Palivizumab Immunoprophylaxis Effectiveness in Children With Cystic Fibrosis

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Summary. Background: Evidence on the effectiveness of respiratory syncytial virus (RSV) immunoprophylaxis with palivizumab in children with cystic fibrosis (CF) is lacking. Methods: We utilized Medicaid Extract files from 27 states from 1999 to 2006 linked to the National Cystic Fibrosis Registry to establish a cohort of children 0–2 years with CF diagnosis. Eligible children entered the cohort after CF diagnosis and after RSV season onset, and were followed until season end, second birthday, death, or hospitalizations for reasons other then the study outcome. Two outcomes were examined: hospitalization for RSV infections (RSV-ha), or hospitalization for acute respiratory infections (ARI-ha). Palivizumab exposure was defined based on pharmacy or procedure claims as current (claim date plus 30 days), former (day 31–60 after a claim), and no exposure (days before the first or >60 days after any claim). Both outcomes were examined in a Cox regression model, adjusting for RSV risk factors and CF severity via exposure propensity score. Results: The matched cohort included 1,974 infants (2,875 infant seasons), who experienced 32 RSV-ha and 212 ARI-ha (3.9 and 26.2/1,000 season months, respectively). Compared to periods of no use, the adjusted hazard ratio for current use was 0.57 (95% confidence interval [CI]: 0.20–1.60) for RSV-related hospitalization and 0.85 (95% CI: 0.59–1.21) for ARI-related hospitalization. Each month of increasing age reduced the ARI-ha by 5.8%. Conclusion: RSV hospitalization incidence was low suggesting either little contribution of the virus to respiratory infections in patients with CF or lack of RSV testing. Unadjusted and adjusted RSV-hospitalization incidence rates suggested potentially positive effects of palivizumab, but results were inconclusive due to small event rates. Hospitalizations for acute respiratory illness with possible RSV contribution showed no association with palivizumab use, suggesting limited overall effect of palivizumab. Younger age greatly increased infection risk. **Pediatr Pulmonol. 2013; 48:874–884.** © 2012 Wiley Periodicals, Inc.

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INTRODUCTION

Respiratory syncytial virus (RSV) is the primary cause for lower respiratory tract infections and a significant contributor to morbidity and mortality among infants and young children.[1] While no vaccination is available, prophylaxis with palivizumab (Synagis®, MedImmune) has been approved in 1998 for the prevention of serious lower respiratory tract disease caused by RSV in children at high risk of RSV disease.[2] Due to the high drug cost and lack of cost-effectiveness,[3,4] prophylaxis with palivizumab is only recommended for patients at highest risk for infection during months of high viral activity. Based on the evidence on palivizumab efficacy from clinical trials[5,6] the American Academy of Pediatrics (AAP) recommends routine prophylaxis for children with congenital heart disease (CHD), chronic lung disease, and certain preterm infants.[7]

For patients with cystic fibrosis (CF), a multisystem disease primarily affecting pulmonary function, RSV infection like other viral infections, is implicated in causing respiratory symptoms.[8] Similar to healthy infants, RSV appears to be the predominant viral infection in infants with CF, but limited epidemiologic data exist.[9,10] Two cohort studies of newborns diagnosed with CF report hospitalizations for respiratory disease with RSV involvement in 7 out of 80 infants over 2 years of follow-up and 7 out of 48 infants over a mean of 28.8 months of follow-up (range 5–59), respectively.[10,11] Furthermore, one cohort study that followed infants with CF less than 2 years of age for one RSV season found three cases of RSV hospitalization in 30 participants.[9] In comparison, annual RSV hospitalization incidence rates estimated by the Centers for Disease Control and Prevention in the general U.S. population range between 1.3 and 2.6% in children less than 1 year of age.[12,13]

Citing limited evidence for palivizumab efficacy in children with CF, the AAP as well as the European Cystic Fibrosis Society Vaccination Group make no recommendation for the use of palivizumab in infants with CF.[7,14] The Cystic Fibrosis Foundation in the United States recommends that immunoprophylaxis be considered but concurs in the recognition of lack of evidence.[15]

Small CF prevalence imposes sample size challenges, resulting to our knowledge in only four controlled studies on palivizumab effectiveness. A systematic Cochrane review[16] detected one randomized controlled trial, which included 186 CF children from 40 centers in the USA who were randomized to receive palivizumab or placebo over five months of one RSV season.[17] Only one participant (1.1%) in each group was hospitalized due to RSV infection, leaving the study inconclusive. A retrospective cohort study evaluating 75 children with CF had similar challenges with sample size with RSV hospitalizations in 3 out of 35 palivizumab recipients and 7 out of 40 non-recipients.[18] Results of a survey ascertaining utilization pattern of palivizumab in CF reported that 14 out of 143 infants with CF received palivizumab across responding CF centers.[19] One of the palivizumab users versus 15 of the 129 non-users had been hospitalized due to RSV. Finally, one study[20] compared 91 CF infants receiving palivizumab in the Palivizumab Outcomes Registry with two historical cohorts.[10,11] With none of the prophylaxed CF infants hospitalized as a result of RSV, the authors concluded that palivizumab has significantly reduced RSV-caused hospitalizations. Given the potential for selection bias and the small sample size, these conclusions are questionable.

