more episodes of wheezing between 6 months and 3 years of age), history of persistent recurrent wheezing events at the age of 6 years, age of onset, number of episodes and number of treatments with bronchodilators or systemic steroids within the first 3 years of life.

The epidemiologic data included age, gender, place of residence, family history of asthma in first-degree relatives, atopic status of the child, including hay fever, allergic rhinitis, conjunctivitis, atopic dermatitis and food allergy (data was based on charts showing chronic disease diagnosed by immunologist in allergy clinics); and environmental risk factors for wheezing, such as smoking in the family and maternal smoking during pregnancy.

Data on the severity and specific pathogens of acute bronchiolitis were collected from the study group's records during hospitalization. The study group comprised of a random sample of children divided into 4 subgroups according to the relative ratios of pathogens detected during the hospitalization: 1) RSV plus one or more pathogens (n=48 patients), 2) RSV alone (n=80 patients), 3) pathogens other than RSV (n=15 patients), and 4) no pathogen (n=7 patients) (Fig.). The study group was also divided into 3 subgroups according to the clinical severity score during hospitalization:[15-17] A. mild (n=60), B. moderate (n=54), and C. severe (n=19). This score was validated in previous studies and is based on five parameters including: subjective clinical scoring at admission,

saturation at admission, number of days of oxygen therapy, number of days of hospitalization and if the child was hospitalized at pediatric intensive care unit (PICU). Every child in the study group had got points from 1 to 3 for every parameter from these 5 parameters mentioned earlier, so he had total score from 5 to 15. Then he was referred to 3 subgroups: mild, moderate or severe depending on the average of their total score (Table 1).[3] Furthermore, the group was divided into 3 subgroups according to the age of the infant during hospitalization due to acute bronchiolitis (as previously noted, all infants were under the age of 6 months): I) <2 months (n=62), II) 2-4 months (n=41), and III) >4 months (n=26). The prevalence of recurrent wheezing events was compared between groups 1-4, A-C and I-III.

Finally, children who had developed recurrent wheezing events by age of 3 years were divided to 2 sub-groups: children with transient recurrent wheezing events (began in the first 3 years of life but resolved beyond 3 years of age) and children with persistent recurrent wheezing events beyond the age of 3 years old (began in the first 3 years of life and continue beyond 6 years of age). We assessed the influence of hospitalization due to acute bronchiolitis and other relevant epidemiologic and clinical factors on the prevalence of both recurrent wheezing events and transient recurrent wheezing events by multivariate analysis.

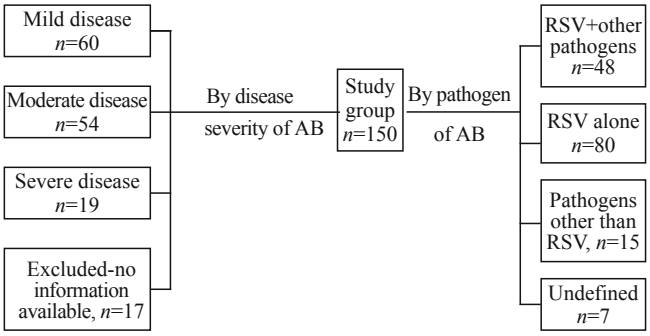

Fig. The study group was divided in parallel according to infectious agents or severity of disease during hospitalization. AB: acute bronchiolitis; RSV: respiratory syncytial virus.

Table 1. Scoring the severity of the bronchiolitis: mild, moderate and severe

Points	1	2	3
Saturation at admission	95%-100%	90%-94%	<90%
No. of days of oxygen therapy	Never	≤3	>3
Hospitalization at PICU	No	1 d	>1 d
No. of days of hospitalization	0-3	4-7	>7
Scoring 1st day disease severity	1	2	3

Severity was according to the average score: mild, 1-1.5; moderate, 1.5-2; severe, 2-3. PICU: pediatric intensive care unit.

Data analysis

Numerical results are presented as the mean±standard deviation, and categorical results are presented as the percentage. To compare results between the subgroups, we used (1) a t test or ANOVA, depending on the number of sub-groups, for the numerical data and (2) Chi-squared or Fisher's exact test, depending on the number of sub-groups, for the categorical data. A multivariate logistic regression model was also used to examine possible risk factors affecting the outcome. A two-sided P value <0.05 was considered statistically significant. All the analyses were performed using SPSS statistical software ver. 20, property of the IBM corporation©.

