PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**: 53–60
Published online 15 September 2011 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2246

ORIGINAL REPORT

Effectiveness of palivizumab prophylaxis in infants and children in Florida

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ABSTRACT

Purpose Palivizumab effectiveness data on respiratory syncytial virus (RSV) infections are limited to trial settings and vary considerably between selected high-risk populations. This study aimed to evaluate effectiveness in a community-based sample.

Methods We conducted a cohort study of children with ≥3 months Florida Medicaid fee-for-service eligibility between 1998 and 2004 who also had matching birth certificates. Children entered the cohort at the beginning of the RSV season, after a minimum of 60 days in ambulatory care, and were followed until the earliest of the following: season end, second birthday, loss of eligibility, hospitalization, or death. Study endpoint was the first RSV-related hospitalization. To evaluate the presence of confounding, a second endpoint, hospitalizations for pneumonia or bronchiolitis secondary to specified bacterial or viral pathogens other than RSV, was used. Palivizumab exposure defined as first use (day 1–30 of first dose), subsequent use (days 1–30 of each subsequent dose), and former use (days 31–60 after any dose if delays or no readministration occurred) was compared with non-use with a Cox regression model, adjusting for confounders.

Results Hazard ratios (HRs) for RSV hospitalizations were 0.89 (95%CI, 0.71–1.12), 0.56 (95%CI, 0.46–0.69), and 0.71 (95%CI, 0.51–0.97) for first, subsequent, and former use, respectively. HRs for hospitalization because of non-RSV infections were 1.31 (95%CI, 1.04–1.65), 1.03 (95%CI, 0.86–1.23), and 1.05 (95%CI, 0.78–1.41), indicating residual confounding for first but not for subsequent and former use.

Conclusion In this community-based study, palivizumab was associated with a reduction in severe RSV infections of a magnitude comparable to the lower clinical trial efficacy estimates. Protection appears to extend beyond the currently recommended monthly dosing schedule. Copyright © 2011 John Wiley & Sons, Ltd.

KEY WORDS—respiratory syncytial virus; cohort studies; infant; palivizumab; prophylaxis

Received 29 April 2011; Revised 2 August 2011; Accepted 2 August 2011

INTRODUCTION

Palivizumab has demonstrated efficacy in clinical trials, with reductions in respiratory syncytial virus (RSV)-related hospital admissions of 39% (children <2 years of age with chronic lung disease),[1] over 45% (children <2 years of age with congenital heart disease),[2] and 78% (premature infants ≤35 weeks gestation and ≤6 months of age at RSV season onset).[1] To date, decreases in mortality have not been demonstrated.[3,4] The major limiting factor to the widespread use of RSV prophylaxis is its high cost, which usually generates expenses of more than $10 000 to immunize one infant through a 6-month season.[5] These cost have resulted in guideline-defined restrictions of prophylaxis to patients at increased risk for infection such as those included in the original efficacy trials or with clinical conditions that might increase RSV infection risk (e.g., human immunodeficiency virus [HIV]).[6,7]

Although clinical trial data offer the most unbiased evidence on expected treatment benefits, their generalizability to real-life settings varies. Specifically, with the demonstrated variation in efficacy across

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populations included in the two available efficacy trials, controlled conditions, and the potential bias toward patients with high disease severity in the efficacy trials, it is unclear what reduction in RSV infections can be expected in populations that received prophylaxis in clinical practice. Effectiveness studies can expand the currently limited information on the clinical benefit of RSV prophylaxis and enhance optimization of palivizumab use.

