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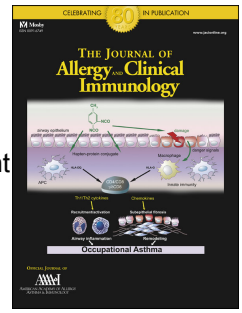

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PII: S0091-6749(16)30096-3

DOI: 10.1016/j.jaci.2016.01.055

Reference: YMAI 12058

To appear in: *Journal of Allergy and Clinical Immunology*

Received Date: 10 March 2015

Revised Date: 20 January 2016

Accepted Date: 29 January 2016

Please cite this article as: Carroll KN, Gebretsadik T, Escobar GJ, Wu P, Li SX, Walsh EM, Mitchel E, Sloan CD, Dupont WD, Hartert TV, Respiratory Syncytial Virus Immunoprophylaxis in High-Risk Infants and Development of Childhood Asthma, *Journal of Allergy and Clinical Immunology* (2016), doi: 10.1016/j.jaci.2016.01.055.

Respiratory Syncytial Virus Immunoprophylaxis in High-Risk Infants and Development of Childhood Asthma

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Funding: This work was supported by a grant from the Agency for Healthcare Research and Quality [R01 HS018454] and NIH K24 AI 077930. The funding agencies did not have any role in the study design, collection, analysis and interpretation of data, the writing of this report, or the decision to submit for publication.

Conflict of Interest: Dr. Tina V. Hartert serves as a consultant to Medimmune through a Vanderbilt University School of Medicine contract to define respiratory outcomes for clinical and vaccine trials. Consultant fees are paid to Vanderbilt.

Abstract

Background: Respiratory syncytial virus (RSV) lower respiratory tract infection is implicated in asthma development. RSV immunoprophylaxis during infancy is efficacious in preventing RSV 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 1996-2003, enrolled in Kaiser Permanente Northern California or Tennessee Medicaid, and eligible to receive RSV immunoprophylaxis. Asthma was defined at 4.5-6 years using asthma-specific healthcare visits and medication fills. We classified children into immunoprophylaxis eligibility groups and calculated adherence (% receipt of recommended doses). We employed a set of statistical strategies (multivariable logistic regression, propensity score (PS)-adjusted and-matched analyses) to overcome confounding by medical complexity, as infants with higher adherence ($\geq$70%) have higher prevalence of chronic lung disease, lower birth weight, and longer nursery stays.

Results: 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 $\geq$70% adherence had decreased odds of asthma compared to those with $\leq$20% adherence (odds ratio 0.62: 95% CI 0.50, 0.78).

Conclusions: This investigation of RSV immunoprophylaxis in high-risk children primarily found non-significant associations on prevention of asthma in specific preterm groups. Findings highlight need for larger studies, prospective cohorts, and provide estimates of potential preventive effect sizes in high-risk children.

Key Messages

- Among infants at high-risk for RSV, greater adherence to RSV immunoprophylaxis is associated with higher medical complexity as measured by factors such as small for gestational age, lower birth weight, and chronic lung disease.
- Using *a priori* defined statistical adjustment strategies in efforts to control for confounding by medical complexity in an observational study of high-risk infants, higher adherence to RSV immunoprophylaxis was not associated with decreased odds of asthma in the combined group of eligible children using standard multivariable and propensity score-adjusted models. Propensity score-matched modeling demonstrated that higher adherence was associated with decreased odds of early childhood asthma.

Capsule Summary

Odds of childhood asthma among high-risk infants receiving RSV immunoprophylaxis varied by eligibility group and statistical method applied. Prospective studies are needed, but these findings provide estimates of effect sizes in specific sub-groups.

Keywords: Respiratory syncytial virus; lower respiratory tract infection; bronchiolitis; RSV immunoprophylaxis; palivizumab; wheezing; asthma; primary prevention

Abbreviations:

RSV: Respiratory syncytial virus

LRTI: Lower respiratory tract infection

RCT: Randomized controlled trial

AAP: American Academy of Pediatrics

KPNC: Kaiser Permanente Northern California

PRIMA: ***P****revention of* ***R****SV:* ***I****mpact on* ***M****orbidity and* ***A****sthma*

CLD: Chronic lung disease

ICD-9: International classification of diseases

CHD: Congenital heart disease

SGA: Small for gestational age

LOS: Length of stay

PS: Propensity score

EGA: Estimated gestational age

OR: Odds ratio

INTRODUCTION

While asthma, a disease for which no known preventive strategies exist, has a strong hereditary basis, risk of disease 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, as the ability to modify risk of developing a lifelong chronic disease has remained elusive.

