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Palivizumab Prophylaxis of Respiratory Syncytial Virus Disease in 2000–2001: Results From the Palivizumab Outcomes Registry

Palivizumab Outcomes Registry Study Group*

Summary. The objective of the Registry was to characterize the population of infants receiving prophylaxis for respiratory syncytial virus (RSV) disease by describing the patterns and scope of usage of palivizumab in a cross section of US infants. RSV hospitalization outcomes were also described. The Palivizumab (Synagis®, MedImmune, Inc., 25 West Watkins Mill Road, Gaithersburg, MD 20878) Outcomes Registry was a prospective multicenter survey conducted at 63 sites. Demographics, injection history, and RSV hospitalization outcomes were collected on 2,116 infants receiving palivizumab. Infants were enrolled in the Registry between September 1, 2000–March 1, 2001, at the time of their first injection. Infants born at less than 32 weeks of gestation accounted for 47% of infants enrolled, and those between 32–35 weeks accounted for 45%; approximately 8% were greater than 35 weeks of gestation. Lower RSV hospitalization rates were observed in infants who had greater adherence to regularly scheduled injections. Nearly one-half of all hospitalizations occurred within the first and second injection intervals, suggesting the importance of early RSV protection. The confirmed RSV hospitalization rate of all infants in the Registry was 2.9%; the rate was 5.8% in infants with chronic lung disease of infancy, and 2.1% in premature infants without chronic lung disease. In conclusion, these data support the continued effectiveness of palivizumab prophylaxis for severe RSV lower respiratory tract disease in a large cohort of high-risk infants from geographically diverse pediatric offices and clinics. The Palivizumab Outcomes Registry provides an opportunity to assess palivizumab utilization and clinical effectiveness in the US. **Pediatr Pulmonol. 2003; 35:484–489.** © 2003 Wiley-Liss, Inc.

INTRODUCTION

Respiratory syncytial virus (RSV) contributes significantly to morbidity in premature infants during the first 2 years of life and in immunocompromised children.[1–5] RSV bronchiolitis was recently estimated to account for up to 126,000 annual hospitalizations in the US.[1] Infants known to be at increased risk for significant disease requiring hospitalization and mechanical ventilation include those who are premature, have chronic lung disease of infancy, and/or have congenital heart disease.[2]

Palivizumab, a humanized monoclonal antibody against RSV, was approved for use in the United States in 1998. The IMpact-RSV trial demonstrated palivizumab efficacy in preventing RSV hospitalizations of children with chronic lung disease who were <24 months of age and of those born prematurely (<35 weeks of gestational age) who were 6 months of age or less.[6] That trial demonstrated a 55% reduction in RSV hospitalization rates in infants receiving palivizumab compared with placebo (4.8% vs. 10.6%, $P < 0.001$). Statistically significant reductions were also demonstrated in infants with chronic lung disease (12.8% vs. 7.9%, relative reduction of 39%, $P = 0.038$) and premature infants without chronic lung disease (8.1% vs. 1.8%, relative reduction of 78%, $P < 0.001$).

Since its FDA approval in 1998, the effectiveness of palivizumab has been further demonstrated in two retrospective surveys of infants during the 1998–1999 and 1999–2000 RSV seasons.[7,8] Those surveys, despite the limitations and bias that may be present in retrospective

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Preliminary results were presented as a poster at the 2001 American Academy of Pediatrics National Conference and Exhibition.

Please be advised that scientific integrity was maintained regarding these data. All investigators on the Advisory Board participated in manuscript preparation and had complete and free access to the data collected and all analyses performed. All data analysis was performed at the EMMES Corporation, who provide statistical analysis and data management for biomedical research programs.

For list of authors, see Appendix.

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*Correspondence to: Marnie Boron, Pharm.D., Medical Affairs, MedImmune, Inc., 35 West Watkins Mill Road, Gaithersburg, MD 20878.
E-mail: boronm@medimmune.com

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studies, demonstrated RSV hospitalization rates of 2.3% and 2.4%, respectively, in infants receiving RSV prophylaxis with palivizumab.

We performed a prospective study to identify infants receiving one or more doses of palivizumab during the 2000–2001 RSV season. The goals of the Palivizumab Outcomes Registry were to characterize the population of infants receiving prophylaxis for RSV disease, and to describe the patterns and scope of use of palivizumab, as well as hospitalization outcomes.