Ethics

The study was approved by the institutional ethics committees of the three hospitals in which the study was performed (HaEmeq Medical Center in Afula and Bnai Zion medical center and Meyer Children Hospital in Haifa). Informed consent was obtained from each parent or guardian before collecting data from HMO ambulatory records.

Results

Both the study and control groups were comparable regarding most epidemiological and demographic parameters. The children in the study group had a higher prevalence of allergic rhinitis and conjunctivitis at the time of study enrollment, while children in the control group had a higher rate of maternal smoking during pregnancy and urban residence (Table 2). These differences were not found in the multivariate analysis (see below).

Prevalence and clinical characteristics of recurrent wheezing events

Overall, 89 (58%) children in the study group suffered

Table 2. Comparison of demographic and atopic parameters between the study and control groups

Parameters	Study group n=150	Control group n=66	P
Age (mon)	63.2±2.3	61.3±1.4	0.551
Male gender, %	56.7	45.5	0.085
Urban place of residence, %	63.3	83.3	0.004
Smoking at home, %	39.3	39.4	0.553
Family history asthma in first-degree relatives, %	27.1	21.2	0.639
Maternal smoking during pregnancy, %	2.9	13.6	0.006
History of allergic conjunctivitis, %	11.6	1.5	0.009
History of food allergy, %	3.4	1.5	0.406
History of atopic dermatitis, %	14.9	7.7	0.108
History of hay fever, %	4.1	3.0	0.526
History of allergic rhinitis, %	21.6	9.1	0.018

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Table 3. Comparison of epidemiological and clinical features of recurrent wheezing episodes between the wheezing children in the study and control groups

Variables	Study group (*n*=89)	Control group (*n*=18)	*P*
Age of onset (mon), mean±standard deviation (SD)	9.8±6.0	10.8±3.0	0.016
Number of attacks, mean±SD (range)	9.3±8.5 (2-50)	4.5±1.8 (2-8)	0.005
Number of attacks treated with systemic steroids, mean±SD	5.0±7.6	1.3±1.6	0.006
Number of attacks treated with bronchodilators, mean±SD	8.9±8.2	4.4±1.8	0.006

Table 4. Prevalence and clinical features of recurrent wheezing episodes according to severity of acute bronchiolitis during hospitalization

Variables	Severe acute bronchiolitis (*n*=19)	Moderate acute bronchiolitis (*n*=54)	Mild acute bronchiolitis (*n*=60)	*P*
Wheezing episodes (prevalence), *n* (%)	11 (57.2%)	4 (62.5%)	35 (59%)	0.84
Age of onset (mon), mean±standard deviation (SD)	11.2±7.4	11.8±8.8	9.0±5.7	0.32
Number of attacks, mean±SD	8.3±7.7	8.8±11.0	6.9±5.5	0.61
Number of attacks treated with bronchodilators, mean±SD	7.4±5.6	8.4±10.8	6.9±5.4	0.73
Number of attacks treated with systemic steroids, mean±SD	4.2±4.8	5.0±9.2	3.6±5.2	0.71

Table 5. Prevalence and clinical features of recurrent wheezing episodes according to infectious agent of acute bronchiolitis

Variables	Group 1 (*n*=48)	Group 2 (*n*=80)	Group 3 (*n*=15)	Group 4 (*n*=7)	*P*
Wheezing episodes (prevalence), *n* (%)	31 (64.8%)	47 (59%)	9 (60.7%)	3 (37%)	0.73
Age of onset (mon), mean±standard deviation (SD)	9.9±6.6	10.2±7.8	11.3±7.2	6.5±0.7	0.88
Number of attacks, mean±SD	7.1±5.6	7.6±8.8	11.6±10.4	18.3±20.6	0.075
Number of attacks treated with bronchodilators, mean±SD	6.9±5.1	7.4±8.6	10.6±8.9	17.7±19.4	0.097
Number of attacks treated with systemic steroids, mean±SD	3.9±4.9	4.3±8.2	6.3±9.4	5.7±6.4	0.81

Table 6. Multivariate analysis of risk factors for the development of recurrent wheezing episodes up to 3 years of age