RSV immunoprophylaxis, given during 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 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, the infants with highest risk of

subsequent asthma are more likely to receive immunoprophylaxis.[23] Thus the drug will appear to be associated with increased disease risk, probably due to 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 4.5-6 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, 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 ***P**revention of **R**SV: **I**mpact on **M**orbidity and **A**sthma* (PRIMA) cohort who were at increased risk for severe RSV and eligible to receive RSV immunoprophylaxis during infancy. The PRIMA cohort is composed of two large population-based birth cohorts followed through age six 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 individuals 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 ages 4.5-6 years. Continuous enrollment was defined as no more than 90 days of non-enrollment during the

first year of life and no more than 60 days of non-enrollment between 4.5-6 years.[23] Eligibility for receipt of RSV immunoprophylaxis was determined according to AAP recommendations in place during the study period (see detailed Methods in the Online Repository).[16;18;19] As previously described, eligible children were classified into 4 hierarchical, mutually exclusive groups: 1) CLD: Chronic lung diseases (CLD) with prescription filled for CLD medication within 6 months of RSV season 2) Prematurity <29: Estimated gestational age (EGA) less than 29 weeks 3) Prematurity <32: EGA < 32 weeks and 4) Other Eligible: 32 to < 35 weeks EGA, less than 6 months of age at RSV season with both maternal smoking and an older sibling or ICD-9 diagnoses of cyanotic or hemodynamically significant congenital heart disease (CHD), neurologic condition, or congenital anomaly of airway.[16;23;28] The start of RSV season was defined as November 1st. Children with CLD who did not require medication were categorized by EGA.

Main Predictor: % 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 percent receipt of recommended doses (adherence) by dividing the number of doses received by 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 4.5-6 years 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 healthcare encounters and medication claims using a modified HEDIS 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 beta-agonist within a 12 month period or a prescription fill for other asthma medications (including inhaled corticosteroids and long-acting beta 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 (gender, EGA, birth weight) and maternal demographics and characteristics (race, education, smoking status during pregnancy, gravidity status, number of previous live births). Small for gestational age (SGA), $<5^{th}$ percentile, was determined using standard methods.[32] Infant birth hospitalization length of stay (LOS) and healthcare visits for bronchiolitis were identified using administrative data.[23]

Statistical Analyses. The main outcome variable was asthma, defined as a dichotomous variable (Asthma present vs. No), ascertained between 4.5-6 years. We have demonstrated that prematurity and SGA are associated with higher adherence to RSV immunoprophylaxis in this cohort,[23] thus, a priori we decided to employ 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-matched analyses (see

detailed Methods and Figure E1 in the Online Repository). In univariate analysis, we compared the proportion of children with asthma by categories defining the degree of adherence using Pearson's Chi-square statistics. Continuity corrections were not used for 2x2 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, <70% adherence, and ≥70% adherence. For PS-matched analyses, the subset of children with extremes of RSV immunoprophylaxis adherence were included (see detailed Methods in the Online Repository).[33] Covariates in the multivariable models included infant gender, EGA, EGA plus birth hospital LOS, birth weight, bronchiolitis diagnosis, season of birth (RSV season: October-March vs. non-RSV season: April-September), birth year, number of living siblings, maternal race, age, education, gravidity, smoking during pregnancy, and site. For TennCare, when birth hospital LOS was missing, it was imputed as previously described.[23]

Each regression adjustment method (multivariable logistic regression, propensity score adjusted, and propensity score matched models) was conducted in the all RSV immunoprophylaxis eligible cohort and in each subgroup based on eligibility criteria (CLD, Prematurity <29, Prematurity <32, and Other Eligible). Adjusted odds ratios (AORs) for asthma were determined by adherence to AAP RSV immunoprophylaxis recommendations, categorized as no receipt, <70%, or ≥70% adherence, in the conventional multivariable and PS-adjusted models. Model fits (for conventional logistic regression methods) were assessed using the goodness of fit test (Cessie–van Houwelingen–Copas–Hosmer) and there were no statistically significant evidence of lack of fit in our logistic regression models. *Propensity score adjustment models*: PS was derived using a proportional odds ordinal logistic regression model for treatment (RSV

immunoprophylaxis) with three level categories (no receipt, <70% adherence, and ≥70% adherence) and included as a covariate in the propensity score adjustment models.[34] Following derivation of the PS, in adjustment models, restricted cubic splines were used to allow for non-linear adjustment between PS and outcome. *Propensity score-matched treatment groups*: We derived the PS for matched analyses using binary logistic regression with high and low ends of receipt, including ≥70% and > 0 to ≤20% adherence.[23] The PS-matched model included 1:1 matching with replacement[33;35] based on the PS to assess the association of % adherence with recommended number of doses of RSV immunoprophylaxis in infancy and subsequent asthma. In the matched analysis, conditional logistic regression and robust sandwich error estimates were used to account for the clustered data. The significance level for all analyses was $p < 0.05$.