METHODS

The Palivizumab Outcomes Registry is a prospective, nationwide registry, initiated during the 2000–2001 RSV season, to track a population of infants receiving monthly doses of palivizumab for prophylaxis of serious lower respiratory tract disease caused by RSV. The Registry included infants enrolled at 63 geographically diverse pediatric offices and clinics across the US. Children who received palivizumab for RSV prophylaxis under the care of a participating site were eligible for enrollment into the Registry if a parent (or legally authorized representative) gave informed consent for participation and the child received the first palivizumab dose for the RSV season between September 1, 2000–March 1, 2001. If an infant received a dose in the hospital before initial birth discharge, enrollment occurred at the time of first dose at the clinical site. There were no exclusion criteria. Follow-up of infants for palivizumab injections continued through April 30, 2001, and through May 31, 2001 for RSV hospitalizations. Participating clinical sites received Institutional Review Board (IRB) approval before enrolling infants into the Registry, and written informed consent was obtained before enrollment at the time of the infant's first office dose.

The information collected after the first palivizumab dose was used to enroll the subject, confirm eligibility, provide data about the first palivizumab injection, and capture demographic and RSV risk factor data. Information collected included demographics (race, birth weight, and gestational age) as well as medical and family history and medical payment information.

Relevant follow-up information was collected prospectively during the RSV season. Injection information included date and dose of each injection and administration setting (e.g., office, clinic, or home). Compliance with the injection regimen was determined by comparing the actual number of injections received with the expected number of doses, based on the month the first injection was given. If an infant received an initial injection in November or earlier, five injections were expected for the RSV season; infants starting injections in February would only be expected to receive two injections. Injection history was examined from two additional perspectives. First, administration of injections within 35-day intervals was evaluated. Second, sites were asked to report on the number of and reasons for missed injections.

Data specific to RSV admission were collected any time a subject was hospitalized with primary or secondarily acquired RSV infection. An RSV hospitalization was defined as any hospitalization with a duration of 24 hr or longer for which the infant had a positive RSV test (either by rapid antigen detection or culture). If a subject had more than one RSV hospitalization, only one was counted in determining the RSV hospitalization rate. Hospitalizations that occurred prior to or within 24 hr after receiving the first palivizumab injection were excluded from this analysis. In addition to admission and discharge dates, information on discharge diagnosis, intensive care unit (ICU) admission, and use of mechanical ventilation was also collected.

RESULTS

Characteristics of Infants in Registry

We enrolled 2,116 infants receiving palivizumab for RSV prophylaxis into the Registry from 63 sites nationwide between September 1, 2000–March 1, 2001. The mean number of infants enrolled at a Registry site was 34 (median, 25; range, 1–215), with 50% of the sites enrolling between 13–43 infants. The majority of sites (50) enrolling subjects were pediatric office settings. Additionally, a few (13) freestanding and hospital-based clinics participated. Demographics, medical and family history, and prior prophylaxis of enrolled subjects are presented in Table 1. Infants born at less than 32 weeks of gestational age (GA) accounted for 46.6% (n = 986) of those enrolled, and those between 32–35 weeks accounted for 45.2% (n = 957); 8.1% (n = 172) were at greater than 35 weeks of gestation.

Risk factors for RSV infection were multiple birth (32%), chronic lung disease (24%), childcare center exposure (either the subject or a sibling of the subject; 24%), ongoing tobacco smoke exposure (17%), congenital heart disease (5%), and cystic fibrosis (<1%) (Table 1). In addition to prematurity, for infants born ≤35 weeks of GA, 71% had at least one other risk factor for RSV infection.

Second-Season Infants

Three hundred and five (14%) infants enrolled in the Registry received prophylaxis with palivizumab for a second season. The majority of this group was <32 weeks of GA (n = 203, 67%), with 64 (21%) children born between 32–35 weeks of gestation. One hundred and sixty-five (54%) infants receiving prophylaxis for a second season had a history of chronic lung disease, and 27 (9%) had a history of congenital heart disease.

