

Letter to the Editor

Season of infant bronchiolitis and estimates of subsequent risk and burden of early childhood asthma

To the Editor:

Viral bronchiolitis is a lower respiratory tract infection (LRTI) that affects 20% to 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 to 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 et al,⁷ RV-wheezing illnesses in early childhood were the strongest predictors of asthma at 6 years among a genetically predisposed birth cohort.

We used our population-based retrospective birth cohort of more than 90,000 children in the Tennessee Asthma Bronchiolitis Study (1) to confirm the above-reported association of cause of bronchiolitis during infancy and risk of early childhood asthma and (2) to estimate the burden of early childhood asthma associated with cause 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 and 5.5 years.⁸ We excluded children with International Classification of Diseases–Ninth edition diagnoses of chronic disease, including chronic lung disease, congenital heart disease, neurologic 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 health care visits for bronchiolitis during the first 12 months of life using International Classification of Diseases–Ninth edition codes for bronchiolitis.⁸ Infants were categorized into mutually exclusive groups based on whether they had no visit for bronchiolitis or had a first bronchiolitis visit that occurred during winter virus season (November–April) or non-winter virus season (May–October). We also defined RSV-predominant periods within winter virus season (December–February) and RV-predominant periods within non-winter virus season (May and August–September).^{4,5}

We identified asthma outcomes between 4 and 5.5 years using health care and pharmacy claims and algorithms similar to those 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 (RR) 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, sex, infant race/ethnicity, maternal smoking during pregnancy, maternal

education, region of residence, and siblings. In the subcohort of children for whom maternal medical histories were available, we evaluated whether maternal asthma modified the association.⁸ Analyses were conducted with SAS version 9.1 (SAS Institute, Inc Cary, NC) and R version 2.7.0.

Among 90,341 children in the birth cohort, 18% had at least 1 health care visit for bronchiolitis during infancy. Children were classified into groups: no bronchiolitis visit (82%), winter virus bronchiolitis (14%), and non-winter virus bronchiolitis (4%). Although median ages at visits were similar, winter virus bronchiolitis was associated with greater likelihood of hospitalization than non-winter virus (31% vs 21%, $P < .001$). Overall, 11% of children were given diagnoses of asthma between 4 and 5.5 years of age. The proportions of children with early childhood asthma by infant bronchiolitis season were as follows: no bronchiolitis visit (9%), winter virus bronchiolitis (18%), and non-winter virus bronchiolitis (21%) (Fig 1). Relative to children without an infant bronchiolitis visit, the adjusted RR for asthma between 4 and 5.5 years of age was 1.94 (95% CI, 1.86–2.03) and 2.22 (95% CI, 2.08–2.38) for the winter virus and non-winter virus bronchiolitis groups, respectively. This relationship between season of bronchiolitis and early childhood asthma was unchanged when adjusting for maternal asthma in the subcohort 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-winter virus bronchiolitis had increased risk of early childhood asthma (adjusted RR, 1.15; 95% CI, 1.06–1.24) compared with the winter virus group. The prevalence of early childhood asthma in children with bronchiolitis in the RV-predominant and RSV-predominant months were 22% and 18% (Fig 1), respectively, with an adjusted RR of 1.25 (95% CI, 1.13–1.38). Overall, 9,853 of the 90,341 children were given diagnoses of asthma at between 4 and 5.5 years. Thirty-one percent of children with asthma had a history of infant bronchiolitis, 24% occurred during the winter virus season, and the remaining 7% occurred during the non-winter virus season.

In summary, there is an increased risk of early childhood asthma associated with bronchiolitis during non-winter virus versus winter virus months, and the risk is even higher when using more specific RSV- and RV-predominant 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 et al⁷ 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. Our findings confirm a similar increased risk of early childhood asthma associated with infant bronchiolitis diagnosed during RV- versus RSV-predominant months, although the effect is smaller in magnitude than the findings of Jackson et al,⁷ who more accurately measured viral etiology. Misclassification resulting from the imprecision in defining RSV and RV seasons, with RV occurring during the 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-predominant group, would result in underestimation of the differential risk between the 2 seasons.

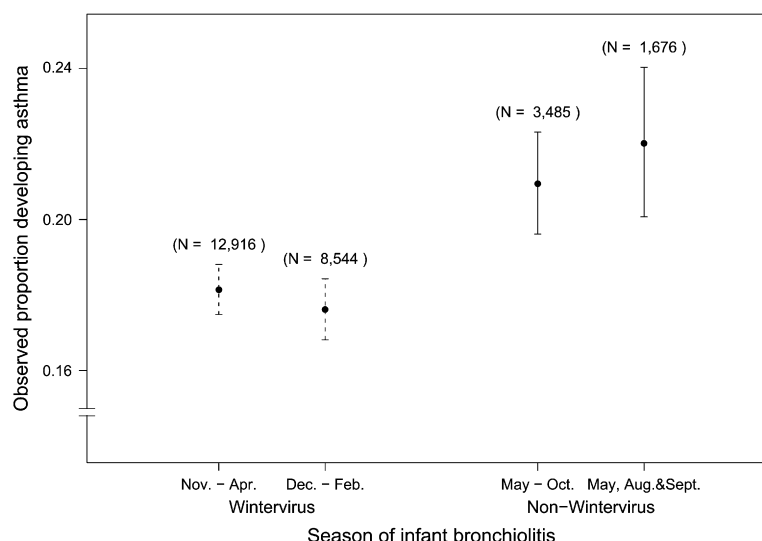


FIG 1. Observed proportion and 95% CI of asthma development by season of infant bronchiolitis. November-April represents the 6-month winter virus season; December-February represents the RSV-dominant period within the winter virus season. May-October represents the 6-month non-winter virus season; May, August, and September represents the RV-dominant period within the non-winter virus season. The total number of infants with bronchiolitis is indicated in parentheses for each period.