To assess the impact of missing covariate data, we conducted conventional multivariable adjustment models using multiple imputation of missing variables. Since the results of these analyses remained unchanged, we present the complete case analyses. Overall, less than 2% of children were excluded from multivariable analyses due to missing/Unknown data. Analyses were conducted using SAS version 9.1 (SAS Institute Cary, NC) and R version 3.0.1(http://www.r-project.org).[34-36]

RESULTS

A total of 6,571 children eligible to receive RSV immunoprophylaxis were included (Table 1). The percentages of children in the RSV immunoprophylaxis eligibility groups were as follows: CLD (10%), <29 week EGA group (33%), 29 to <32 week EGA group (48%) and the Other Eligibility Group (9%). Asthma prevalence at age 4.5-6 years varied according to eligibility group, affecting 45%, 23%, 19%, and 17% in the CLD, <29 week EGA group, 29 to < 32 week EGA group, and the Other Eligibility group, respectively. Overall, the majority of infants received at least one dose of RSV immunoprophylaxis, categorized as no receipt (36%), <70% adherence (30%), and ≥70% adherence (34%). There were notable differences between eligible infants who did and did not receive immunoprophylaxis (Table 1). Although the no receipt group and those with ≥70% adherence had a similar EGA (30 vs. 29 weeks, respectively), substantial bias was evident. Compared to the no receipt group, infants with ≥70% adherence were more likely to have CLD (45% vs. 22%), lower median birth weight (1179 grams vs. 1510 grams), be small for gestational age (8% vs. 4%), and have longer median birth hospital LOS (50 vs. 31 days).

Table 2 shows that 23% of children eligible for RSV immunoprophylaxis were diagnosed with asthma between age 4.5-6 years, including 19%, 22%, and 28% in the no receipt, <70% adherence, and ≥70% adherence groups respectively. In the multivariable and PS-adjusted regression models of the combined group, statistically significant differences in the relative odds of asthma were not detected in the most adherent group (≥70%) or those with <70% adherence (Table 2) compared to children with no receipt. In the PS-matched model that compared children who received ≥70% of recommended doses to those who received at least one dose, but were

≤20% adherent, a decreased odds of early childhood asthma was detected, 0.62 (0.50-0.78), see Table 3.

We also investigated adherence to RSV immunoprophylaxis and childhood asthma by eligibility groups. For children in the CLD group, 45% of the 651 children were diagnosed with asthma between age 4.5-6 years, including 36%, 42%, and 51% in the no receipt, <70% adherence, and ≥70% adherence groups, respectively. In comparison to the no receipt group, children in the <70% or the ≥70% adherence groups did not have a statistically significant difference in relative odds of early childhood asthma in the multivariable or PS-adjusted models (Table 2). An increased odds of early childhood asthma was detected in the propensity score matched model, adjusted OR 1.76 (1.41-2.20), Table 3. Additionally, separate multivariable and propensity score-adjusted analyses were conducted for children in the EGA <29 week, EGA 29 to <32 week, and the Other Eligible group, however statistically significant differences were not detected in the relatives odds of early childhood asthma by percent adherence to RSV immunoprophylaxis (Table 2). In contrast, in PS-matched analysis that compared children in the ≥70% adherence group to those in the ≤20% adherence group (of children who received at least one dose) a decreased odds of early childhood asthma was detected in the EGA <29 week group [adjusted OR 0.62 (95% CI 0.50-0.78)] and the EGA 29 to <32 week group [adjusted OR 0.63 (95% CI 0.42-0.93)], Table 3.

DISCUSSION

Viral LRTIs during infancy are associated with increased asthma risk in childhood, representing a potentially modifiable risk factor.[2;37;38] Observational studies designed to test whether therapeutic agents that are efficacious in preventing severe RSV can prevent asthma are plagued by the problem of confounding by indication and medical risk. Within our risk categories, there was a spectrum of illness severity, with those at higher-risk more likely to receive RSV immunoprophylaxis and also have higher adherence, while infants with lower or non-adherence were healthier. In the multivariable and PS-adjusted models, greater adherence to RSV immunoprophylaxis was not associated with decreased asthma later in life. In the analyses of the sub-cohort with matching by PS design, we detected a protective effect in the combined eligibility group and prematurity groups, although an increased odds was found in the CLD group. Although PS matching limits sample size and relies on appropriate and available data, it provides the best balance between treatment groups.