TABLE 1— Subject Demographics, by Gestational Age Categories[1]

	Total (n = 2,116)		<32 weeks (n = 986)		32–35 weeks (n = 957)		>35 weeks (n = 172)	
Variable	N	%	N	%	N	%	N	%
Female	969	45.8	461	46.8	445	46.5	63	36.6
Race								
Caucasian	1,248	59.0	531	53.9	591	61.8	126	73.3
African-American	409	19.3	234	23.7	157	16.4	18	10.5
Hispanic	289	13.7	140	14.2	129	13.5	19	11.0
Other	170	8.0	81	8.2	80	8.4	9	5.2
Mean (SD) birth weight (g)[2]	1,707 (710)		1,190 (408)		2,023 (484)		2,908 (632)	
Age at enrollment								
<3 months	866	40.9	294	29.8	528	55.2	44	25.6
3–6 months	553	26.1	277	28.1	235	24.6	41	23.8
6–12 months	451	21.3	266	27.0	144	15.0	40	23.3
>12 months	246	11.6	149	15.1	50	5.2	47	27.3
Prophylaxed with palivizumab in prior season[2]	305	14.4	203	20.6	64	6.7	38	22.2
Risk factors								
Of multiple birth	676	31.9	309	31.3	348	36.4	19	11.0
Chronic lung disease	500	23.6	383	38.8	76	7.9	41	23.8
Congenital heart disease	102	4.8	39	4.0	22	2.3	41	23.8
Cystic fibrosis[2]	12	0.6	2	0.2	2	0.2	8	4.7
Childcare center exposure[2]	476	24.1	199	21.5	221	24.8	56	34.8
Smoke exposure[2]	334	16.9	143	15.5	158	17.6	33	20.6
Any risk factor[3]	1,510	71.4	745	75.6	630	65.8	135	78.5

[1]Gestational age was not available for one subject.
[2]Birth weight not available for 8 subjects, prior prophylaxis for 2 subjects, cystic fibrosis status for one subject, daycare exposure for 136 subjects, and smoke exposure for 134 subjects. Percentages for factors with missing data are calculated based on available data.
[3]Irrespective of gestational age.

Palivizumab Administration Information

The injection information and hospitalization rates described below include 2,049 infants of the 2,116 infants enrolled, based on 97% of follow-up information submitted. The overall mean number of injections per subject was 4.7 (4.5 for >35 weeks of GA and 4.8 for <32 weeks of GA). The median was 5 injections (range, 1–9) for all GA categories. The majority of infants initiated their prophylaxis regimen in the pediatrician's office (74%), and 26% received their first dose in the hospital. Of the entire Registry population, 46% (982/2,116) were either born or discharged from the Neonatal Intensive Care Unit (NICU) during the 2000–2001 RSV season (defined as September 1, 2000–March 1, 2001 for the Registry). Of this subset, the locale of the first injection was evenly distributed among infants who received their initial dose in the office (48%) and the hospital (52%).

Five percent of first injections occurred in September 2000, 30% in October and in November 2000, 17% in December 2000, 13% in January 2001, 5% in February 2001, and <1% in March 2001 (two initial injections occurred on March 1, 2001). Fifty percent of last injections occurred in March 2001, and 30% in April 2001. The mean follow-up time between the first and last injection was 114 days.

Overall, 80% (1,638/2,049) of infants were compliant and received the expected number of injections based on their month of first dose. The RSV hospitalization rate for noncompliant infants was somewhat higher than those who were compliant (3.4% vs. 2.8%, $P = 0.48$). Twenty-three percent (472/2,049) of infants were reported either as missing one or more injections or as having a delay in receiving an injection. The hospitalization rate for these infants was nearly double that of infants not reporting any missed or delayed injections (4.4% vs. 2.4%, respectively) ($P = 0.020$).

RSV Hospitalizations

Fifty-nine (2.9%) of the 2,049 infants with follow-up information had a virologically confirmed RSV hospitalization (Table 2). Infants with chronic lung disease had the highest hospitalization rate (5.8%), followed by those infants <32 week of GA (4.5%). The hospitalization rate was 2.8% in infants receiving palivizumab for a second season.

