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**Effectiveness of Palivizumab in High-Risk Infants and Children: A Propensity Score Weighted Regression Analysis**

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**Disclosures:** EJA, EAFS, and RY received financial remuneration to their institutions for the original conduct of this study and for ongoing clinical trial work on other studies from MedImmune and/or AstraZeneca. EJA has served as a consultant for Abbvie regarding RSV. EJA has received financial remuneration to his institution for an unrelated clinical trial. This work was unfunded.

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## ABSTRACT

**Background.** Infants with premature birth  $\leq 35$  weeks gestational age (wGA), chronic lung disease of prematurity (CLD), and congenital heart disease (CHD) are at increased risk for lower respiratory tract infections (LRTI) and hospitalization from respiratory syncytial virus (RSV) which has been shown in randomized trials to be prevented by palivizumab. However palivizumab effectiveness (PE) has not been studied in a large clinical setting.

**Methods.** A multicenter study among high risk US and Canadian children  $< 24$  months of age hospitalized with LRTI and whose nasopharyngeal aspirates were tested for HMPV and RSV were the subjects of the trial. We conducted a test-negative case-control study in these subjects to determine palivizumab effectiveness. We used an inverse propensity score-weighted multiple logistic regression model (IPSW) to adjust palivizumab effectiveness.

**Results.** Palivizumab was used in 434 (51%) of 849 eligible children. RSV was identified in 403 (47%). The unadjusted PE was 43% (95% CI, 34 – 51%). After IPSW adjustment, the adjusted PE was 58% (95% CI 43 – 69%). Palivizumab prevented ICU admissions (PE 62%, 95% CI 35 – 78%). PE for 29 – 35 wGA and  $\leq 6$  months of chronologic age without CLD or CHD was 74% (95% CI, 56 – 85%).

**Conclusions.** Using a test-negative case-control design with RSV molecular detection, palivizumab is shown to prevent RSV hospitalizations and ICU admissions in high risk infants.

**Key Words:** Test negative design, respiratory syncytial virus (RSV), chronic lung disease of prematurity, prematurity, case control study

## Introduction

Respiratory syncytial virus (RSV) has been estimated to cause between 50,000 to 125,000 annual hospitalizations of US children under 5 years of age.(1, 2) Risk factors for developing severe RSV disease (hospitalization, intensive care unit [ICU] admission) in young children include preterm birth  $\leq 35$  weeks gestational age (wGA), chronic lung disease of prematurity (CLD), hemodynamically significant congenital heart disease (hsCHD), and young chronologic age ( $< 6$  months).(3-6) Daycare attendance and young siblings are additional risk factors in 32–35 wGA infants.(7-10) Palivizumab is an RSV-specific monoclonal antibody licensed for the prevention of serious lower respiratory tract disease (LRTI) caused by RSV in high risk children. Several prospective clinical trials have demonstrated an efficacy of 45 – 82% against RSV-related hospitalizations in high risk infants.(7, 11, 12) However the effectiveness of palivizumab in clinical practice using a test-negative controlled study design has not been conducted.

In 2014, the American Academy of Pediatrics (AAP) recommended restriction of palivizumab prophylaxis to infants born at  $< 29$  weeks and 0 days of gestation or those with hsCHD, CLD, or other high-risk conditions.(13) This recommendation was based upon an assessment that in preterm infants 29 to 35 weeks gestation palivizumab has “limited effect on RSV hospitalizations on a population basis, no measurable effect on mortality, and a minimal effect on subsequent wheezing.”(13) This change from previous recommendations(14) leaves many of these at risk premature infants and children without an option for RSV prevention.(15)

Vaccine effectiveness (VE) studies based on polymerase chain reaction (PCR)-confirmed infections and vaccination history are essential for evaluating how well a vaccine works in preventing disease outside the tightly controlled setting of a randomized controlled clinical trial.

These studies provide important information on the public health value of vaccines and help in developing vaccination policies. Test-negative controls in acute respiratory VE studies are used to control for significant differences that might exist due to access to care.(16-19) Since palivizumab effectiveness has not been evaluated in clinical practice, we used a rigorous test-negative study design from a multicenter study conducted to determine the prevalence of respiratory pathogens to answer this question.(20) We enrolled children <24 months of age at high risk for severe respiratory disease who were hospitalized with acute lower respiratory tract infection (LRTI) between 2002 and 2006. As part of this study, PCR for RSV was performed, and epidemiologic and clinical data, including administration of palivizumab within the preceding 30 days, were collected. We analyzed the data collected during this study to determine palivizumab effectiveness (PE) in preventing RSV hospitalizations. In order to address potential confounding and bias,(21) we used an inverse propensity score weighted, test-negative case-control study design to estimate the protective effect of palivizumab.