Several findings in the previous literature led us to investigate whether increased adherence to RSV immunoprophylaxis recommendations would be associated with decreased odds of subsequent asthma. Multiple independent cohorts have demonstrated that children with RSV bronchiolitis during infancy have an increased relative odds of early childhood asthma and[37-39]our group has demonstrated a severity dependent association.[3] In addition, we have found that birth in relationship to winter virus season is associated with subsequent asthma risk,[2] a finding that suggests that exposure to viruses during susceptible periods in early life may play a causal role in asthma inception. Previous research findings have demonstrated efficacy of RSV immunoprophylaxis in decreasing risk of RSV hospitalization[14;15] and in a RCT of infants born

at 33 to 35 weeks EGA, Blanken et al. found that RSV immunoprophylaxis was associated with decreased wheezing days, including the post-prophylaxis period, and decreased recurrent wheezing in the first year of life.[11] Importantly, recent animal studies provide insights into the biologic mechanisms through which RSV could cause asthma.[5-7]

It is important to note that for the most high risk infants, such as infants with CLD and/or extreme prematurity, with currently available knowledge our research question can only be addressed using an observational study design as it may be considered unethical in certain countries to conduct a RCT of RSV immunoprophylaxis among infants for whom RSV immunoprophylaxis is recommended. Although the most recent AAP guidelines, which were not in place during our study period, recommend RSV immunoprophylaxis in fewer children, recommendations for use remain in place for children with CLD and/or extreme prematurity, although in our study we were not able to capture CLD as defined in the current guidelines.[40] As found in this current study, groups that have the highest risk for severe RSV also have the highest prevalence of asthma during childhood, reaching 45% in the CLD group. Therefore even given the narrowing of the scope of recommendations for RSV immunoprophylaxis and the policy statement that RSV immunoprophylaxis should not be used for asthma prevention, investigations using observational study designs to assess the association of adherence to asthma development have the potential to provide important insights into whether a currently used therapeutic agent is associated with a decrease in the burden of a potentially life-long chronic disease in a relevant and disproportionately affected subset of children for whom receipt is recommended.

Findings in our multivariable and PS-adjusted models did not demonstrate that RSV immunoprophylaxis decreased asthma odds. Although we used a set of statistical adjustment strategies to address differences between comparison groups, it is possible that we were not able to control for important confounders that influenced adherence and imbalance in prognostically important variables. In addition, although this KPNC-TennCare collaboration provided the largest retrospective cohort study to date that addressed our primary research question, a larger sample size may have enhanced our ability to overcome confounding bias, particularly in the subgroups with smaller numbers. In an attempt to reduce substantial indication bias, PS-matching with replacement was used, limiting sample size (for example: in CLD subgroup, we had 90 subjects in >0,<=20% adherence and 324 with >=70%). This may have contributed to the inconsistent results. We were not able to quantify the extent to which sample size affected the results [33;41] In our analyses with PS matching, we detected a protective effect of immunoprophylaxis on asthma in the combined eligibility group and the two prematurity groups, although an increased odds was found in the CLD group. Since the underlying pulmonary architecture and physiology differs between children with and without CLD, it is biologically plausible that prevention of RSV would prevent subsequent pathologic airway changes or host responses in children without chronic lung pathology or with milder disease, but not alter the course of asthma development in children with the most severe CLD.

There are several limitations of this retrospective cohort study. We categorized infants into RSV immunoprophylaxis eligibility groups using administrative data and we were not able to identify all risk factors used to determine eligibility for infants born between 32 to 35 weeks EGA. In addition there were likely unmeasured factors related to neonatal course severity that influenced

which children received immunoprophylaxis. We defined asthma outcomes using ICD-9 diagnoses and medication use and may not detect asymptomatic or undiagnosed individuals. Although our method of detecting asthma is similar to a definition found to be sensitive and specific for persistent asthma, it is possible that this definition captures diverse wheezing phenotypes.[30;31] Strengths of our study include a large population of children recruited from a managed care plan as well as a state Medicaid health care plan and objective information on administration of RSV immunoprophylaxis and asthma diagnosis.

In summary, we investigated the association of adherence to RSV immunoprophylaxis during infancy and asthma diagnosis at 4.5-6 years. Using standard statistical adjustment methods, our results suggest that we were unable to overcome confounding by indication with the highest risk children having the highest adherence to RSV prophylaxis. For example, we found increased asthma in children with CLD who were most adherent to RSV immunoprophylaxis, but these infants also had the most severe neonatal course, the highest prevalence of RSV LRTI, and the highest prevalence of developing asthma. The results obtained in PS-matched analysis in preterm infants provide insights into what the protective effect size might be across gestational ages to inform future prospective and intervention studies. Our findings support the need for larger studies to overcome potential sample size limitations, prospective cohorts with more precise measurement of exposure data, continued methods development to overcome bias in observational data, and long-term follow-up of respiratory outcomes in ongoing vaccine trials should these vaccines prove to be effective.