A limited number of observational studies have attempted to quantify effectiveness in real life. Longitudinal studies have reported reductions in RSV incidence rates following palivizumab approval, but changes in season severity and factors that have improved infection control offer alternative explanations.[8–12] Another study with a single treated cohort compared hospitalization rates with those from the placebo group of a clinical trial, raising concerns about the adequacy of this comparison.[13] Studies furthermore either ignored the impact of gaps in palivizumab prophylaxis or limited their analyses to children who received doses according to the recommended monthly schedule, resulting in limited ability to evaluate the effect of noncompliance. Home administration of palivizumab, which increased the proportion of children with the appropriate number of doses during RSV season from 81 to 88% reduced RSV-associated hospitalizations from 1.2 to 0.4% according to analyses of the 2000–2004 Palivizumab Outcomes Registry, a decrease so dramatic that doubts about the comparability of the two groups are warranted.[14] Whether and to what extent delays in the recommended monthly administration schedule impact protection against the virus are critical knowledge in light of limited pharmacokinetic data and significant immunization cost.[15] In fact, concerns about the impact of non-adherence on cost-effectiveness—besides concerns about unnecessary exposure to pathogens in physician offices—have caused decision makers to consider reimbursement for home administration of palivizumab.[16,17] Questions about the effect of administration delays and the effectiveness of palivizumab in real-life populations, which might not resemble highly selected clinical trial samples, created the impetus for this study.

This population-based study aimed to quantify palivizumab effectiveness in children who received RSV prophylaxis with palivizumab in clinical practice.

METHODS

Study design

We utilized a retrospective cohort design to compare hospitalization rates for RSV infections between children who received and children who did not receive palivizumab. The cohort was established from the Florida Medicaid program, which covers more than half of all children in the state, totaling 1 148 773 during the study period. The dataset provides monthly updated information on eligibility and beneficiary demographics as well as claims data for medications and inpatient and outpatient encounters. We supplemented these data with electronic birth and death certificates linked through social security numbers and dates of birth. This study was approved by the University of Florida and the Florida Department of Health institutional review board with waivers of informed consent and Health Insurance Portability and Accountability Act authorization.

Patients

Infants and children with at least 3 months of continuous eligibility from birth to the Medicaid fee-for-service program between 1998/1999 and 2004/2005 with available birth certificates were included in the analysis. Inclusion in the study did not require the presence of guideline-defined indications for RSV prophylaxis. At least 1 month of eligibility had to occur during the RSV season, defined as October through March, based on Centers for Disease Control and Prevention surveillance data.[18,19] Children entered the study at the beginning of the season and after they had spent a minimum of 60 days in ambulatory care, whichever came last (index date). We used the 60-day ambulatory care period to determine risk factors for RSV as well as the presence of immunoprophylaxis, which is not accessible from inpatient claims data. Infants and children were censored at the earliest of the following: end of the season, end of eligibility, second birthday, death, or hospitalization for reasons other than the primary endpoint. The latter criterion ensured complete information on palivizumab use and excluded children at risk for hospital-acquired RSV infections. Subjects were re-entered into the study for a second season if they had not reached their second birthday and met otherwise all study inclusion criteria.

Primary endpoint

The primary endpoint was the first hospitalization for RSV-related pneumonia (International Classification of Diseases, 9th revision, Clinical Modification code 480.1), RSV bronchiolitis (466.11), or other RSV infections (079.6), the latter contributing less than 1% of cases. To allow testing for residual confounding, we utilized a secondary endpoint that is affected by similar risk factors but unaffected by palivizumab prophylaxis.

DOI: 10.1002/pds

This endpoint included hospitalizations for bronchiolitis or pneumonia for specific causes other than RSV: acute bronchiolitis caused by other specified organisms (466.19), pneumonia caused by adenovirus (480.0), parainfluenza (480.2), severe acute respiratory syndrome (480.3), other virus (480.8), pneumococcus (481), other bacterial pneumonia (482.xx), and pneumonia caused by other specified organisms (483.xx). If adjustment for baseline differences in the overall infection risk was successful, children who received palivizumab would be expected to have similar risk as children who did not receive palivizumab.

Exposure

Exposure to palivizumab was defined based on pharmacy claims or physician office visit claims for palivizumab administration. Pharmacy claims had to be concurrent ($\pm$10 days) with a physician office visit for any reason to minimize instances where the pharmacy delivered vials to the office, but palivizumab was not administered.