Variables	Study group % (*n*=150)	Control group % (*n*=66)	Odds ratio	95% confidence interval	*P*
Male gender	57	45	0.629	0.33-1.19	0.154
Nationality (non-Jewish)	45	62	0.588	0.28-1.09	0.880
Smoking at home	37	39	0.610	0.32-1.15	0.130
Maternal smoking during pregnancy	3	14	0.492	0.13-1.75	0.274
Family history of asthma in first related members	26	21	2.191	1.08-4.45	0.030
History of allergic hay fever	4	3	2.620	0.4-15.55	0.289
History of atopic dermatitis	15	8	2.245	0.75-6.71	0.809
Food allergy	3	1.5	0.423	0.52-3.45	0.422
History of allergic conjunctivitis	11	1.5	1.040	0.28-3.89	0.954
History of allergic rhinitis	21	9	0.577	0.24-1.41	0.225
Hospitalization due to acute bronchiolitis at <6 mon of age	100	0	3.910	2-7.6	0.001

from recurrent wheezing events, compared to 18 (27%) children in the control group (*P*=0.001). Children in the study group were significantly younger at recurrent wheezing events onset and experienced more episodes, bronchodilator treatments, and systemic steroids treatments (Table 3). Based on these data, the actual power of the study was 98%, with a high ability to differentiate between the two groups.

The prevalence of recurrent wheezing events up to 3 years of age was not associated with the clinical severity of acute bronchiolitis during hospitalization (Table 4) or with the causative agents (Table 5). The prevalence of recurrent wheezing events up to 3 years was not associated with the infant's age at hospitalization: age less than 2 months (69%), age between 2 and 4 months (66%) and age more than 4 months (44%) (*P*=0.6).

RSV was detected as a single pathogen or with another pathogen in the 128 children of the subgroups 1 and 2 and was not identified in the 22 children of the subgroups 3 and 4. Recurrent wheezing events occurred in 61% of the children in subgroups 1 and 2, compared to 54.5% of the children in the subgroups 3 and 4 (*P*=0.32). However, the 78 children with recurrent wheezing events in the subgroups 1 and 2 experienced significantly more episodes and more bronchodilator treatments than those with recurrent wheezing events in subgroups 3 and 4 (13.0±12.5 *vs.* 7.9±7.5, respectively, *P*=0.021; 12.1±11.3 *vs.* 7.1±7.3, respectively, *P*=0.034).

There was no significant difference between the

Table 7. Multivariate analysis of risk factors for the development transient recurrent wheezing episodes up to 3 years of age

Variables	Study group % (*n*=150)	Control group % (*n*=66)	Odds ratio	95% confidence interval	*P*
Male gender	57	45	0.705	0.35-1.40	0.330
Nationality (non-Jewish)	45	62	0.896	0.44-1.84	0.770
Smoking at home	37	39	1.045	0.52-2.10	0.920
Maternal smoking during pregnancy	3	14	0.759	0.13-4.30	0.760
Family history asthma in first related members	26	21	2.007	0.03-3.35	0.360
History of allergic hay fever	4	3	1.210	0.22-6.60	0.826
History of atopic dermatitis	15	8	1.021	0.34-3.05	0.971
History of food allergy	3	1.5	6.605	0.48-76.13	0.163
History of allergic conjunctivitis	11	1.5	0.960	0.26-3.60	0.952
History of allergic rhinitis	21	9	1.147	0.45-2.88	0.770
Hospitalization due to acute bronchiolitis at <6 mon of age	100	0	4.910	2.2-11.7	0.001

study and the control groups in the prevalence of persisting recurrent wheezing events beyond 3 years of age, 16 patients (24%), and 11 patients (17%), respectively (*P*=0.46).

Multivariate analysis

According to the multivariate analysis, hospitalization with acute bronchiolitis during the first six months of life and familial history of asthma in first-degree relatives were significant risk factors for developing recurrent wheezing events by 3 years of life (Table 6).

When the analysis was performed on transient wheezing children who had recurrent wheezing episodes in the first 3 years of life but stop wheezing beyond 3 years of age (at the time of performing the study-6 years of age), the only significant risk factor was hospitalization due to acute bronchiolitis during the first six months of life (Table 7).

Discussion

Most studies have assessed the effect of hospitalization due to acute bronchiolitis in the first 1-2 years of life on the development of recurrent wheezing events later in childhood. While several studies have evaluated the effect of acute bronchiolitis at age of less than 6 months in preterm infants on the prevalence of recurrent wheezing events later in childhood,[16,17] studies assessing full term infants are scarce.[8] In addition to the increased prevalence of recurrent wheezing events in children with a history of acute bronchiolitis, this study also found that recurrent wheezing events appeared at a younger age, occurred more frequently, and required a higher rate of acute treatment with bronchodilator inhalation or systemic steroids in children with a history of acute bronchiolitis. To our knowledge, these details have not been published previously in the relevant literature.