Acknowledgements: The authors are indebted to the Tennessee Bureau of TennCare of the Department of Finance and Administration, and the Tennessee Department of Health, Office of Policy, Planning & Assessment, for providing the data.

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Table 1: Infant and Maternal Characteristics of the PRIMA* Cohort, by Adherence to RSV Immunoprophylaxis, Births 1996-2003

Characteristic	**No Receipt** (N=2344)	**> 0 to <70 Adherence** (N=1966)	**≥70% Adherence** (N=2256)	**All Eligible** (N=6571)
Eligibility Group (N=6566) (n, %)				
CLD†	146 (6)	181 (9)	324 (14)	651 (10)
<29 week EGA	759 (32)	645 (33)	746 (33)	2150 (33)
29 to <32 week EGA	1327 (57)	807 (41)	1014 (45)	3148 (48)
Other Eligible Group	112 (5)	333 (17)	172 (8)	617 (9)
Estimated gestational age, wks Median (IQR)	30 [28, 31]	30 [28, 31]	29 [27, 31]	30 [28, 31]
Birth Weight, grams Median (IQR)	1510 [1074, 2438]]	1531 [1049, 2523]	1179 [879, 1560]	1365 [992-2070]
Small for gestational age (<5th %) (n, %)	105 (4)	106 (5)	172 (8)	383 (6)
Infant Sex (n, %)				
Male	1244 (53)	1035 (53)	1205 (53)	3486 (53)
Female	1100 (47)	931 (47)	1051 (47)	3085 (47)
Chronic lung disease (n, %)	518 (22)	501 (25)	1010 (45)	2030 (31)
Birth length of stay, days Median, IQR	31 [9, 38]	30 [6, 58]	50 [30, 75]	38 [14,65]
Maternal Race (n, %)				
White	1082 (46)	948 (48)	1057 (47)	3087 (47)
Black	987 (42)	920 (47)	835 (37)	2743 (42)
Latino	121 (5)	52 (3)	175 (8)	349 (3)
Asian	92 (4)	21 (1)	102 (5)	215 (3)
Other	62 (3)	23 (1)	87 (4)	175(3)
Maternal smoking (n, %)	614 (26%)	710 (36%)	571 (25%)	1898 (29)
Bronchiolitis in first year of life (n, %)				
None	1672 (71)	1354 (69)	1551 (69)	4581 (70)
Clinic	294 (13)	186 (9)	281 (12)	762 (12)
ED	150 (6)	123 (6)	131 (6)	404 (6)
Hospitalization	228 (10)	303 (15)	293 (13)	824 (13)
Early childhood asthma n, %	441 (19)	426 (22)	630 (28)	1498 (23)

* Prevention of RSV: Impact on Morbidity and Asthma

[†]Inclusion in CLD eligibility group required diagnosis of CLD and prescription for medication for CLD (bronchodilator, corticosteroid, diuretics) within 6 months of RSV season. Therefore there are children with CLD who did not meet this requirement and are included in other groups.

Table 2: Percent and Adjusted Odds Ratios for Asthma, by Adherence to RSV Immunoprophylaxis Recommendations among Children in PRIMA,* Births 1996-2003

Palivizumab Adherence	(n, %asthma)	Multivariable Model† Odds Ratio (95% CI)	Propensity Score Adjusted†† Odds Ratio (95% CI)
All Eligibility groups	**N=6566**		
No receipt	441 (19)	Reference	Reference
<70%	426 (22)	1.06 (0.89-1.26)	0.93 (0.78-1.10)
≥70%	630 (28)	1.13 (0.95-1.35)	1.17 (0.98-1.39)
CLD	**N=651**		
No receipt	52 (36)	Reference	Reference
<70%	78 (43)	1.28 (0.78-2.09)	1.30 (0.80-2.11)
≥70%	165 (51)	1.50 (0.90-2.50)	1.45 (0.86-2.42)
EGA <29 week	**N=2150**		
No receipt	142 (19)	Reference	Reference
<70%	139 (22)	1.04 (0.78-1.39)	0.93 (0.69-1.24)
≥70%	213 (29)	1.21 (0.88-1.67)	1.35 (0.98-1.86)
EGA 29 to <32 week	**N=3148**		
No receipt	231 (17)	Reference	Reference
<70%	152 (19)	1.03 (0.79-1.34)	0.91 (0.70-1.19)
≥70%	221 (22)	1.05(0.81-1.36)	1.02 (0.79-1.34)
Other risk factors	**N=617**		
No receipt	16 (14)	Reference	Reference
<70%	57 (17)	1.15 (0.50-2.66)	1.30 (0.44-3.88)
≥70%	31 (18)	0.91 (0.37-2.26)	1.28 (0.40-4.16)

* **P**revention of **R**SV: **I**mpact on **M**orbidity and **A**sthma

†Adjusted for infant gender, EGA, birth weight, maternal race, maternal age, education, gravidity status, maternal smoking status, number of siblings, EGA+infant birth hospital LOS, bronchiolitis diagnosis during infancy, season of birth, year of infant birth, and site (TC or KP).