Because palivizumab use can be intermittent when patients do not follow the monthly recommended dosing schedule (and thus, efficacious plasma concentrations might not be achieved), we applied time-dependent exposure definitions where patients can switch exposure groups, and thus, exposure periods rather than subjects were compared. We modeled the follow-up period subsequent to a palivizumab claim according to the manufacturer's dosing recommendation. Consequently, exposure was defined as follows: (1) first use, including days 0–30 after the first palivizumab claim; (2) subsequent use, including days 0–30 after any subsequent claim; (3) former use, including days 31–60 after any palivizumab claim; and (4) no use, including days before the first palivizumab dose and more than 60 days after a palivizumab claim. A subsequent dose was set to override times attributed to first, former, or no use. Accordingly, the no-use period included time of children who never received palivizumab and users' periods that preceded or followed palivizumab use periods.

Risk factors

We operationalized guideline-defined indications[5] for palivizumab based on claims data preceding the index date as follows: (1) chronic lung disease (770.7, 496x) requiring medical therapy defined as oral or inhaled corticosteroids, oxygen, bronchodilators, or diuretics within 6 months before index date; (2) gestational age less than 32 weeks; (3) gestational age 32–35 weeks; (4) hemodynamically significant cyanotic heart disease (745.0–745.3, 746.1, 746.2, 746.7, 747.3–747.4x) or acyanotic congenital heart disease (745.4–745.9, 746.0x, 746.3–746.6, 746.8–746.9, 747, 747.0–747.2x, 747.5–747.9) requiring therapy (angiotensin-converting enzyme inhibitors, digoxin, diuretics, or oxygen); (5) cystic fibrosis (277.0x); and (6) severe combined immunodeficiency (SCID) or acquired immunodeficiency syndrome (279.11, 279.2, 758.32, 042xx).

Other measures of frailty included whether hospital stays within the first month of age exceeded a total of 7 days, Medicaid eligibility because of disability, and Down's syndrome (758.0). Three variables were introduced to capture emerging risk factors: physician or emergency department visits for any respiratory diagnosis (460xx–466xx, 480xx–487xx) or acute otitis media (381.0x, 381.4, 382.0x, 382.9), three or more physician office or emergency department visits for any reason, and claims for inhaled or oral bronchodilators or corticosteroids in the preceding 1–30 days.

Finally, the analysis considered age (updated for every day of follow-up), race, gender, and geographic location expressed as longitude and latitude of the centroids of the Medicaid district listed as primary residence at the index date. We established the existence of siblings up to 5 years older by matching birth certificates with maternal names in the Vital Statistics records. Differences in RSV epidemiology were accounted for through a variable for each study season and each calendar month. Other variables considered in the analysis, but not significantly associated with infection risk and ultimately dropped from the multivariate model, included failure to thrive, multiple birth, and cancer.

Risk for RSV hospitalizations among the exposure groups was compared using a time-dependent Cox proportional hazard model. We further calculated adjusted incidence rates, defined as first event per patient-years of follow-up, for first, subsequent, and former use periods using the crude incidence rate of non-use multiplied by the respective adjusted hazard ratio (HR). Data management and analysis were conducted using SAS Version 9.1.3 (SAS Institute, Cary, NC, USA). Coordinates for district centroids were obtained with ArcGIS 9.1 (ESRI, Redlands, CA, USA).

RESULTS

The analysis included a total of 645 313 infants and children representing 980 521 child-seasons with more than half (564 649) starting at the beginning of the RSV season. Children were followed for an average of 107.9 ± 64.3 days. Censoring occurred predominantly because of season end ($n = 588\,587$), loss of Medicaid eligibility ($n = 226\,644$), and age ($n = 122\,316$). A total of 35 980 infants and children were censored for

DOI: 10.1002/pds

hospitalizations for non-RSV causes and 531 because of death.

Infants and children who received palivizumab were less likely to be Hispanic, younger, and more commonly had guideline-defined risk factors for severe RSV disease such as chronic lung disease or congenital heart disease (Table 1).

A total of 6463 RSV-related hospitalizations occurred during 105 802 812 days of follow-up, with an incidence rate of 22.3 hospitalizations per 1000 patient-years of RSV season. The 6-month all-cause mortality of those hospitalized for RSV infections was 27 per 6463 hospitalizations or 0.42%. Crude RSV hospitalization rates were lower in non-users than in users, reflecting significant channeling of palivizumab to high-risk patients (Table 2).