This study attempts to alleviate the small sample size problem by using a population-based CF cohort assembled from Medicaid fee-for-services (FFS) beneficiaries in 27 U.S. states from 1999 to 2006. We aimed to evaluate the effectiveness of palivizumab immunoprophylaxis in 0–2-year-old patients with CF in clinical practice.

METHODS

Data Sources

The study cohort was assembled from Medicaid Analytic eXtract (MAX) files provided by the Centers for Medicare and Medicaid Services. MAX data include monthly detail on Medicaid eligibility, demographic information, as well as inpatient and outpatient claims with detail on physician diagnosis and performed procedures, and pharmacy claims with details on dispensed prescriptions. We extracted data for 27 states, which were selected based on highest Medicaid FFS enrollment, and highest CF prevalence, between 1999 and 2006, representing approximately 9.9 million children between the ages of 0–2 years.

MAX data were linked to the National Cystic Fibrosis Registry (NCFR) in order to validate a claims-based CF diagnosis. Because patients might enter the registry after their second birthday as result of late CF diagnosis, have no Medicaid insurance, and because some patient identifiers (SSN) were incomplete in the registry, 33% (n = 1,420) of registry patients could be linked to MAX data.

We supplemented death information in MAX by further matching against the Social Security Administration (SSA) Death File. Social security number and date of birth of all children with suggested death according to MAX or SSA were then forwarded to the National Death Index to verify deceased status and obtain cause of death.

The study was approved by the University of Florida institutional review board with waivers of informed

consent and Health Insurance Portability and Accountability Act authorization.

Definition of RSV Season

To address variation in RSV season onset and offset across the 27 study states, we defined RSV seasons empirically. Specifically, we calculated monthly RSV hospitalization incidence as the proportion of 0–2-year-old Medicaid-eligible patients with at least one claim for RSV hospitalization for each state, each year, and each month. Season onset was determined visually as the first month with a spike in RSV incidence. The season was then continued for 5 months or until the monthly incidence dropped below 0.1%, whichever was longer. Since incidence rates vary even within the core season and across states, the season months were further classified into RSV risk categories as low (incidence of 0.1–0.33%), medium (0.33–0.67%), and high (>0.67%). The median monthly RSV incidence rates across all seasons and states were 0.24% or 2.4 RSV hospitalizations in 1,000 patient months.

Study Population

Based on validation results within the MAX/NCFR matched subsample, we required presence of at least two in- or out-patient CF-related claims with diagnoses (ICD9-CM 277.0x) for study inclusion. Patients linked to the registry or who were born in the states with mandatory newborn screening were only required to have at least one CF diagnosis claim.

Patients entered the cohort after the date of the second CF claim or first registry encounter date, whichever came first, after state-specific season onset and after they had spent at least 30 days in ambulatory care, whichever came last (cohort entry date). In order to ascertain presence of RSV risk factors prior to study entry, we also required patients to have at least 2 months of continuous eligibility prior to cohort entry. Patients with palivizumab exposure during the month preceding cohort entry were excluded. We censored patients at the end of the RSV season, when they turned 2 years old, when they lost Medicaid eligibility, died, or when they were admitted to the hospital for any reason other than the study endpoints, whichever came first. This latter censoring criterion was introduced to assure complete information on palivizumab exposure, as drug utilization detail is not available from inpatient claims data. Patients could re-enter the study for a second season if they had not reached their second birthday and otherwise met all study inclusion criteria.

Since the initiation of palivizumab could be delayed after season onset and might be triggered by acute respiratory symptoms, it was important to capture the period immediately preceding palivizumab initiation to adjust for channeling of palivizumab to those children at greatest RSV infection risk. To accomplish this, the start of the follow-up period for palivizumab users was set to coincide with palivizumab initiation (index date). Specifically, each user was matched with four randomly selected non-users with the same cohort entry month. The index dates (start of follow-up) for these non-users were set to the midpoint of the index month of the corresponding user.

Study Endpoints

The primary study endpoint was hospitalization for RSV-related pneumonia (ICD9-CM code 480.1) or RSV bronchiolitis (466.11) at any diagnosis field, or other admissions with RSV infections (079.6) as secondary diagnosis provided it was accompanied by a principal diagnosis code for upper respiratory tract infections (465.xx), acute bronchitis or bronchiolitis (466.xx), infectious pneumonia (480.xx–483.xx, 485, 486), influenza (487, 487.0, 487.1), other respiratory disease (519.8), or CF (277.0, 277.00, 277.02, 277.09).