In conclusion, although bronchiolitis diagnosis during infancy was associated with an approximately 2-fold increased risk of early childhood asthma, this risk differed by season of bronchiolitis. Bronchiolitis occurring during RV-predominant months was associated with an estimated 25% increased risk of early childhood asthma compared with RSV-predominant 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 the winter virus season, the proportion of associated asthma after winter virus bronchiolitis, however, is greater.

We thank the Tennessee Bureau of TennCare of the Department of Finance and Administration and the Tennessee Department of Health, Office of Policy, Planning and Assessment for providing the data.

Kecia N. Carroll, MD, MPH^{a,e,*}

Pingsheng Wu, PhD^{b,c,*}

Tebeb Gebretsadik, MPH^c

Marie R. Griffin, MD, MPH^{b,d,f,h,j}

William D. Dupont, PhD^{c,d}

Edward F. Mitchel, MS^d

Tina V. Hartert, MD, MPH^{b,g,i}

From the Departments of ^aPediatrics, ^bMedicine, ^cBiostatistics, and ^dPreventive Medicine; the Divisions of ^eGeneral Pediatrics, ^fGeneral Internal Medicine, and ^gAllergy, Pulmonary and Critical Care Medicine; and ^hthe Center for Education and Research on Therapeutics and ⁱthe Center for Health Services Research, Vanderbilt University School of Medicine, Nashville, Tenn, and ^jthe Mid-South Geriatric Research Education and Clinical Center and Clinical Research Center of Excellence, Veterans Affairs Tennessee Valley Health Care System, Nashville, Tenn. E-mail: tina.hartert@vanderbilt.edu.

*These authors contributed equally to this work.

Supported by National Institutes of Health (NIH) grant U01 HL 072471 (T.V.H.), the Thrasher Research Fund (T.V.H. and P.W./T.V.H.), NIH grant KO1 AI070808 (K.N.C.), NIH grant K24 AI 077930 (T.V.H.), NIH grant F32 HL 086048 (P.W./T.V.H.), NIH grant RO1 AI 50884 (T.V.H.), and the Parker B. Francis Fellowship in Pulmonary Research (K.N.C.).

Disclosure of potential conflict of interest: K. N. Carroll has received research support from the National Institutes of Health and the Parker B. Francis Foundation. P. Wu has

received research support from the National Institutes of Health and the Thrasher Research Fund. M. R. Griffin has received research support from MedImmune, Pfizer, the Centers for Disease Control and Protection, and the Agency for Healthcare Research and Quality. W. D. Dupont has received research support from the National Institutes of Health/National Cancer Institute and the National Institutes of Health/National Institute of Allergy and Infection Diseases. T. V. Hartert has served as a consultant/speaker for Merck, has received extramural grants from the National Institutes of Health and the Thrasher Research Fund, and is a committee member of the American Thoracic Society. The rest of the authors have declared that they have no conflict of interest.

REFERENCES

1. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child* 1986;140:543-6.
2. Wright AL, Taussig LM, Ray CG, Harrison HR, Holberg CJ. The Tucson Children's Respiratory Study. II. Lower respiratory tract illness in the first year of life. *Am J Epidemiol* 1989;129:1232-46.
3. Lemanske RF Jr, Jackson DJ, Gangnon RE, Evans MD, Li Z, Shult PA, et al. Rhinovirus illnesses during infancy predict subsequent childhood wheezing. *J Allergy Clin Immunol* 2005;116:571-7.
4. Heymann PW, Carper HT, Murphy DD, Platts-Mills TA, Patrie J, McLaughlin AP, et al. Viral infections in relation to age, atopy, and season of admission among children hospitalized for wheezing. *J Allergy Clin Immunol* 2004;114:239-47.
5. Gwaltney JM Jr. The Jeremiah Metzger lecture. Climatology and the common cold. *Trans Am Clin Climatol Assoc* 1985;96:159-75.
6. Sigurs N, Gustafsson PM, Bjarnason R, Lundberg F, Schmidt S, Sigurbergsson F, et al. Severe respiratory syncytial virus bronchiolitis in infancy and asthma and allergy at age 13. *Am J Respir Crit Care Med* 2005;171:137-41.
7. Jackson DJ, Gangnon RE, Evans MD, Roberg KA, Anderson EL, Pappas TE, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med* 2008;178:667-72.
8. Wu P, Dupont WD, Griffin MR, Carroll KN, Mitchel EF, Gebretsadik T, et al. Evidence of a Causal Role of Winter Virus Infection During Infancy on Early Childhood Asthma. *Am J Respir Crit Care Med* 2008;178:1123-9.
9. Wakefield DB, Cloutier MM. Modifications to HEDIS and CSTE algorithms improve case recognition of pediatric asthma. *Pediatr Pulmonol* 2006;41:962-71.
10. Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702-6.