Four infants had multiple hospitalizations, with one having three hospitalizations and the other three having two hospitalizations each. The majority (80%) of hospitalizations occurred between December and February. In the subset of subjects receiving doses within a 35-day

TABLE 2— Infants With RSV Hospitalizations in Selected Subgroups

Risk factor	No. of infants with RSV hospitalization/total (%)
All infants	59/2,049 (2.9)
Gestational age	
<32 weeks	43/949 (4.5)
32–35 weeks	15/936 (1.6)
>35 weeks	1/164 (0.6)
Premature without chronic lung disease	30/1,444 (2.1)
Chronic lung disease	28/482 (5.8)
Of multiple birth	14/655 (2.1)
Cystic fibrosis	0/12 (0.0)
Congenital heart disease	4/93 (4.3)
Daycare exposure	11/468 (2.4)
Smoke exposure	9/333 (2.7)
Any risk factor (other than prematurity)	45/1,463 (3.1)

interval, hospitalizations were examined in relation to injection number in the administration course of palivizumab (Table 3). Seventy-five percent of all hospitalizations occurred within the first and second injection intervals.

Based on the initial RSV hospitalization for the 59 infants, the discharge diagnosis for nearly 70% of hospitalizations included RSV bronchiolitis, and the mean length of stay was 8.1 days (median, 6 days). Fewer than 1% (18/2,049) of enrolled infants required an ICU admission, and the mean length of ICU stay was 9.9 days (median, 8 days). Of these, 12 infants required mechanical ventilation.

DISCUSSION

The Palivizumab Outcomes Registry provides the first US prospective analysis of infants receiving palivizumab since its FDA approval in 1998. The characterization of infants receiving prophylaxis from this geographically diverse population serves as a benchmark for consideration of palivizumab use for both community-based and academically-based physicians. Additionally, the prospective method utilized in the Registry offers advantages over the previously published outcome analyses.[7,8] These advantages include the ability to capture nearly complete demographic information and over 97% of follow-up information on all enrolled infants, a figure not readily achieved by retrospective methods.

TABLE 3— Occurrence of RSV Hospitalizations in Subjects Who Received All Injections Within 35-Day Intervals by Injection Interval[1]

Injection interval	Hospitalizations (%)
1	22 (46)
2	14 (29)
3	5 (10)
4	2 (4)
5	4 (8)
6	1 (2)

[1]n = 48. Injection intervals for all subjects whose hospitalizations occurred within 5 days of preceding injection were added to previous injection interval.

The demographic information from infants enrolled in the Registry demonstrates use of palivizumab to be generally consistent with American Academy of Pediatrics (AAP) guidelines.[9] A percentage of enrolled infants did not fall into the AAP guidelines for prophylaxis. These included (6% of the entire Registry cohort) infants born >35 weeks of GA who did not have chronic lung disease (CLD). Risk factors for RSV in this group included cystic fibrosis, congenital heart disease, and specific medical conditions (e.g., Down syndrome, respiratory distress syndrome, or apnea). This group may warrant further investigation as to pediatricians' perceived risk of severe RSV disease and indications for prophylaxis in this group.

The RSV hospitalization rate for infants enrolled in the Registry was 2.9%, which is lower than the 4.8% reported in the IMpact-RSV trial.[6] While there are no contemporary US data on the rate of hospitalization for RSV in untreated infants, recently reported rates from approximately 25% of the birth cohort in Spain were consistently as high as 13%.[10,11] RSV hospitalization outcomes in this analysis remain low and support the effectiveness of palivizumab outside of a controlled clinical study, as was shown in retrospective analyses performed in each of two prior RSV seasons.[7,8]

The temporal distribution of hospitalizations observed in the Registry is consistent with Centers for Disease Control (CDC) data for previous seasons for occurrence of RSV epidemic activity, typically between December–February nationwide.[12] With respect to injection number, the distribution in this study revealed an increased occurrence of hospitalizations within the first and second injection intervals. This may reflect lower trough levels of palivizumab in some infants early in the course of prophylaxis; these levels are expected to increase to protective levels, as observed in the IMpact-RSV trial where trough serum drug concentrations after the first dose were 37 ± 21 mcg/ml, rising to 72 ± 50 mcg/ml after the fourth injection.[6] As infants in this study were enrolled throughout the entire RSV season, this observation suggests the need for initiating RSV protection before the onset of epidemic RSV activity within the community and/or before potential viral exposure.

Compliance with the injection regimen is another important consideration when evaluating hospitalizations in the face of RSV prophylaxis. Although noncompliant infants appear to have higher hospitalization outcomes, factors other than compliance would most likely have an impact on hospitalization rates. These factors should be taken into consideration when evaluating compliance with any prescribed regimen of prophylaxis.