We introduced a secondary endpoint based on a broader definition of acute respiratory illness (ARI)-related hospitalizations with the expectation that clinical practice may not always test for RSV. This endpoint included all RSV-related hospitalizations as defined above or a diagnosis of upper respiratory tract infections (465.xx), acute bronchitis or bronchiolitis (466–466.11), unspecified pneumonia (480, 480.9, 485, 486) or CF pulmonary exacerbations (277.02) at any diagnosis field.

Palivizumab Exposure

Exposure to palivizumab was defined based on pharmacy claims and/or outpatient claims for palivizumab administration (see Appendix A). All pharmacy claims had to be concurrent with a physician office visit claim for any reason within 10 days before or after the palivizumab claim to assure administration. For pharmacy claims the date of palivizumab administration was defined as the physician office visit date closest to the pharmacy claim. Since patients may not follow the monthly recommended dosing schedule resulting in intermittent exposure to palivizumab, a time-dependent exposure variable was created for the outcome models to reflect real-time exposure status. The active period for a palivizumab dose was set to 30 days according to the manufacturer's dosing recommendation. Accordingly, current use included 0–30 days after a palivizumab claim, former use 31–60 days after a palivizumab claim, and no use included all days before the first and more than 60 days after a palivizumab claim. Any subsequent palivizumab claim was set to override former or no use.
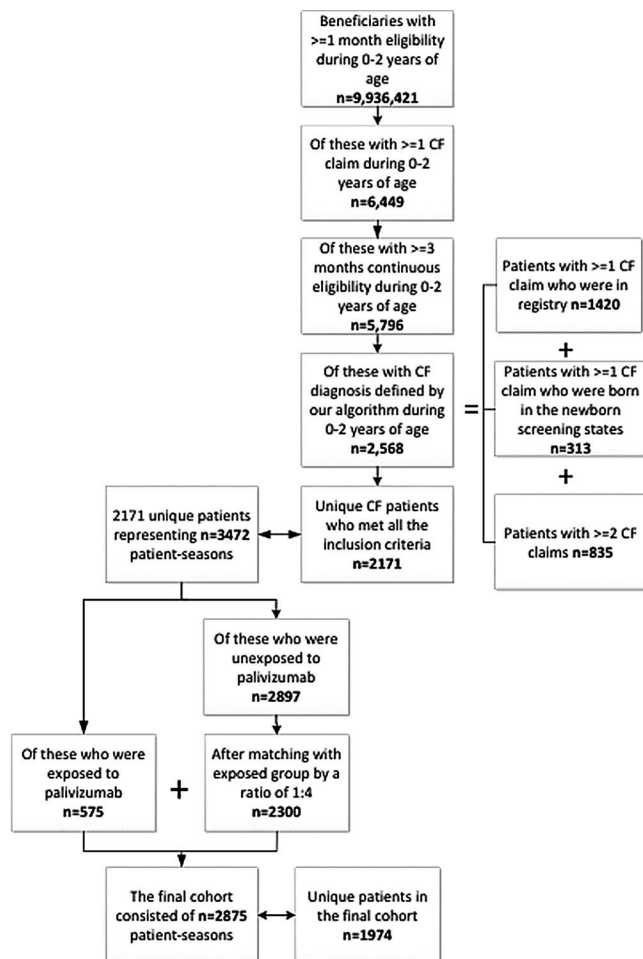
Fig. 1. Flow chart for deriving the final CF cohort.

Propensity Score Development

We utilized exposure propensity scores derived from a logistic regression analysis, which modeled the likelihood of palivizumab exposure defined as having at least one dose of palivizumab during the follow-up period. Variables in the logistic regression model included demographic characteristics, calendar year and state of residence at index date, presence in CF registry, and newborn screening status. Additional variables that were extracted from the 2 months time period prior to index date included: presence of respiratory symptoms indicative of pulmonary illness, diagnoses- and treatment-defined measures of CF severity, and established RSV risk factors such as CHD or bronchopulmonary dysplasia (Appendix A). After fitting the model, the predicted probability of palivizumab use (propensity score) was calculated for each patient season. The propensity scores were stratified into quintiles and included in the outcome models.

In addition to the propensity score quintiles, we included the following time-dependent variables in the outcome models: age as continuous variable (updated for every day of follow-up) and monthly RSV risk categories as defined above. The final outcome models compared the risks for RSV-related hospitalizations and ARI-related hospitalizations among the exposure groups using time-dependent Cox regression. Adjusted incidence rates for palivizumab use periods were estimated by multiplying the unadjusted incidence rates during no exposure with the adjusted hazard ratio (HR). Data management and analysis were conducted using SAS Version 9.2 (SAS Institute, Cary, NC).

