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Season of Infant Bronchiolitis and Estimates of Subsequent Risk and Burden of Early Childhood Asthma

Kecia N. Carroll, MD, MPH^{a,e,*}, Pingsheng Wu, PhD^{b,c,*}, Tebeb Gebretsadik, MPH^c, Marie R. Griffin, MD, MPH^{b,d,f,j}, William D. Dupont, PhD^{c,d}, Edward F. Mitchel, MS^d, and Tina V. Hartert, MD, MPH^{b,g,i}

^aDepartment of Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^bDepartment of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^cDepartment of Biostatistics, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^dDepartment of Preventive Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^eDivision of General Pediatrics, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^fDivision of General Internal Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^gDivision of Allergy, Pulmonary and Critical Care Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^hCenter for Education and Research on Therapeutics, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

ⁱCenter for Health Services Research, Vanderbilt University School of Medicine, Nashville, Tennessee, U.S.A.

^jMid-South Geriatric Research Education and Clinical Center, and Clinical Research Center of Excellence, Veterans Affairs Tennessee Valley Health Care System, Nashville, Tennessee, U.S.A.

Capsule Summary

There is a population-based increased risk of early childhood asthma following infant bronchiolitis occurring during rhinovirus-predominant months compared to asthma following infant bronchiolitis during RSV-predominant months.

Keywords

Bronchiolitis; asthma; season

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Corresponding author, Tina V. Hartert, M.D., M.P.H., Division of Allergy, Pulmonary and Critical Care Medicine, Center for Health Services Research, 6107 MCE, Vanderbilt University School of Medicine, Nashville, TN 37232-8300, Phone: 615-322-3412, Fax: 615-936-1269, E-mail: tina.hartert@vanderbilt.edu.

*Carroll and Wu contributed equally to the study.

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To the Editor

Viral bronchiolitis is a lower respiratory tract infection (LRTI) that affects 20–30% of infants.^{1,2} Respiratory syncytial virus (RSV) and rhinovirus (RV) are the most common viruses associated with bronchiolitis or LRTI during infancy.^{3,4} During the winter season RSV predominates and is the major cause of bronchiolitis in temperate climates north of the equator November–April.^{2,4} RV peaks in autumn and spring, and use of molecular techniques have helped elucidate RV as the other predominant pathogen associated with LRTI in infants and young children.^{3,5} Studies have found that RSV and non-RSV bronchiolitis/LRTI during infancy are risk factors or markers for wheezing and asthma in later childhood.^{3,6} In a recent investigation by Jackson and colleagues, RV-wheezing illnesses in early childhood were the strongest predictors of asthma at 6 years among a genetically predisposed birth cohort.⁷

We used our population-based retrospective birth cohort of over 90,000 children in the Tennessee Asthma Bronchiolitis Study (TABS): (1) to confirm the above reported association of etiology of bronchiolitis during infancy and risk of early childhood asthma, and (2) to estimate the burden of early childhood asthma associated with etiology of infant bronchiolitis, by studying season of bronchiolitis among term, non-low birth weight, otherwise healthy infants, enrolled in Tennessee Medicaid (TennCare) during the first year of life and between 3.5–5.5 years.⁸ We excluded children with ICD-9 diagnoses of chronic disease including chronic lung disease, congenital heart disease, neurological disorders, airway anomalies, or an immunodeficiency. Data were obtained from linked TennCare administrative data files and Tennessee State vital records. The protocol was approved by the Institutional Review Board of Vanderbilt University and reviewed and approved by representatives of the Tennessee Department of Health and Bureau of TennCare.

We identified healthcare visits for bronchiolitis during the first 12 months of life using ICD-9 codes for bronchiolitis.⁸ Infants were categorized into mutually exclusive groups based upon whether they had no visit for bronchiolitis, or had a first bronchiolitis visit that occurred during wintervirus season (November to April) or non-wintervirus season (May to October). We also defined RSV-predominant periods within wintervirus season (December–February) and RV-predominant periods within non-wintervirus season (May, August–September).^{4,5}

We identified asthma outcomes between 4–5.5 years using healthcare and pharmacy claims employing similar algorithms used for epidemiology and outcomes research.^{8,9} The primary predictor variable was season of infant bronchiolitis. We used a modified Poisson regression model to measure the adjusted relative risk of early childhood asthma associated with infant bronchiolitis season. This approach uses a robust Huber-White sandwich estimate of the model's variance-covariance matrix.¹⁰ Statistical models were adjusted for birth weight, gender, infant race/ethnicity, maternal smoking during pregnancy, maternal education, region of residence, and siblings. In the sub-cohort of children for whom maternal medical histories were available, we evaluated whether maternal asthma modified the association.⁸ Analyses were conducted using SAS version 9.1 (SAS Institute Cary, NC) and R version 2.7.0.