††Propensity score derived with the variables: infant gender, EGA, birth weight, maternal race, maternal age, education, gravidity status, maternal smoking status, number of siblings, EGA+infant birth hospital LOS, CLD diagnosis, season of birth, year of infant birth, and site (TC or KP). Propensity score was included as a covariate in the model.

Table 3: Propensity Score Matched Odds Ratios* for Asthma among Subset With Highest and Lowest Immunoprophylaxis among Children in PRIMA,* Births 1996-2003

RSV immunoprophylaxis Adherence	Odds ratio (95% CI) Method : 1:1 with replacement caliper .25
Propensity score matched: ≥70% versus >0, ≤20	
All Eligibility groups	0.62 (0.50-0.78)
CLD	1.76 (1.41-2.20)
EGA <29 week	0.36 (0.13-0.97)
EGA 29 to <32 week	0.63 (0.42-0.93)
Other risk factors	0.77 (0.44-1.33)

* **P**revention of **R**SV: **I**mpact on **M**orbidity and **A**sthma

†Propensity score derived with the variables: infant gender, gestational age, birth weight, SGA, CLD, maternal age, maternal race, education, gravidity status, maternal smoking status, siblings, EGA+infant LOS, RSV birth season, year of infant birth, and site (TC or KP) and CLD presence if all eligible or EGA <29, or EGA 29 to 32. Conditional logistic regression with robust standard errors estimates were used to account for the matched design correlated data.

Online repository: Detailed Methods

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, Vanderbilt University Medical Center, and representatives of the Tennessee Department of Health, and the Bureau of TennCare.[1] We conducted a retrospective cohort investigation of children enrolled in the ***P**revention of **R**SV: **I**mpact on **M**orbidity and **A**sthma* (PRIMA) cohort who were at increased risk for severe RSV and eligible to receive RSV immunoprophylaxis during infancy. The PRIMA cohort is composed of two large population-based birth cohorts followed through age six years from KPNC and Tennessee Medicaid (TennCare).[1] 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.[1] For KPNC, data were obtained from linked administrative and clinical databases, the electronic medical record, and California vital records files as previously described.[1] In 1994, TennCare replaced the federal Medicaid program, as a state-based managed health care program that covered Medicaid-eligible individuals and the uninsured; approximately 50% of infants in Tennessee are covered by TennCare.[1-3] For the TennCare population, all data were obtained from linked TennCare administrative files and Tennessee vital records files as previously described.[1;4-6]

Eligibility to receive RSV immunoprophylaxis. Children eligible for study inclusion were continuously enrolled in either KPNC or TennCare during their first year and between ages 4.5-6

years. Continuous enrollment was defined as no more than 90 days of non-enrollment during the first year of life and no more than 60 days of non-enrollment between 4.5-6 years.[1] Eligibility for receipt of RSV immunoprophylaxis was determined according to AAP recommendations in place during the study period:.[7-9] including 1) infants < 2 years of age with CLD who required medical therapy within 6 months of RSV season, 2) infants born at 28 weeks estimated gestation age (EGA) during their first RSV season, 3) infants born at 29-32 weeks EGA and particularly less than 6 months of age at the start of RSV season, and 4) infants who were born between 32-35 weeks EGA, were less than 6 months at the start of RSV season, and had 2 or more risk factors (attended child care, had school-aged siblings, had exposure to environmental air pollutants, had congenital abnormalities of the airways, or had severe neuromuscular disease."[7;8] As previously described, for this current study eligible children were classified into 4 hierarchical, mutually exclusive groups: 1) CLD: Chronic lung diseases (CLD) with prescription filled for CLD medication within 6 months of RSV season 2) Prematurity <29: EGA less than 29 weeks 3) Prematurity <32: EGA < 32 weeks and 4) Other Eligible: 32 to < 35 weeks EGA, less than 6 months of age at RSV season with both maternal smoking and an older sibling or ICD-9 diagnoses of cyanotic or hemodynamically significant congenital heart disease (CHD), neurologic condition, or congenital anomaly of airway.[1;7;10] The start of RSV season was defined as November 1st. Children with CLD who did not require medication were categorized by EGA.