RESULTS

We identified 2,171 unique, 0–2 years old patients with CF (3,472 patient seasons) who met the study inclusion criteria (Fig. 1). After matching palivizumab users to non-users in a ratio of 1:4 to align index dates within the RSV season, the final cohort used in the analysis consisted of 1,974 unique patients representing 2,875 patient seasons. The mean age at CF diagnosis was 4.4 months and the mean age at first palivizumab exposure was 1.04 years, respectively. The predominant reasons for censoring were end of RSV season (n = 1,293), age (n = 652) and loss of Medicaid eligibility (n = 443). A total of 450 (337) patient seasons were censored for non-RSV-related (non-ARI-related) hospitalizations and 5 because of death. About one-third of these hospitalizations were attributed to CF.

The characteristics of the patient seasons when palivizumab was administered (exposed) and when not (unexposed) are shown in Table 1. There were higher proportions of in-registry patients and patients diagnosed via newborn screening in the exposed group than in the unexposed group. We also observed that the exposed group had higher proportions of patients with respiratory symptoms indicative of pulmonary decline, and increased CF severity, as well as respective treatment. While there was considerable overlap in the lower range of the propensity score, higher scores were disproportionally attributed to the exposed group, suggesting a correlation between disease severity and propensity for immunoprophylaxis (Appendix B, Fig. B1).

We identified 32 RSV-related hospitalizations and 212 ARI-related hospitalizations in a total of 2,875 patient seasons. With 8,106 follow-up months, the incidence rates for RSV-related and ARI-related hospitalizations were 3.9/1,000 season months and 26.2/1,000 season months, respectively.

When adjusted for the propensity score quintiles, season months RSV risk category, and patient age, the HR for RSV hospitalizations for the comparison of current palivizumab use versus no use was 0.57 (95% confidence

TABLE 1— Cohort Characteristics by Exposure Status

Characteristics	Patient seasons with palivizumab use (n = 575)	Patient seasons without palivizumab use (n = 2,300)
Race, n (%)		
Black	38 (6.61)	227 (9.87)
Hispanic	56 (9.74)	209 (9.09)
Other	97 (16.87)	308 (13.39)
White	384 (66.78)	1,556 (67.65)
Female, n (%)	273 (47.48)	1,088 (47.3)
Year of index date, n (%)		
1999	9 (1.57)	238 (10.35)
2000	44 (7.65)	312 (13.57)
2001	60 (10.43)	350 (15.22)
2002	74 (12.87)	280 (12.17)
2003	99 (17.22)	300 (13.04)
2004	106 (18.43)	268 (11.65)
2005	113 (19.65)	279 (12.13)
2006	70 (12.17)	273 (11.87)
State, n (%)		
Alabama	1 (0.17)	7 (0.3)
Arkansas	21 (3.65)	71 (3.09)
Florida	52 (9.04)	209 (9.09)
Georgia	22 (3.83)	138 (6)
Iowa	12 (2.09)	31 (1.35)
Idaho	18 (3.13)	33 (1.43)
Illinois	33 (5.74)	130 (5.65)
Indiana	5 (0.87)	93 (4.04)
Kansas	7 (1.22)	33 (1.43)
Louisiana	29 (5.04)	68 (2.96)
Massachusetts	16 (2.78)	124 (5.39)
Minnesota	9 (1.57)	42 (1.83)
Missouri	19 (3.3)	56 (2.43)
Mississippi	6 (1.04)	74 (3.22)
North Carolina	32 (5.57)	129 (5.61)
Nebraska	5 (0.87)	32 (1.39)
New Hampshire	3 (0.52)	17 (0.74)
New Jersey	4 (0.7)	14 (0.61)
New York	72 (12.52)	249 (10.83)
Ohio	53 (9.22)	188 (8.17)
Pennsylvania	28 (4.87)	125 (5.43)
South Carolina	17 (2.96)	80 (3.48)
Tennessee	32 (5.57)	34 (1.48)
Texas	53 (9.22)	190 (8.26)
Vermont	6 (1.04)	29 (1.26)
Wisconsin	8 (1.39)	79 (3.43)
West Virginia	12 (2.09)	25 (1.09)
Presence in registry, n (%)	392 (68.17)	1,311 (57)
Newborn screening status, n (%)	255 (44.35)	823 (35.78)
Disease history, n (%)		
Failure to thrive	102 (17.74)	170 (7.39)
Pancreatic insufficiency	73 (12.7)	130 (5.65)
Other non-specified lung disease	20 (3.48)	27 (1.17)
CHD	8 (1.39)	12 (0.52)
Severe respiratory problems	184 (32)	554 (24.09)
Bronchopulmonary dysplasia	58 (10.09)	22 (0.96)
Medication history, n (%)		
Pancreatic enzymes	309 (53.74)	874 (38)
Tobramycin	97 (16.86)	187 (8.13)

(*Continued*)

TABLE 1— (*Continued*)