The Palivizumab Outcomes Registry allowed collection of prospective data regarding compliance and hospitalization outcomes in a community setting. These data are consistent with outcomes previously collected from retrospective studies.[7,8] These observations clarify the importance of initiation and prophylaxis prior to the onset of RSV season and compliance with the dosing schedule, once initiated.

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APPENDIX

Members of the Palivizumab Outcomes Registry Study Group

Curt Parnes, M.D., Judith Guillermin Abington Pediatric Associates, L.L.P., Abington, PA; Rolf Habersang, M.D., Peggy Nicholes, R.N., Amarillo Area Healthcare Specialists, L.L.P., Amarillo, TX; Vijay Chawla, M.D., F.F.A.P., Tammy Kelly, L.P.N., Austin Medical Center, Mayo Health System, Austin, MN; Judith Fishbein, M.D., Patty McRae, Baton Rouge General Clinic, Baton Rouge, LA; Mary Goessler, M.D., Antoinette Gatti, R.N., Bellevue Pediatric Associates-AMPD, Pittsburgh, PA; John A. Calcagno, M.D., Cheryl Eki, Kristen A. Harris, F.N.P., Calcagno Pediatrics, Gresham, OR; Joseph Joyave, M.D., Kathy McFarland, L.P.N., Calhoun Pediatric Care, Calhoun, GA; Paul Protter, M.D., Mary Sullivan, B.S.N., M.S.N., Camino Medical Group, Sunnyvale, CA; Allan Stanford, M.D., Nancy Lovett, A.P.N., Central Arkansas Pediatric Clinic, Bryant, AR; Marisol Ortiz, M.D., Sharon Rojas, R.N., Child Study Clinic, Victoria, TX; Scott Cyrus, D.O., Janell Cyrus, Children and Adolescent Medical Services, Inc., Tulsa, OK; Stuart Cohen, M.D., M.P.H.,* Debbie Buchin, R.N., Children's Primary Care Medical Group, San Diego, CA; Linda Riordan, M.D., Monica Zuniga, Children's Pulmonary Specialists, Tucson, AZ; Rupa Shah, M.D., Carmen Minard, Clackamas Pediatrics, Clackamas, OR; Arden Quintin, M.D., Glenda Douglas, Southeast Texas Community Health Clinic, Beaumont, TX; John van Houten, M.D., Sharyn Freutner, Community Memorial Hospital of Ventura, Ventura, CA; Stephen Chartrand (deceased), M.D.,* Patsy Nowatzke, B.S.N., Jose Romero, M.D.,* Creighton University, Omaha, NE; Torunn Rhodes, M.D., Michelle Benoit, Dartmouth Hitchcock Medical Center, Lebanon, NH; Emmanuel Walter, M.D., Leslie Walker, R.N., Duke Children's Primary Care, Durham, NC; Laurie DeBonnett, M.D., Mia Cross, Family Christian Health Center, Harvey, IL; Teresa Free, A.R.N.P., Ph.D., Sharman Martin, Karen Shank, Family Care Center Children's Clinic, Lexington, KY; Ben Guedes, M.D., Lee Ann Atkinson, R.N., B.S.N., Florida Children's Medical Group, Orlando, FL; George J. Halpin, M.D., M.P.H., Kathy Rouse, R.N., B.S.N., Greenspring Pediatric Associates, Baltimore, MD; Ivan Hand, M.D.,* Donna Geiss, N.N.P., Jacobi Medical Center, Bronx, NY; James R. Marshall, D.O., Lois Burleson, Abilene, TX; Jim Boland, M.D., Kelsey Seybold, Missouri City, TX; Vicki Hunter, R.N., Kelsey Seybold, Houston, TX; Susan Unfer, M.D., Jackie Schmucker, R.N., Margaret Gley, R.N., Lutheran General Children's Hospital, Park Ridge, IL; Michael Marcus, M.D., Patricia Thompson, C.P.N.P., Maimonides Medical Center, Brooklyn, NY; Paulino Milla, M.D., Connie Young, R.N., Milla Pediatrics, Gainesville, FL; Robert Zanni, M.D., Virginia Zinno, R.N., Monmouth Medical Center, Long Branch, NJ; Alexandra Fetter-Zarzeka, M.D., Amanda Busey, Monroeville Medical Clinic, Monroeville, AL; Modupe A. Sokunbi, M.D., Sherrie Airington, Nancy Richard, Nacogdoches Pediatrics PA, Nacogdoches, TX; Vellore Muraligopal, M.D., Stephanie Lewis, M.N., P.N.P., Arrowhead Regional Medical Center, Colton, CA; F. Thomas Weber, M.D., Beverley P. Giordano, A.R.N.P., Denise Linehan, A.R.N., North Florida Pediatrics, PA, Lake City, FL; Jane Roach, M.D., Randle Davis, Olentangy Pediatrics, Inc., Columbus, OH; Andrew A. Rzepka, M.D., Terri Booth, Park Nicollet Health Services, Brooklyn Park, MN; David Smeltzer, M.D., Jeanne Walsh, L.P.N., Partners in Pediatrics, Brooklyn Park, MN; Emilio Arispe, M.D., Rhonda Rowley, PCI-Pediatrics, Omaha, NE; Christopher Bolling, M.D., Tanya Botts, R.N., Kateri Haskett, Pediatric Associates, PSC, Crestview Hills, KY; Deana Raby, A.R.N.P.-P.N.P., Evelyn Batiz, Pediatric Professional Association, Overland Park, KS; Andrew Gelfand, M.D., Lynn Farrell, Pediatric Pulmonary Specialists, PA, Dallas, TX; Stephen Butler, Linda Colby, Perinatal and Pediatric Specialist Medical Group, Sacramento, CA; Peter Schochet, M.D., Julie Bentler, Plano, TX; David Hirsch, M.D., Lisa Wilkinson, R.N., Phoenix Pediatrics Ltd., Phoenix, AZ; Allen Aaronson, M.D., Eleanora Bennett, R.N., Dawn Quinn, Pratt Medical Center Pediatrics, Fredericksburg, VA; Katherine Komendowski, M.D., Marcia Deckard, Rainbow Pediatrics, Florissant, MO; Michael Frogel, M.D.,* Cliff Nerwen, M.D., Schneider Children's Hospital, New Hyde Park, NY; Steven Copenhaver, M.D., Michele Prater, C.P.N.P., Scott and White Clinic, Temple, TX; Jacob Wolsztein, M.D., Kristine Mackey, R.N., C.P.N.P., South Coast Pediatrics, Santa Ana, CA; Marshall Benbow, M.D., Marisela Naranjo, L.V.N., Southwest Children's Center, San Antonio, TX; Sandra Hensley, M.D.,Cindy Hayes, R.N., B.S.N., Spectracare, Louisville, KY; Hossein Sadeghi, M.D., Sally May Lawson, A.P.R.N., Stamford Hospital, Stamford, CT; Mark McCall, M.D.,