Our study revealed that children who were hospitalized due to acute bronchiolitis at age less than 6 months have a substantially greater risk for developing recurrent wheezing events during the first 3 years of life. This finding is in accordance with recent studies suggesting that acute bronchiolitis is a major risk factor for the development of recurrent wheezing events later in childhood,[2] which raises the question of whether this increase in prevalence is due to the damage caused by the virus, the specific infectious agents or the severity of acute bronchiolitis.

The present study found no association between the severity of acute bronchiolitis during hospitalization and the prevalence of recurrent wheezing events in early childhood. The relevant data are limited, though Mannsbach et al[7] found that severe acute bronchiolitis requiring hospitalization increased the prevalence of recurrent wheezing events in comparison with mild acute bronchiolitis treated in an ambulatory setting.

No association was found between the prevalence of recurrent wheezing events and specific infectious agents. These findings do not agree with previous studies.[18-21] In a large retrospective study of 416 children hospitalized due to acute bronchiolitis before two years of age, Valkonen et al[20] demonstrated that children who were hospitalized with acute bronchiolitis caused by viruses other than RSV developed recurrent wheezing events at substantially higher rates during a 3-year follow-up period compared to children with RSV-induced acute bronchiolitis. After 3 years of follow-up, 59 of 217 (27.2%) children with non-RSV bronchiolitis developed recurrent wheezing compared with 16 of 199 (8%) children with RSV bronchiolitis [relative risk, 3.4; 95% confidence interval (CI), 2.0-5.7].[20] Pippo-Savolainen et al[21] found higher rates of asthma 19 years after hospitalization in participants with a history of admission at age <2 years with non-RSV bronchiolitis compared to RSV bronchiolitis: 22 of 54 (41%) in the non-RSV group *vs.* 10 of 54 (18%) in the RSV group (odds ratio, 8.34; 95% CI, 1.18-58.69). Garcia-Garcia et al[22] suggested that acute bronchiolitis

due to human Metapneumovirus (hMPV) in the first 2 years of life is associated with an increased prevalence of recurrent wheezing episodes in comparison with RSV bronchiolitis after 3-5 years of follow up. Our study showed that hMPV was the most important risk factor for asthma in the preschool years, followed by RSV.[22] However, additional studies have suggested an important and specific role for RSV and/or rhinovirus as major risk factors for recurrent wheezing events and other atopic diseases later in life.[23,24] In our study, there was another co-infectious agent in the vast majority of acute bronchiolitis cases due to rhinovirus or hMPV, so we could not analyze the specific effect of rhinovirus and hMPV on the prevalence of recurrent wheezing events. In addition, our study's failure to demonstrate a significant difference in the prevalence of recurrent wheezing events between the subgroups according to the infectious agent can be explained by the small size of the non-RSV group: 22 patients compared to 128 in the RSV group.

In logistic regression analysis, we found that familial history of asthma and hospitalizations resulting from acute bronchiolitis at ages less than 6 months were independent significant risk factors for the development of recurrent wheezing events during the first 3 years of life. No influences of another atopic disease of the child, smoking by the parents or other epidemiologic factors on the prevalence of recurrent wheezing events in childhood were observed. These results suggest that both genetic factors (familial history of asthma) and environmental factors (hospitalization due to acute bronchiolitis at less than 6 months of age) but not a tendency to develop other atopic diseases are associated with a greater risk of recurrent wheezing events during the first 3 years of life. A possible explanation for this finding is the association between atopic diseases and persistent wheezing or asthma after 3 years of age, rather than early transient wheezing, which may be attributed to prematurity, previous acute bronchiolitis or recurrent viral-induced wheezing.[9]

When the analysis was restricted to children who wheezed during the first 3 years of life and stopped wheezing beyond the age of 3 years (transient recurrent wheezing events), we found that familial history of asthma stopped being a significant independent risk factor but hospitalization due to acute bronchiolitis remained a risk factor. No significant difference in the prevalence of persistence of wheezing beyond 3 years of age (at 6 years of age) was found between children who suffered from acute bronchiolitis and children who didn't. In addition, we did not find any marker in the early life which can predict which infants will suffer from persistent wheezing later in childhood; this could be attributed to the small groups and to the relative short duration of follow-up.

These results suggest that familial history of asthma affects the prevalence of persistent wheezing but doesn't affect early transient wheezing, suggesting that the pathogenesis, risk factors and natural history are different in these two types of wheezing; and while persistent wheezing is affected mainly by familial or personal history of atopy, transient wheezing is mainly viral induced wheezing and is associated strongly with a history of acute bronchiolitis during infancy.