Characteristics	Patient seasons with palivizumab use (n = 575)	Patient seasons without palivizumab use (n = 2,300)
DNAse	150 (26.08)	315 (13.69)
N-acetylcysteine	8 (1.39)	22 (0.95)
Inhaled/oral corticosteroids	198 (34.43)	535 (23.26)
Oxygen	33 (5.74)	37 (1.61)
Inhaled bronchodilators	338 (58.78)	884 (38.43)
Leukotriene antegonists or cromolyn	34 (5.91)	147 (6.39)
Antibiotics (macrolides, ampicillins, cephalosporines, fluoroquinolones, sulfonamides)	319 (55.47)	1,073 (46.65)
Influenza vaccination	115 (20.00)	228 (9.91)
Acute respiratory problems (within 10 days prior to index date), n (%)	87 (15.13)	172 (7.48)

interval [CI]: 0.20–1.60). Using ARI-related hospitalizations as endpoint, the adjusted HR was 0.85 (95% CI: 0.59–1.21; Table 2). Noteworthy is the significant risk reduction of 5.5% with each month of increasing age. Adjusted incidence rates for RSV-hospitalizations were 2.4 (95% CI: 0.8–6.6) per 1,000 season months for palivizumab use (compared to 4.1, 95% CI: 2.8–6.0) for non-use (Table 3). Rates for ARI-hospitalizations were 20.2 (14.2–28.7) versus 23.8 (20.4–27.8), respectively.

DISCUSSION

To our knowledge this is the first large population-based study that has investigated the effectiveness of palivizumab in patients with CF. Despite its size, the observed low seasonal incidence of RSV-specific hospitalizations limited our ability to make inferences about palivizumab effectiveness. To place the observed incidence rates into context, we found an age-adjusted incidence rate of 2.1 RSV hospitalizations per 1,000 season months (1.5% per season assuming 5 season months) across all 0–2-year-old children, compared to 4.5 RSV hospitalizations in children with diagnosed CF (2.3% per season), and 9.7 for children who met the palivizumab indication for CHD (11.4 when adjusted for palivizumab exposure using the clinical trial efficacy estimate, equating to 5.7% per season). Published RSV hospitalization incidence estimates from prospective CF cohorts range from 8.8% per 2-year follow-up (approximately 4.4% per season)[10] to 10% per season (estimated based on three events).[9] The key palivizumab efficacy trial reported incidence rates of 16 and 26 per 1,000 season

TABLE 2—Multivariate Analysis for RSV-Related and ARI-Related Hospitalizations

	RSV-related hospitalizations		ARI-related hospitalizations	
	HR	95% Confidence limits	HR	95% Confidence limits
Current vs. no palivizumab use	0.57	0.20–1.60	0.85	0.60–1.21
Age (month)	0.94	0.88–0.99	0.95	0.92–0.97
Low season category		Reference		Reference
Medium season category	5.2	2.41–10.97	1.30	0.93–1.80
High season category	7.0	1.54–31.96	1.62	0.66–3.96
Propensity score quintile 1		Reference		Reference
Propensity score quintile 2	0.49	0.13–1.83	1.37	0.80–2.34
Propensity score quintile 3	0.81	0.26–2.50	1.73	1.04–2.86
Propensity score quintile 4	1.44	0.53–3.90	1.95	1.18–3.21
Propensity score quintile 5	1.74	0.61–5.00	3.73	2.30–6.04

months for the placebo group with prematurity or bronchopulmonary dysplasia, much higher than any report in CF patients.[5] Of note, the protocol of the clinical trial and the prospective CF cohorts assured testing for RSV when children were hospitalized with respiratory problems, while standard clinical practice may not always test for RSV and thus assign non-pathogen-specific diagnoses, resulting in lower RSV incidence rates. In addition, the use of low sensitivity RSV antigen tests in clinical practice, if not followed up with a high sensitivity viral screen, may also result in lower RSV incidence rates.

It is plausible that the severity and clinical importance of bacterial infections in CF patients may have altered the perceived need for viral testing, resulting in the surprisingly low incidence of diagnosed RSV infections. A previous retrospective analysis[18] observed the absence of data regarding the contribution of RSV and other respiratory viruses in a medical records database of CF patients. It is also possible that knowledge of CF diagnosis resulted in a CF-centered principal diagnosis code in the Medicaid claim with no further consideration to assign pathogen-specific ICD9-CM codes because of little effect on capitated reimbursement amounts.