Karla Combs, C.M.A., Summerville Pediatrics, PA, Summerville, SC; Joel Ledbetter, M.D., Karen Sarnosky, Cathy Swafford, T.C. Thompson Children's Hospital, Chattanooga, TN; Michael Speer, M.D.,* Texas Children's Hospital, Houston, TX; Wendy J. Barton, M.D., Julie Wingate, Thedacare Physicians-Pediatricians, Appleton, WI; J.W. Mink, M.D., Dianne Lemm, R.N., Tidewater Children's Association, Chesapeake, VA; Mark Hudak, M.D.,* Elizabeth Case, R.N., University of Florida-Jacksonville, Jacksonville, FL; Judith Rowen, M.D., Sandra Fuentes, University of Texas Medical Branch, Galveston, TX; Carly Pane, M.D., Leslie Richardson, Valley Hospital, Ridgewood, NJ; Cesar Chavarria, M.D., Deanne Cassino, Valley Inpatient Pediatrics, Inc., Tarzana, CA; Kourosh Ghaffari, M.D., Carol Carroll, Valley View Pediatrics, Cedar City, UT; Haesoon Lee, M.D., Lydia Guclu, Winthrop University Hospital, Mineola, NY; Christopher Johnson, M.D., Valerie Blum, Woodinville Pediatric Clinic, PLLC, Woodinville, WA; Marnie L. Boron, Pharm.D.,* Mark Sorrentino, M.D.,* Robert L. Hirsch, Ph.D.,* MedImmune, Inc., Gaithersburg, MD; and Paul C. Van Veldhuisen, M.S.,* Carol Smith, M.P.H.,* EMMES Corp. (Palivizumab Outcomes Registry Coordinating Center), Rockville, MD.

*Indicates Advisory/Writing Committee.

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