The pathogenesis of an increased incidence of recurrent wheezing events after acute bronchiolitis is still not completely understood. Atopic children may be prone to severe acute bronchiolitis requiring hospitalization more frequently than non-atopic children. Thus, the difference in the prevalence of recurrent wheezing events may be associated with atopic tendency rather than hospitalization or acute bronchiolitis.[25,26] Tal et al[27] demonstrated that specific genetic mutations (mutation in Toll-like receptor 4) were associated with an increased risk of severe RSV bronchiolitis. These mutations may also explain the higher incidence of recurrent wheezing events later in childhood. It is also possible that acute bronchiolitis causes damage to the airways, which interrupts the physiological function of the lungs, enhances the development of "allergic" inflammatory responses when the host is exposed to allergens after an episode of bronchiolitis and increases the risk of recurrent wheezing events later in life.[28-31]

In a recently published controlled trial, Blanken et al[16] examined the efficacy of monthly palivizumab injections versus placebo during the RSV season on the total number of wheezing days in the first year of life in healthy preterm infants and found a significant relative reduction in the palivizumab group. In this study 24 of the 214 (11.5%) children in the palivizumab group *vs.* 45 of the 215 (20.9%) children in the control group developed recurrent wheezing episodes in the first year of life (AR-absolute risk reduction, 9.7; 95% CI, 14-80). Our study demonstrated no effect of RSV bronchiolitis in infancy compared to non-RSV bronchiolitis, apart from a difference in the number of episodes and bronchodilator treatments. Our study was limited by the small number of patients in the non-RSV group (22 patients) and the high percentage of other pathogens (48 of 128, 37.5%) in the RSV group. As the majority of children in our study group (128 of 150 patients, 85%) had RSV-induced acute bronchiolitis and were at greater risk for recurrent wheezing events compared to the control group, it is reasonable that palivizumab may be effective in the reduction of recurrent wheezing events. Palivizumab may prevent RSV infection, decrease acute bronchiolitis incidence during early infancy and indirectly decrease recurrent wheezing events prevalence later in childhood.

However, we did not examine the effect of RSV prophylaxis on the prevalence of recurrent wheezing events later in childhood.

Overall, the limitations of our study include the observational design and the relatively small number of patients in the non-RSV subgroups. In addition, data regarding atopy status was based on charts only. Secondly, acute bronchiolitis severity was scored by different physicians during hospitalization, and there were some differences in group characteristics. Finally, severity of recurrent wheezing events was based on medication use (bronchodilators and systemic steroids) and number of recurrent wheezing events without assessing the number of episodes needs hospitalization or oxygen supply. Larger prospective studies are needed to support our results.

In conclusion, our study suggests that children who are hospitalized due to acute bronchiolitis at ages younger than 6 months have a substantially greater risk for developing recurrent wheezing episodes during the first 3 years of life. Limiting the age of acute bronchiolitis up to 6 months during hospitalization minimized the possibility of false diagnosis of acute bronchiolitis, which occurs occasionally between the ages 6 months and 3 years old. Secondly, in this study in addition to the higher prevalence of recurrent wheezing episodes, we demonstrated more severe episodes in children who suffered from acute bronchiolitis during childhood in comparison to the control group, as demonstrated by the higher number of episodes requiring aggressive treatment with systemic steroids. Thirdly, although the high prevalence of recurrent wheezing episodes in the study group at 3 years of age, the effect of this increasing was transient and resolved at the age of 6 years, which may indicate different etiologies of wheezing in different age groups. Finally, although there was no effect of the specific etiologic agent or the severity of acute bronchiolitis on the prevalence of recurrent wheezing episodes later in childhood, further studies should be performed to determine whether specific infectious agents have different roles in inducing wheezing or asthma later in life.

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Contributors: RF designed the study and the data collection instruments, carried out the initial analyses, drafted the initial manuscript, and approved the final manuscript as submitted. KI coordinated and supervised data collection at one of the three sites, critically reviewed the manuscript, and approved the final submitted manuscript. TR carried out the initial analyses, critically reviewed the manuscript, and approved the final submitted manuscript. KA critically reviewed the manuscript and approved the final submitted manuscript. SI coordinated and supervised data collection at one of the three sites, critically reviewed the manuscript, and approved the final submitted manuscript. MD carried out the initial analyses, designed the study and the data collection instruments, coordinated and supervised data collection at one of the three sites, critically reviewed the manuscript, and approved the final version.

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