TABLE 3—Incidence Rates for RSV-Related and ARI-Related Hospitalizations

	Unadjusted rate (per 1,000 season months)	Adjusted rate (per 1,000 season months)
RSV-related hospitalization		
No use	4.1 (2.8–6.0)	
Current use	2.9 (1.2–6.8)	2.4 (0.8–6.6)
ARI-related hospitalization		
No use	23.8 (20.4–27.8)	
Current use	32.8 (25.4–42.3)	20.2 (14.2–28.7)

On the other hand, some have hypothesized that the incidence of RSV hospitalization in children with CF does not differ from the normal population,[11] presumably due to usually normal lung function at birth.[21] A recent virologic study of 20 young children with CF with age-matched healthy controls reported that seasonal frequencies of respiratory illnesses and occurrences of respiratory viruses were similar, with picornaviruses and coronaviruses being the most frequent.[22] Another review of 11 studies that identified pathogens in CF children with pulmonary exacerbations reports that RSV was present in 0–58% (median 20%) of all cases, reflecting similar rates as found in healthy children.[23]

To circumvent the misclassification of outcomes, we employed a broader definition of acute respiratory illness (ARI) as secondary study endpoint. This included serious hospitalizations associated with acute respiratory illness due to RSV, non-specified, or bacterial pathogens to improve our ability to capture a potential contribution of RSV to the overall acute respiratory illness in CF and thus, estimate the effect of palivizumab prophylaxis indirectly.

Utilizing the strictly RSV-related outcome resulted in an incidence rate too small for valid statistical inferences, although the point estimate suggested a trend towards palivizumab effectiveness. Of note, in trying to overcome the sample size problem in CF research, our study employed a population-based sampling frame resulting in a cohort more than 10 times larger than previous studies. The analysis of ARI-related outcomes suggested no or little effect of palivizumab immunoprophylaxis. Of note, the study was powered sufficiently to allow detection of a 55% reduction in ARI-hospitalization incidence, similar to palivizumab efficacy estimates in clinical trials of other high-risk patients (alpha = 5%, power = 80%). One could argue that little effect might be expected considering the composite nature of our

endpoint, including infections that would be unaffected by palivizumab prophylaxis. Interestingly, the unadjusted incidence estimates for RSV-hospitalization for palivizumab exposure were smaller than those for unexposed periods, while this relationship was reversed for ARI-hospitalizations. Thus, palivizumab users were sicker with respect to a greater propensity for respiratory problems, which, however, did not seem to be true for RSV-hospitalizations, further supporting a potentially beneficial effect of immunoprophylaxis.

This notwithstanding, it is important to note that palivizumab did not seem to have a noticeable effect on the occurrence of hospitalizations due to respiratory infections in young patients with CF as a whole, suggesting the contribution of RSV (whether diagnosed or not diagnosed) is either subtle or the effectiveness of palivizumab in reducing RSV infections is only moderate.

Since immunoprophylaxis is targeted to prevent RSV-related hospitalizations, we did not consider less severe forms of RSV infections reported at the level of physician office or emergency department visits. While milder forms of RSV infections could improve the number of study endpoints, the propensity to test for RSV in ambulatory practice is even smaller, which would have resulted in an even less specific outcome measure. Furthermore, it is not known what impact less severe RSV infections have on lung health and CF progression and thus hospitalization-related outcomes were preferable.[24]

Although our study did not show a significant reduction in RSV-related hospitalization, previous in-vitro studies[24] demonstrate that in normal healthy lungs, RSV could induce the production of chemokines such as IL-8 by the airway epithelial cells, that may in turn participate in the recruitment of neutrophils and other inflammatory cells known to aggravate pulmonary exacerbations. It should be noted that the lung epithelia in patients with CF are normal at birth and decline over time, which might support the notion that patients with CF in infancy have similar RSV risk than healthy children.[8] Conversely, it has been shown that RSV can serve as a coupling agent between *Pseudomonas aeruginosa* and the lung epithelia suggesting a possible role for the increased risk of early acquisition of *P. aeruginosa* infections in early infancy.[25]

Our study does have one additional important finding. We observed that with increasing age, there was a linear drop in the risk for ARI-related hospitalizations, similar to other epidemiologic reports of respiratory infections in infants and young children.[26] Even though CF progresses with increasing age, these effects are not noticeable during the first 2 years of age resulting in similar age-related infection profiles as found in healthy children. Thus, if immunoprophylaxis is considered, efforts should focus on young infants (<1 year) and early detection of CF.

As with all observational studies, we cannot rule out the possibility of residual confounding. To control for this we developed a propensity score to classify patients according to their probability for exposure, but some clinical risk factors such as pulmonary function data are not available in infants. Our sensitivity analysis, removing patients with pronounced disease severity who received palivizumab preferentially did not alter results suggesting fairly balanced comparisons. We furthermore recognize that some palivizumab doses that were charged to Medicaid might not have been administered and resulted in misclassification of palivizumab use. We tried to alleviate this concern with the requirement to have a physician office visit accompany each pharmacy claim. Finally, even though our study population was assembled from records of almost 10 million infants and young children, our analyses were compromised by small event rates.

CONCLUSION

RSV hospitalization incidence was low suggesting either little contribution of the virus to acute respiratory infection pathogenesis in patients with CF or lack of RSV testing and diagnosis. Unadjusted and adjusted RSV-hospitalization incidence rates suggested potentially positive effects of palivizumab, but results were inconclusive due to small event rates. Hospitalizations for acute respiratory illness with possible RSV contribution showed no or minimal association with palivizumab prophylaxis, suggesting little overall effect of palivizumab. Age greatly affected infection risk with incidence rates for 1–2 year olds reduced to half when compared to 0–1 year old infants.