Among 90,341 children in the birth cohort, 18% had at least one healthcare visit for bronchiolitis during infancy. Children were classified into groups: no bronchiolitis visit (82%), wintervirus bronchiolitis (14%), and non-wintervirus bronchiolitis (4%). Although median ages at visits were similar, wintervirus bronchiolitis was associated with greater likelihood of hospitalization than non-wintervirus (31% vs. 21%, $p < 0.001$). Overall, 11% of children were diagnosed with asthma between 4–5.5 years. The proportions of children with early childhood asthma by infant bronchiolitis season were: no bronchiolitis visit (9%), wintervirus bronchiolitis (18%), and non-wintervirus bronchiolitis (21%) (see Figure 1). Relative to children without an infant bronchiolitis visit, the adjusted relative risk (RR) for asthma between

4–5.5 years were 1.94 [95% confidence interval (CI) 1.86–2.03] and 2.22 (95% CI 2.08–2.38) for the wintervirus and non-wintervirus bronchiolitis groups respectively. This relationship between season of bronchiolitis and early childhood asthma was unchanged when adjusting for maternal asthma in the sub-cohort of children whose mothers were enrolled in TennCare before delivery (n=51,669) (data not shown). In the multivariable model estimating the risk of early childhood asthma, children with non-wintervirus bronchiolitis had increased risk of early childhood asthma [Adjusted RR 1.15 (95% CI 1.06–1.24)] compared to the wintervirus group. The prevalence of early childhood asthma in children with bronchiolitis in the RV-predominant and RSV-predominate months were 22% and 18% (see Figure 1), respectively with an adjusted RR 1.25 (95% CI 1.13–1.38). Overall, 9,853 of the 90,341 children were diagnosed with asthma between 4–5.5 years. Thirty-one percent of children with asthma had a history of infant bronchiolitis, 24% occurred during wintervirus season, and the remaining 7% occurred during non-wintervirus season.

In summary, there is an increased risk of early childhood asthma associated with bronchiolitis during non-wintervirus versus wintervirus months, the risk is even higher when using more specific RSV and RV-predominate months. Although this study estimates the association of season of bronchiolitis with early childhood asthma risk, we did not perform viral detection which is a limitation of our study. Jackson and colleagues conducted longitudinal surveillance for respiratory infections over several years in children in a high-risk birth cohort with multiple episodes of illness which were primarily outpatient.⁷ Our findings confirm a similar increased risk of early childhood asthma associated with infant bronchiolitis diagnosed during RV versus RSV-predominate months, although the effect is smaller in magnitude than the findings of Jackson and colleagues who more accurately measured viral etiology.⁷ Misclassification resulting from the imprecision in defining RSV and RV seasons, with RV occurring during RSV season, but RSV not occurring during the late spring and fall RV season, as well as our inability to capture RV-wheezing illnesses for which medical care was not sought in the RV-predominate group, would result in underestimation of the differential risk between the two seasons.

In conclusion, while bronchiolitis diagnosis during infancy was associated with approximately two-fold increased risk of early childhood asthma, this risk differed by season of bronchiolitis. Bronchiolitis occurring during RV-predominate months was associated with an estimated 25% increased risk of early childhood asthma compared to RSV-predominate months. This work supports recent findings that early RV-wheezing illnesses are associated with higher risk of subsequent asthma than other viruses.⁷ Because of higher rates of bronchiolitis during wintervirus season, the proportion of associated asthma following wintervirus bronchiolitis, however, is greater.

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Abbreviations

LRTI, lower respiratory tract infection; RSV, respiratory syncytial virus; RV, rhinovirus; TABS, Tennessee Asthma Bronchiolitis Study; TennCare, Tennessee Medicaid; ICD-9,

International Classification of Diseases, Ninth Revision; RR, relative risk; CI, confidence interval.

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Figure 1.

Observed proportion and 95% CI of developing asthma by season of infant bronchiolitis. November-April represents the six month wintervirus season; December-February represents the RSV-dominant period within wintervirus season. May-October represents the six month non-wintervirus season; May, August, and September represents the RV-dominant period within non-wintervirus season. The total number of infants with bronchiolitis is indicated in parentheses for each period.