Adjusted rates obtained from the multivariate model showed a pronounced difference when compared with crude rates. Compared with no use periods, children appeared to maintain a similar risk for RSV hospitalizations after the first palivizumab dose (Table 3). Subsequent doses were associated with a 44% reduction in risk (HR=0.56, 95%CI, 0.46–0.69), and periods of former use maintained a protective association with a 29% decrease in hospitalization risk (HR = 0.71; 95% CI, 0.51–0.97).

With the exception of HIV/SCID, the model confirmed the relevance of guideline-defined risk factors, with HRs ranging from 1.46 for chronic lung disease to 1.83 for congenital heart disease, but the small sample size limits conclusions (Table 3). Noteworthy is the independent risk of Down syndrome, which is currently not included in prophylaxis recommendations. Furthermore important is the pronounced effect of age, which determined RSV hospitalization risk much stronger than any of the clinical indications (HR for infants 2–4 months compared with children >12 months of age: 8.64 (95%CI, 7.90–9.45).

Hazard ratios for the identical model on the secondary endpoint of specific non-RSV-related hospitalization for bronchiolitis or pneumonia were 1.31 (1.04–1.65) for first use of palivizumab, 1.03 (0.86–1.23) for subsequent use, and 1.05 (0.78–1.41) for former use. These findings suggest the presence of some residual confounding for first but not for subsequent and former use periods in the RSV hospitalization model.

DISCUSSION

To our knowledge, this is the first cohort study that examined palivizumab effectiveness taking explicit dosing intervals into account, which allowed the examination of periods when readministration of palivizumab was delayed. In addition, unlike most observational analyses, our study was able to apply a control endpoint that tested whether comparison groups were balanced and, accordingly, whether reported effectiveness estimates were unconfounded. Lastly, we had the opportunity to obtain birth certificates for more accurate estimates of gestational age,

Table 1. Children characteristics by prophylaxis and respiratory syncytial virus hospitalization

	Palivizumab prophylaxis		RSV-related hospitalization	
	≥ 1 dose (n = 14 288)	No dose (n = 966 233)	Yes (n = 6463)	No (n = 974 058)
Female (%)	6651 (46.6)	471 454 (48.8)	2747 (42.5)	475 358 (48.8)
White (%)	4229 (29.6)	338 277 (35.0)	2344 (36.2)	340 162 (34.9)
Black (%)	4043 (28.3)	290 466 (30.1)	1776 (27.5)	292 733 (30.0)
Hispanic (%)	2331 (16.3)	275 527 (28.5)	1818 (28.1)	276 040 (28.3)
Other (%)	3685 (25.8)	61 963 (6.4)	525 (8.1)	65 123 (6.7)
Hospitalization at birth >7 days (%)	7929 (55.5)	32 061 (3.3)	674 (10.4)	39 316 (4.0)
Eligibility because of disability (%)	4870 (34.1)	19 362 (2.0)	507 (7.8)	23 725 (2.4)
Chronic lung disease (%)	2157 (15.1)	2769 (0.3)	164 (2.5)	4762 (0.5)
Gestational age <32 weeks (%)	8561 (60.0)	22 531 (2.3)	529 (8.2)	30 563 (3.1)
Gestational age 32–35 weeks (%)	3522 (24.7)	40 129 (4.2)	522 (8.1)	43 129 (4.4)
Congenital heart disease (%)	2022 (14.2)	8589 (0.9)	252(3.9)	10 359 (1.1)
Cystic fibrosis (%)	87 (0.6)	640 (0.1)	10 (0.2)	717 (0.1)
SCID/AIDS (%)	101 (0.7)	1783 (0.2)	11 (0.2)	1873 (0.2)
Down syndrome (%)	181 (1.3)	1381 (0.1)	49 (0.8)	1513 (0.2)
Siblings up to 5 years older (%)	3290 (23.0)	247 094 (25.6)	2052 (31.8)	248 332 (25.5)
Age at index date (±SD, days)	189.7 (±155.9)	277.2 (±213.8)	164.4 (±146.6)	276.6 (±213.5)
Age at index date <6 months (%)	8548 (59,8)	428 083 (44.3)	4411 (68.3)	432 220 (44.4)
Recent respiratory problems/acute otitis media (%)	9246 (64.7)	491 007 (50.8)	4095 (63.4)	496 158 (50.9)
Recent frequent physician/ED visits (%)	10,497 (73.5)	283 535 (29.3)	2698 (41.8)	291 334 (29.9)
Recent use of asthma medications (%)	6,364 (44.5)	221 670 (22.9)	2737 (42.4)	225 297 (23.1)