ACKNOWLEDGMENTS

Appendix A. Operational definitions for study variables

Variables	Operational definitions
Calendar year	Year of index date
Race/ethnicity	White, Hispanic, Black, Other
Congenital heart failure	ICD code group 1 at least one of the following ICD-9 codes at any inpatient Dx field: 745.10, 747.41, 745.0, 745.11, 745.2, 747.42, 745.3, 746.1, 746.7, 745.1, 745.12, 745.19, 746.2, 747.3, 747.4, 747.40, 747.49 (cyanotic heart disease) OR [ICD9 code group 2 at least one of the following ICD-9 codes at any inpatient Dx field: 746.86, 747.11, 747.22, 745.4, 745.5, 745.6, 745.60, 745.61, 745.69, 745.7, 745.8, 745.9, 746.0, 746.00, 746.01, 746.02, 746.09,746.3, 746.4, 746.5, 746.6, 746.8, 746.81, 746.82, 746.83, 746.84, 746.85, 746.87, 746.89, 747.0, 747.1, 747.10, 746.9, 747, 747.2, 747.20, 747.21,747.29, 747.5, 747.6, 747.60, 747.61, 747.62, 747.63, 747.64, 747.69, 747.8, 747.81, 747.82, 747.83, 747.89, 747.9 (acyanic CHD) AND [drugs: at least one of the following CHD medications based on AHFS codes: 243204 ACE-inhibitors 402808 Loop diuretics 402816 Potassium-sparing diuretics 402820 Thiazide diuretic 402824 Thiazide-like diuretic 240408 Cardiotonic Agents (Digoxin) OR Oxygen Procedure Codes: 93.96, E1390, E1392, E1400, E1401, E1402, E1403, E1404, E1405, E1406, E0424, E0431, E0434, E0439, E0441, E0442, E0443, E0444, E0450]]
Presence in the registry	Based on MAX-to-Registry matching
Bronchopulmonary dysplasia	At least one diagnosis for 770.7 in IP or OT file (any diagnosis field) with 2 months pre-index date
Newborn Screening Status	1. DoB falls in state/year with mandatory screening 2. Presence of any of the following codes within 60 days of birth: Outpatient sweat test procedure code: 89230, 82438, 89360 and 82806 Outpatient genetic sequencing procedure code: 83891, 83892, 83900, 83901, 83914, 83909 and 83912 Outpatient CF screening code: V77.6 Outpatient diagnosis for IRT 796.6 Outpatient diagnosis for cystic fibrosis (277.0, 277.00) Patients not eligible for Medicaid within 60 days after birth were designated as not screened
Other disease of the lung	In- or out-patient diagnosis of 518.89 (any diagnosis field) within 2 months before index date
Severe respiratory infections	Hospitalization or office visits for severe respiratory problems (principal or secondary diagnosis field) within 2 months before index date: 465.0, 465.8, 465.9, 466, 466.0, 466.1, 466.11, 466.19, 480, 480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482, 482.0, 482.1, 482.3, 482.30, 482.31, 482.32, 48.39, 482.4, 482.40, 482.41, 482.42, 482.49, 482.8, 482.81, 482.82, 482.83, 482.84, 482.89, 482.9, 483, 483.0, 483.1, 483.8, 484, 484.1, 484.3, 484.5, 484.6, 484.7, 484.8, 485, 486, 487, 487.0, 487.1, 487.8, 488
Acute respiratory illness	Outpatient diagnosis with 10 days prior to index date: 460, 461, 4610, 4611, 4612, 4613, 4618, 4619, 462, 463, 464, 4640, 46400, 46401, 4641, 46410, 46411, 4642, 46420, 46421, 4643, 46430, 46431, 4644, 4645, 46450, 46451, 381.0, or 382.0
Oxygen therapy requirement	Procedure codes: 93.96, E1390, E1392, E1400, E1401, E1402, E1403, E1404, E1405, E1406, E0424, E0431, E0434, E0439, E0441, E0442, E0443, E0444, E0450 within 2 months prior to index date
Failure to thrive	In- or out-patient diagnosis (any field) 783.41, 779.3, 783.3 within 2 months before index date
Use of Pancreatic enzymes	Pharmacy claim with NDC: 00482002006, 59879050501, 54569351102, 54569351101, 00031465063, 10432027702, 10432027701, 54022103303, 54022103302, 54022103301, 17317039705, 17317039704, 17317039701, 10106284001 within 2 months prior to index date
Palivizumab use	Pharmacy claim NDC code 60574411101, 60574411201, 60574411301, 60574411401 and physician office visit claim for any reason within 10 days OR Outpatient procedure codes 90387, C9003, X7439, 1086X, 1095X