Main Predictor: % 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.[1] 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.[1] We calculated the percent receipt of recommended doses (adherence) by dividing the number of doses received by number of recommended doses, and used this value as continuous or categorized for comparison of different levels of adherence by type of analysis.[1]

Outcome of early childhood asthma. We determined diagnoses of asthma between 4.5-6 years to allow a window for diagnosis and to exclude potential "transient early wheezers."[3;11] We defined asthma using a validated algorithm that incorporates asthma-specific healthcare encounters and medication claims using a modified HEDIS definition.[3;12;13] 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 beta-agonist within a 12 month period or a prescription fill for other asthma medications (including inhaled corticosteroids and long-acting beta 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 (gender, EGA, birth weight) and maternal demographics and characteristics (race, education, smoking status during pregnancy, gravidity status, number of previous live births). Small for gestational age (SGA), $<5^{th}$ percentile, was determined using standard methods.[14] Infant birth hospitalization length of stay (LOS) and healthcare visits for bronchiolitis were identified using administrative data.[1]

Statistical Analyses. The main outcome variable was asthma, defined as a dichotomous variable (Asthma present vs. No), ascertained between 4.5-6 years. We have demonstrated that prematurity and SGA are associated with higher adherence to RSV immunoprophylaxis in this cohort,[1] thus, a priori we decided to employ 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-matched analyses. We examined the association between the asthma outcome and the adherence predictor included as a flexible smooth parameter using cubic spline regression (2 degrees of freedom with 3 knots) in multivariable analyses and did not detect non-linearity (see Figure E1 in the online Repository). In univariate analysis, we compared the proportion of children with asthma by categories defining the degree of adherence using Pearson's chi-square statistics. 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, <70% adherence, and ≥70% adherence. We selected ≥70% as estimation of a fairly high degree of adherence in the absence of a widely recognized metric for immunoprophylaxis.[1] We classified % adherence into 3 levels, including no receipt, as although individuals with and without receipt of immunoprophylaxis varied regarding medical complexity, limiting the analyses to only individuals with receipt did not change the results (data not shown). For PS-matched analyses, the subset of children with extremes of RSV immunoprophylaxis adherence were included..[15] Covariates in the multivariable models included infant gender, EGA, EGA plus birth hospital LOS, birth weight, bronchiolitis diagnosis, season of birth (RSV season: October-March vs. non-RSV season: April-September), birth year, number of living siblings, maternal race, age,

education, gravidity, smoking during pregnancy, and site. For TennCare, when birth hospital LOS was missing, it was imputed as previously described.[1]

Each regression adjustment method (multivariable logistic regression, propensity score adjusted, and propensity score matched models) was conducted in the all RSV immunoprophylaxis eligible cohort and in each subgroup based on eligibility criteria (CLD, Prematurity <29, Prematurity <32, and Other Eligible). Adjusted odds ratios (AORs) for asthma were determined by adherence to AAP RSV immunoprophylaxis recommendations, categorized as no receipt, <70%, or ≥70% adherence, in the conventional multivariable and PS-adjusted models. Model fits (for conventional logistic regression methods) were assessed using the goodness of fit test (Cessie–van Houwelingen–Copas–Hosmer) and there were no statistically significant evidence of lack of fit in our logistic regression models. *Propensity score adjustment models*: PS was derived using a proportional odds ordinal logistic regression model for treatment (RSV immunoprophylaxis) with three level categories (no receipt, <70% adherence, and ≥70% adherence) and included as a covariate in the propensity score adjustment model.[16] Following derivation of the PS, in adjustment models, restricted cubic splines were used to allow for non-linear adjustment between PS and outcome. *Propensity score-matched treatment groups*: We derived the PS for matched analyses using binary logistic regression with high and low ends of receipt, including ≥70% and > 0 to ≤20% adherence.[1] The PS-matched model included 1:1 matching with replacement[15-17] based on the PS to assess the association of % adherence with recommended number of doses of RSV immunoprophylaxis in infancy and subsequent asthma. In the matched analysis, conditional logistic regression and robust sandwich error estimates were used to account for the clustered data. The significance level for all analyses was $p < 0.05$.

To assess the impact of missing covariate data, we conducted conventional multivariable adjustment models using multiple imputation of missing variables. Since the results of these analyses remained unchanged, we present the complete case analyses. Overall, less than 2% of children were excluded from multivariable analyses due to missing/Unknown data. Analyses were conducted using SAS version 9.1 (SAS Institute Cary, NC) and R version 3.0.1(http://www.r-project.org).[18]