AIDS, acquired immunodeficiency syndrome; ED, emergency department; RSV, respiratory syncytial virus; SCID, severe combined immunodeficiency.

DOI: 10.1002/pds

Table 2. Crude and adjusted respiratory syncytial virus hospitalization rates by palivizumab utilization

Palivizumab use	Patient-years	RSV hospitalization	Crude rate (per 1000 patient-years)	Adjusted rate
No use	286 519	6216	21.7	21.7
First use	591	84	142.1	19.2
Subsequent use	1997	123	61.6	12.2
Former use	764	40	52.4	15.3

which greatly improved our ability to balance comparison groups and adjust for confounding.

Our analysis detected an insignificant reduction in risk for RSV hospitalization after a first palivizumab dose and a significant reduction in size similar to the lower range of clinical trial estimates after administration of subsequent doses. The significant HR for former use periods suggests that effectiveness may expand beyond the recommended time for dose readministration.

Differences in clinical trial efficacy reports and population-based effectiveness studies are common and usually attributed to differences in population risk and artificially high levels of surveillance and patient compliance in trial settings. Trial results on palivizumab are limited to high-risk patients, whereas this analysis has included a real-life clinician-guided selection of immunized children, some with risk profiles outside American Academy of Pediatrics (AAP) recommendations. In the same population, about one-third of palivizumab recipients did not meet guideline-defined indications, predominantly because they had exceeded the recommended age cutoff for prophylaxis based on prematurity.[20] With efficacy estimates in trials varying from 39 to 78%, it is conceivable that our cohort reflected a clinician-selected composition of children with a moderate response to palivizumab. In this context, it is important to note that data on palivizumab efficacy has important gaps. For example, although inclusion criteria in the palivizumab clinical trial on Congenital heart disease (CHD) encompassed children up to 2 years of age, the study reported an average age of 6 months at study entry, limiting inferences about palivizumab efficacy in children in their second year of life.[2] Similar paucity of evidence exists for different age cutoffs related to gestational age and all proposed indications that have not been evaluated in controlled studies including cystic fibrosis, compromised immune status, cancer, or ventilator dependence. Because cost-effectiveness is driven by the underlying RSV hospitalization incidence and the magnitude by which this risk can be reduced, optimization of palivizumab utilization requires both detailed evidence on RSV infection risk *and* palivizumab efficacy.

