Respiratory syncytial virus immunoprophylaxis in high-risk infants and development of childhood asthma

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Background: Respiratory syncytial virus (RSV) lower respiratory tract infection is implicated in asthma development. RSV immunoprophylaxis during infancy is efficacious in preventing RSV-related hospitalizations and has been associated with decreased wheezing in the first years of life.
Objective: We investigated whether greater adherence to immunoprophylaxis in infants at high risk for severe RSV would be associated with decreased childhood asthma.
Methods: We conducted a retrospective cohort investigation including children born from 1996-2003 who were enrolled in Kaiser Permanente Northern California or Tennessee Medicaid and eligible to receive RSV immunoprophylaxis. Asthma was defined at 4.5 to 6 years of age by using asthma-specific health care visits and medication fills. We classified children into immunoprophylaxis eligibility groups and calculated adherence (percentage receipt of recommended doses). We used a set of statistical strategies (multivariable logistic regression and propensity score [PS]–adjusted and PS-matched analyses) to overcome confounding by medical complexity because infants with higher adherence (≥70%) have higher prevalence of chronic lung disease, lower birth weight, and longer nursery stays.
Results: By using multivariable logistic regression and PS-adjusted models in the combined group, higher adherence to RSV immunoprophylaxis was not associated with decreased asthma. However, in PS-matched analysis, treated children with 70% or greater adherence had decreased odds of asthma compared with those with 20% or less adherence (odds ratio, 0.62; 95% CI, 0.50-0.78).
Conclusions: This investigation of RSV immunoprophylaxis in high-risk children primarily found nonsignificant associations on prevention of asthma in specific preterm groups. Our findings highlight the need for larger studies and prospective cohorts and provide estimates of potential preventive effect sizes in high-risk children. (J Allergy Clin Immunol 2017;139:66-71.)

Key words: *Respiratory syncytial virus, lower respiratory tract infection, bronchiolitis, respiratory syncytial virus immunoprophylaxis, palivizumab, wheezing, asthma, primary prevention*

Although asthma, a disease for which no known preventive strategies exist, has a strong hereditary basis, disease risk is likely modified by environmental and early-life exposures. One such early-life exposure, infant respiratory syncytial virus (RSV) lower respiratory tract infection (LRTI), has a strong association with asthma.[1-3] Infant RSV LRTI precedes asthma and is associated with a severity-dependent odds of asthma.[3] Furthermore, risk of asthma has been linked with birth timing in relationship to respiratory virus circulation,[2] and animal studies demonstrate biologic mechanisms through which RSV LRTI could contribute to asthma development.[4-8] Both observational studies and a recent randomized controlled trial (RCT) demonstrate that preventing RSV LRTI decreases recurrent wheezing and 1-year wheezing outcomes, respectively.[8-11] Determining whether prevention of infant RSV LRTI prevents asthma is important because the ability to modify the risk of a lifelong chronic disease has remained elusive.

RSV immunoprophylaxis administered during the RSV season to high-risk infants is efficacious in the prevention of RSV hospitalization, and the American Academy of Pediatrics (AAP) has issued recommendations for its use in infants at high risk for severe RSV.[12-20] To address the question of whether prevention of severe infant RSV decreases the risk of early childhood asthma, we took advantage of the known high risk of severe RSV and asthma among groups for whom immunoprophylaxis is recommended.[12,21,22] The use of observational methods to study whether RSV immunoprophylaxis decreases asthma in high-risk infants allows estimation of effect size in this select population within a real-world context. However, confounding by indication is important: among patients eligible for immunoprophylaxis, infants with the highest risk of subsequent asthma are more likely to receive immunoprophylaxis.[23] Thus the drug will appear to be

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Abbreviations used
AAP: American Academy of Pediatrics
CLD: Chronic lung disease
EGA: Estimated gestational age
ICD-9: International Classification of Diseases, Ninth Revision
KPNC: Kaiser Permanente Northern California
LOS: Length of stay
LRTI: Lower respiratory tract infection
OR: Odds ratio
PRIMA: Prevention of RSV: Impact on Morbidity and Asthma
PS: Propensity score
RCT: Randomized controlled trial
RSV: Respiratory syncytial virus
SGA: Small for gestational age

associated with increased disease risk, probably because of residual confounding related to medical complexity. In this report we describe how we tested the hypothesis that increased adherence to RSV immunoprophylaxis would be associated with a decreased odds of asthma at age 4.5 to 6 years.