Appendix B. Exposure propensity model results

	Odds ratio	95% Confidence interval	
Race			
Black	0.738	0.472	1.153
Hispanic	1.472	0.977	2.219
Other	1.305	0.953	1.786
Gender			
Female	1.007	0.818	1.240
Year of index date			
1999	0.177	0.082	0.381
2000	0.687	0.430	1.098
2001	0.765	0.499	1.174
2002	1.093	0.721	1.657
2003	1.310	0.886	1.936
2004	1.509	1.022	2.226
2005	1.530	1.043	2.243
State			
Alabama	0.313	0.032	3.088
Arkansas	0.677	0.260	1.762
Florida	0.403	0.175	0.930
Georgia	0.226	0.091	0.561
Iowa	0.720	0.251	2.065
Idaho	1.050	0.393	2.802
Illinois	0.422	0.178	1.000
Indiana	0.096	0.029	0.324
Kansas	0.442	0.140	1.392
Louisiana	1.194	0.483	2.954
Massachusetts	0.376	0.145	0.979
Minnesota	0.356	0.115	1.104
Missouri	0.626	0.244	1.609
Mississippi	0.170	0.053	0.549
North Carolina	0.472	0.198	1.127
Nebraska	0.267	0.077	0.932
New Hampshire	0.321	0.070	1.474
New Jersey	0.511	0.120	2.184
New York	0.535	0.236	1.211
Ohio	0.437	0.192	0.994
Pennsylvania	0.346	0.144	0.829
South Carolina	0.273	0.101	0.737
Tennessee	1.495	0.592	3.777
Texas	0.419	0.179	0.982
Vermont	0.461	0.139	1.525
Wisconsin	0.080	0.025	0.260
Presence in registry	1.666	1.290	2.151
History of failure to thrive	1.882	1.373	2.581
History of pancreatic insufficiency	1.359	0.948	1.947
History of oxygen use	1.835	0.946	3.560
Newborn screening status	1.579	1.253	1.991
History of other non-specified lung disease	1.237	0.600	2.551
History of bronchopulmonary dysplasia	12.906	7.087	23.502
History of pancreatic enzyme use	1.405	1.110	1.779
History of inhaled tobramycin use	1.353	0.988	1.851
History of DNAse use	1.335	1.007	1.770
History of N-acetylcysteine (NAC)	1.333	0.484	3.670
History of inhaled bronchodilator use	1.711	1.337	2.190
History of leukotriene, cromolyn use	0.860	0.539	1.371
History of antibiotic use	1.086	0.868	1.359
History of influenza vaccination	2.284	1.707	1.359
History of CHD	2.952	0.926	9.413
History of acute respiratory problems (10 days prior to index date)	1.981	1.385	2.833
History of severe respiratory problems	1.108	0.849	1.445

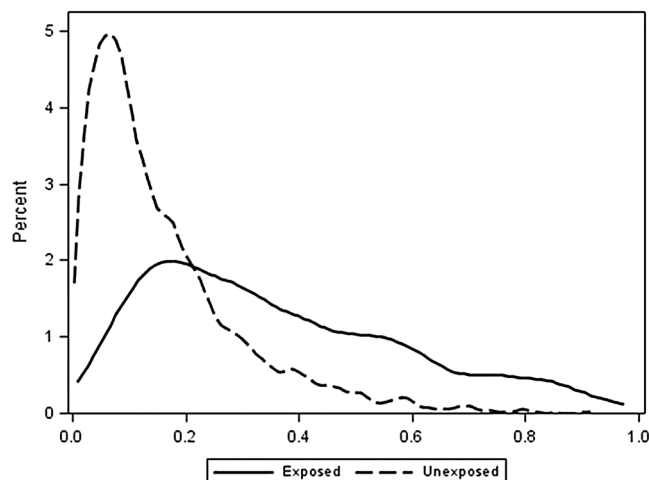The final exposure propensity score model had a c-statistics of 0.785.

Fig. B1. Propensity score distribution for children exposed and unexposed to palivizumab. Propensity scores range from 0 to 1 with 1 being the greatest probability for palivizumab use. The distribution shows good overlap allowing for balanced comparisons of exposed versus unexposed subjects, except at high scores (>0.8). Because exposed and unexposed groups showed only limited overlap in both tails of the propensity score distribution, we performed a sensitivity analysis by excluding patient seasons in the lower (PS < 0.08) and upper (PS > 0.8) tails. Event numbers dropped to 23 RSV-related hospitalizations and 110 ARI-related hospitalizations in a total of 2,037 patient seasons after trimming. Current exposure to palivizumab showed an HR of 0.57 (95% CI: 0.20–1.63) in the updated model for RSV-related hospitalizations and 0.78 (95% CI: 0.48–1.25) in the updated model for ARI-related hospitalizations.

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