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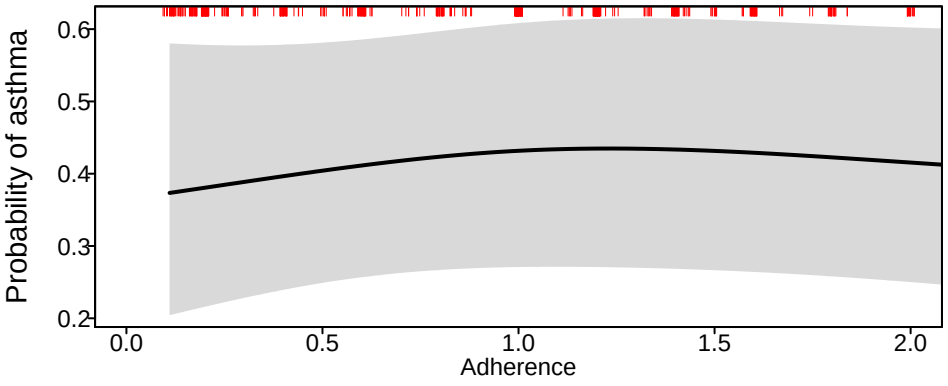
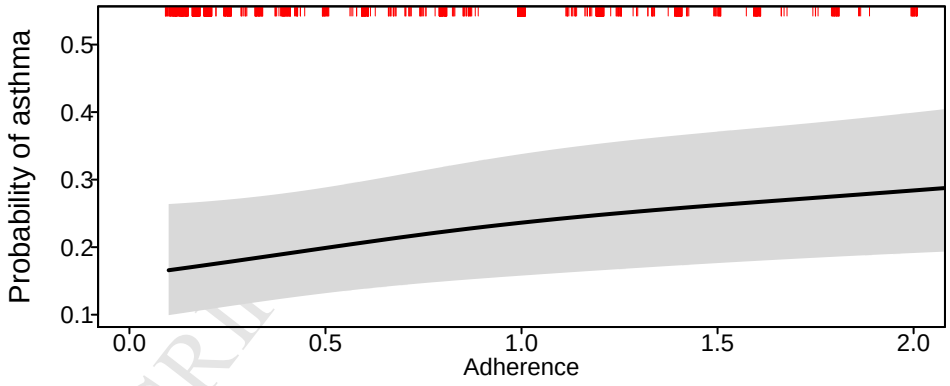
Online repository

Figure E1. Among infants with non-zero adherence, the adjusted association of adherence (black lines) with childhood asthma outcome (predicted probability) was evaluated using restricted cubic splines (2 degrees of freedom with 3 knots) in multivariable logistic regression for combined and risk eligibility groups. Adherence of 1 indicates 100% adherence and x -axes were trimmed to about 200% adherence. The histograms in red on top axis show adherence distribution.

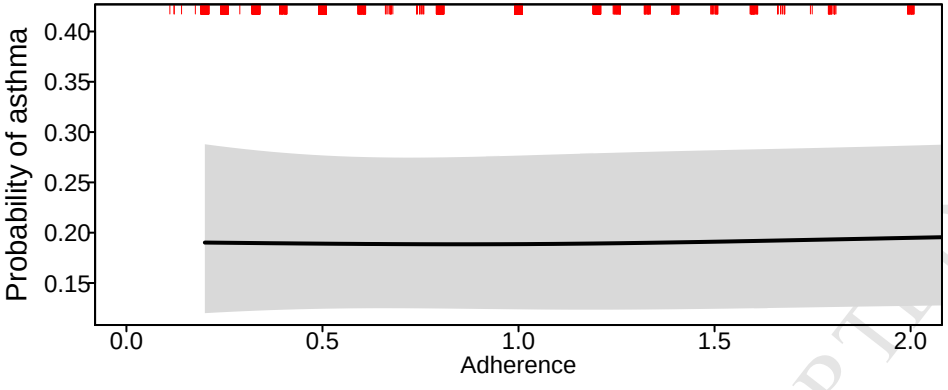
CLD



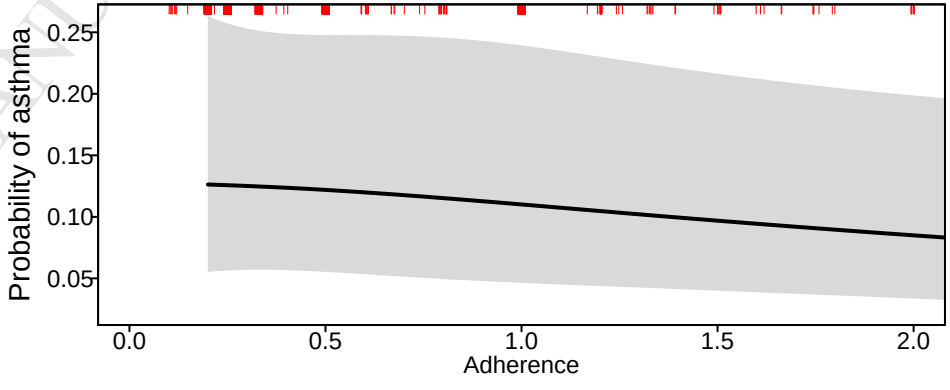
<29 week EGA



29 to <32 week EGA



Other Eligible Group



All Eligibility groups