METHODS

Study design

This study was approved by the Institutional Review Boards of Kaiser Permanente Northern California (KPNC), the State of California Committee for the Protection of Human Subjects, and Vanderbilt University Medical Center and representatives of the Tennessee Department of Health and the Bureau of TennCare.[23] We conducted a retrospective cohort investigation of children enrolled in the Prevention of RSV: Impact on Morbidity and Asthma (PRIMA) cohort who were at increased risk for severe RSV and eligible to receive RSV immunoprophylaxis during infancy. The PRIMA cohort is composed of 2 large population-based birth cohorts followed through age 6 years from KPNC and Tennessee Medicaid (TennCare).[23] This investigation of receipt of RSV immunoprophylaxis during infancy and early childhood asthma included infants born between January 1, 1996, and December 31, 2003, to allow adequate follow-up time to age 6 years.[23] For KPNC, data were obtained from linked administrative and clinical databases, the electronic medical record, and California vital records files, as previously described.[23] In 1994, TennCare replaced the federal Medicaid program as a state-based managed health care program that covered Medicaid-eligible subjects and the uninsured; approximately 50% of infants in Tennessee are covered by TennCare.[3,23,24] For the TennCare population, all data were obtained from linked TennCare administrative files and Tennessee vital records files, as previously described.[23,25-27]

Eligibility to receive RSV immunoprophylaxis

Children eligible for study inclusion were continuously enrolled in either KPNC or TennCare during their first year and between the ages of 4.5 and 6 years. Continuous enrollment was defined as no more than 90 days of nonenrollment during the first year of life and no more than 60 days of nonenrollment between the ages of 4.5 and 6 years.[23] Eligibility for receipt of RSV immunoprophylaxis was determined according to AAP recommendations in place during the study period (see the Methods section in this article's Online Repository at www.jacionline.org).[16,18,19] As previously described, eligible children were classified into 4 hierarchical, mutually exclusive groups: (1) *Chronic lung disease* (CLD) was defined as CLD with prescriptions filled for CLD medication within 6 months of RSV season; (2) *Prematurity <29* was defined as estimated gestational age (EGA) of less than 29 weeks; (3) *Prematurity <32* was defined as EGA of less 32 weeks; and (4) *Other eligible* was defined as 32 to less than 35 weeks of EGA and less than 6 months of age at the RSV season with both maternal smoking and an older sibling or International Classification of Diseases, Ninth Revision (ICD-9), diagnoses of cyanotic or hemodynamically significant congenital heart disease, neurologic condition, or congenital anomaly of airway.[16,23,28] The start of the RSV season was defined as November 1. Children with CLD who did not require medication were categorized by EGA.

Main predictor: Percentage adherence to RSV immunoprophylaxis during infancy

During the study period, the AAP recommended that eligible children receive monthly injections throughout the RSV season, typically November to March. We identified all RSV immunoprophylaxis encounters throughout the study period.[23] We calculated the recommended number of doses each infant should have received based on their eligibility group, birth date, and month of hospital discharge in relation to RSV season.[23] We calculated the percentage receipt of recommended doses (adherence) by dividing the number of doses received by the number of recommended doses and used this value as continuous or categorized for comparison of different levels of adherence by type of analysis.[23]

Outcome of early childhood asthma

We determined diagnoses of asthma between 4.5 and 6 years of age to allow a window for diagnosis and to exclude potential "transient early wheezers."[3,29] We defined asthma using a validated algorithm that incorporates asthma-specific health care encounters and medication claims by using a modified Healthcare Effectiveness Data and Information Set definition.[3,30,31] Children with an asthma-specific ICD-9 code (493) from a hospitalization, 23-hour observation, or emergency department visit or 2 or more clinic visits were classified as having asthma. In addition, children with 2 or more prescription fills for a short-acting β-agonist within a 12-month period or a prescription fill for other asthma medications (including inhaled corticosteroids and long-acting β-agonists) were classified as having asthma.

Covariates

We used administrative data linked with vital records to identify covariates. Birth certificate data were used to determine infant characteristics (sex, EGA, and birth weight) and maternal demographics and characteristics (race, education, smoking status during pregnancy, gravidity status, and number of previous live births). Small for gestational age (SGA) (<5th percentile) status was determined by using standard methods.[32] Infant birth hospitalization length of stay (LOS) and health care visits for bronchiolitis were identified by using administrative data.[23]

Statistical analyses

The main outcome variable was asthma, which was defined as a dichotomous variable (asthma present vs no) ascertained between 4.5 and 6 years of age. We have demonstrated that prematurity and SGA are associated with higher adherence to RSV immunoprophylaxis in this cohort,[23] and thus *a priori*, we decided to use different multivariable adjustment approaches to address confounding. Therefore in addition to conventional multivariable logistic regression, we used propensity score (PS) methods to perform PS-adjusted and PS-matched analyses (see the Methods section and Fig E1 in this article's Online Repository at www.jacionline.org). In univariate analysis we compared the proportion of children with asthma by categories defining the degree of adherence using Pearson χ^2 statistics. Continuity corrections were not used for 2×2 tables. RSV immunoprophylaxis predictor categories were specified by the type of multivariable analyses conducted. For the multivariable and PS-adjusted analyses, we defined the degree of adherence as no receipt, less than 70% adherence, and 70% adherence or greater. For PS-matched analyses, the subset of children with extremes of RSV immunoprophylaxis adherence were included (see the Methods section in this article's Online Repository).[33] Covariates in the multivariable models included infant sex, EGA, EGA plus birth hospital LOS, birth weight, bronchiolitis diagnosis, season of birth (RSV season: October-March vs