Table 3. Hazard ratios for palivizumab exposure and other risk factors

	HR	95%CI
Palivizumab use		
First dose	0.89	0.71–1.12
Subsequent dose	0.56	0.46–0.69
Former use	0.71	0.51–0.97
No use	1.00	
Season month		
October	1.73	1.52–1.96
November	2.49	2.21–2.80
December	2.30	2.05–2.57
January	1.75	1.55–1.96
February	1.27	1.12–1.44
March	1.00	
Season		
1998/1999	1.00	
1999/2000	0.91	0.83–1.01
2000/2001	1.21	1.11–1.33
2001/2002	0.90	0.82–1.00
2002/2003	0.97	0.88–1.06
2003/2004	0.84	0.76–0.93
2004/2005	0.85	0.76–0.93
Children age		
2–4 months	8.64	7.90–9.45
4–6 months	4.67	4.28–5.10
6–8 months	3.14	2.85–3.45
8–10 months	2.18	1.97–2.43
10–12 months	1.89	1.69–2.11
>12 months	1.00	
Gender (female)	0.85	0.81–0.90
Race		
White	1.00	
Black	0.94	0.88–1.00
Hispanic	0.91	0.85–0.98
Others	0.80	0.72–0.89
Longitude (degree)	0.91	0.89–0.93
Latitude (degree)	0.95	0.92–0.97
Hospitalization at birth >7 days	1.43	1.30–1.59
Recent use of asthma medications	3.56	3.35–3.78
Recent respiratory problems/AOM	2.51	2.37–2.65
Recent extensive physician/ED visits	1.53	1.43–1.63
Eligibility because disability	2.48	2.16–2.83
Chronic lung disease	1.46	1.21–1.77
Gestational age <32 weeks	1.57	1.38–1.79
Gestational age 32–35 weeks	1.76	1.60–1.94
Congenital heart disease	1.83	1.58–2.12
Cystic fibrosis	1.49	0.80–2.78
SCID/AIDS	0.76	0.42–1.38
Down syndrome	1.68	1.24–2.27
Siblings <5 years older	1.34	1.28–1.42

HR, hazard ratio.

Unfortunately, sample size restrictions did not allow stratified examination of high-risk subgroups, which should be a focus of follow-up studies to inform

DOI: 10.1002/pds

guidelines. A separate analysis of our study cohort was restricted to children with chronic lung disease or congenital heart disease and yielded almost identical effectiveness estimates, but CIs were wider and allowed less precise inferences. Of note, only half of these two risk groups received prophylaxis.[19] Missing information about palivizumab utilization in inpatient settings in claims data further limited our ability to include very young infants and those requiring multiple hospitalizations.

Utilization of a clinician-select cohort (as opposed to strict reliance in guideline-defined populations) offered the advantage for a broad examination of RSV risk factors. Age was the single most important determinant of hospitalization with very pronounced risk in the first 6 months of life and rapid decrease thereafter. In fact, the predictive ability of age is so significant that age restrictions are evidently the key approach to optimize palivizumab utilization and control cost. Unfortunately, sample size limitations did not allow us to determine how age affects RSV risk within specific indications such as prematurity, a heavily debated issue after guidelines for prophylaxis were changed in 2009.[7]

An interesting finding is the discrepancy between effectiveness of the first and subsequent doses. Several explanations are plausible. First, considering the model on specific non-RSV hospitalizations, first dose estimates may be affected by residual confounding and may underestimate palivizumab effectiveness. Applying the same reasoning to subsequent periods of use, confounding appears remediated and baseline risk between palivizumab recipients and non-recipients balanced. It is conceivable that confounding factors for the initial decision to start prophylaxis were more pronounced, especially when first symptoms of an RSV infection resulted in a physician office visit and respective treatment decision. Subsequent doses would be expected to occur more or less automatically throughout the season irrespective of health status. However, even after adjusting for respiratory problems in the period immediately preceding the hospital admission, we were not able to establish palivizumab effectiveness for the first dose.

Alternatively, the difference in effectiveness could reflect pharmacokinetic properties of the medication. Data suggest that in the majority of patients, plasma levels drop below 40 μg/mL, the reported threshold for effective immunoprophylaxis, before the second dose is administered.[21] Subsequent doses accomplish a steady state above this threshold.[22] Similar observations were made in the IMpact trial, where average serum levels reached 37 μg/mL 30 days after the first dose, but increased to 57 and 68 μg/mL after the second and third doses, respectively.[2] Accumulation of higher plasma concentrations with subsequent doses also may explain the residual effectiveness observed during periods of past exposure to palivizumab (former use).

Interestingly, a pharmacokinetic model aimed at optimizing dosing intervals published by Zaaijer *et al.* recommend that the second dose be administered at day 23 and subsequent doses every 30 days thereafter.[23] Utilizing this revised schedule, therapeutic plasma concentrations could be accomplished with a first dose of 15 mg/kg bodyweight and only 10 mg/kg for all subsequent injections. Unfortunately, clinical trials have only reported cumulative efficacy over a multiple-month course of prophylaxis, and additional data supporting current dosing recommendations are needed.

Our study had several limitations. First, we obtained information on drug exposure from pharmacy claims data, and palivizumab administration may have lagged behind dispensing. We conducted a sensitivity analysis where first and subsequent use periods were lagged by 7 days and truncated at 30 days. Results of this analysis were almost identical to those presented. Second, the study population was established from Medicaid recipients in Florida, a state with different RSV seasonality pattern than other states in the USA or Europe. According to our own analyses across four US states, we found longer but less pronounced seasons in Florida when compared with California, Texas, and Illinois.[24] As long as palivizumab can be expected to reduce the infection risk proportionally (regardless of the underlying background rate), reported effectiveness estimates should be generalizable to any geographic area and period.

Third, reported RSV hospitalization rates may underestimate the true incidence, as we decided to narrow our definition to pneumonia and bronchiolitis with explicit attribution to RSV. Using this definition, we found an infection rate of 1.72% during the RSV season, compared with 1.6% in Medicaid recipients in the Palivizumab Outcomes Registry.[25] Finally, most observational studies have limited ability to assess residual confounding, and our analysis was not able to account for day care attendance or exposure to cigarette smoke, which may have been unbalanced between palivizumab recipients and non-recipients. However, the commonality of risk factors for RSV and non-RSV respiratory infections provided the opportunity for a validation model. This model relied on the assumption that non-RSV lower respiratory infections were accurately distinguished from RSV infections. Two observations speak for the accuracy of diagnoses. First, testing in the inpatient setting has become customary practice.[26] Second, the distribution of RSV-related and defined non-RSV-related hospitalizations matched national background

DOI: 10.1002/pds

rates. For example, a multicenter cohort study on the viral etiology of bronchiolitis during RSV season reported RSV as the causative agent in 64% of the cases.[27] Our analysis included 57% RSV cases among all cases of bronchiolitis or pneumonia caused by specified pathogens. Finally, other viral or bacterial pathogens in combination with RSV have been found in about 5–15% of children with lower respiratory tract infections.[26–28] Thus, only a small portion of non-RSV hospitalizations would have potentially benefited from palivizumab prophylaxis, which suggests that the validation model offered a valid test for residual confounding.

CONCLUSION

Palivizumab was associated with a significant decrease in the risk for RSV-related hospitalizations in this population-based cohort, with effectiveness rates comparable to lower clinical trial efficacy estimates. The initial palivizumab dose may not achieve optimal coverage, but coverage may extend beyond the recommended 30-day dosing schedule after multiple doses have been given. Age had a more pronounced impact on RSV risk than any high-risk indications. Further studies on differences in effectiveness across high-risk and across age groups as well as on dosing schedules are warranted to optimize allocation of resources for palivizumab prophylaxis.

KEY POINTS

- Palivizumab was associated with a reduction in RSV hospitalizations, which was similar in magnitude as the lower published efficacy estimates.
- First dose of palivizumab may not achieve optimal protection, whereas subsequent doses might protect beyond the currently recommended re-dosing schedule.
- Age was the single most important risk factor for RSV hospitalization.

CONFLICT OF INTEREST

Dr Winterstein has served as advisor for risk communication initiatives to Eli Lilly. She also serves on the FDA Drug Safety and Risk Management Advisory Board. The research was completed while Dr Hampp was a postdoctoral associate at the University of Florida. The views expressed are those of the authors and not necessarily those of the US Department of Health and Human Services or the FDA.

ACKNOWLEDGEMENTS

This study was funded by a grant from the Florida Agency of Healthcare Administration, AHCA. This study was conducted at the University of Florida and in collaboration with the University of Florida Center for Medicaid and the Uninsured. We would like to thank Public Health Statistics, Office of Vital Statistics, Florida Department of Health, for provision of vital statistics data. We thank Efe Odia, MS, and Nerrissa Alday, BS, for their support in finalizing the manuscript. This manuscript contains original data, and both Dr Almut Winterstein and Dr Christian Hampp had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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DOI: 10.1002/pds