## **Methods**

### ***Study design***

A large, prospective, international, multi-center study was conducted between 2002 – 2006, to determine the prevalence of HMPV in high risk children <24 months of age during the fall to spring seasons at 24 sites in the northern hemisphere (United States, Canada, Italy, and the Netherlands) and at 3 sites in the southern hemisphere (Australia).(20) Local institutional review boards approved the study prior to subject enrollment. Eligibility included children  $\leq 12$  months of age who were born prematurely (<36 weeks gestation), children <24 months of age with hsCHD, and/or CLD of prematurity who required medical intervention (e.g. supplemental oxygen, corticosteroids, bronchodilators, or diuretics within the previous 6 months) who were

hospitalized with acute LRTI (e.g., bronchiolitis, bronchitis, pneumonia or cardiac decompensation associated with respiratory infection). Demographic data, medical history, use of certain medications, and use of palivizumab within 30 days of enrollment were recorded. Routine PCR testing for respiratory viruses (e.g., HMPV, RSV, parainfluenza, and influenza) was performed. This study enrolled 1,126 children across all the study sites, detailed elsewhere.(20)

We compared the odds of palivizumab administration within the preceding 30 days between RSV cases and controls. *Cases* were defined as subjects hospitalized with LRTI whose nasopharyngeal aspirates (NPAs) or endotracheal aspirates collected within 2 days of admission tested positive for RSV by reverse transcription (RT)-PCR. *Controls* were defined as subjects hospitalized for LRTI who tested negative for RSV. For the analyses of the subgroups of patients 1) treated in the ICU and 2) requiring mechanical ventilation (MV), cases and controls were defined as described above, and analyzed within their respective subgroups.

Since the decision to hospitalize and the use of palivizumab differ substantially between countries, and since we were primarily interested in evaluating palivizumab administration during high-risk RSV periods, we limited the analysis to subjects enrolled in the U.S. and Canada from November 1 – April 30.

### ***Laboratory Methods***

NPAs or endotracheal aspirates were obtained from subjects on enrollment and endotracheal aspirates were collected within 2 days of initiation of MV. Samples were stabilized in viral transport medium and frozen before being tested at Focus Diagnostics, Inc. (Cypress, CA). A multiplex RT-PCR enzyme hybridization assay (Hexaplex; Prodesse, Inc., Waukesha, WI) was used for detection of RSV A and B; influenza A and B; and parainfluenza-1, -2 and -

3.(20) Samples with a negative RSV result were retested for RSV B at Cogenics Inc. (Houston, TX) to optimize recovery. HMPV was detected by a real-time RT-PCR assay.(20)

### *Statistical Analysis*

**Univariate Analysis:** Univariate analysis was used to identify factors which could confound the relationship between palivizumab administration and RSV outcome. Categorical variables were summarized by the number and percentage of subjects in each category. Continuous variables were summarized by descriptive statistics including mean, standard deviation (SD), median and range. Mean values were compared using Student's t-test only when test assumptions were met. Otherwise the median values were compared using the Wilcoxon Rank-Sum test. Proportions between 2 groups were compared using Fisher's exact test, and proportions between more than 2 groups were compared using  $\chi^2$  test. All statistical analyses were conducted using SAS v.9.4 (SAS Institute Inc., Cary, NC).

To identify potential confounding factors, we examined statistical associations between potential confounders and palivizumab administration. Potential confounders included age, sex, race/ethnicity, wGA, birthweight, single versus multiple birth, family composition (e.g. presence and number of children <6, 6 – 12, and >12 – 18 years), daycare attendance, breastfeeding, maternal education level, maternal age, maternal and paternal employment, family atopy status, history and duration of NICU admission, other medical conditions, household smoking, timing of admission relative to disease onset, timing from beginning of the RSV season to admission (as the disease risk may vary during the season), and the year.

**Propensity Score:** Given that subjects who are treated with palivizumab are more likely to have a number of risk factors (e.g., earlier gestational age, exposure to daycare, hsCHD) known to be associated with hospitalization, we planned to reduce selection biases by developing



an inverse propensity score weight (IPSW) using the significant ( $P < 0.05$ ) risk factors associated with palivizumab administration.(22) Proc GLM (SAS v.9.4) was used to compare the palivizumab group to the control group to identify covariate significance prior to adjustment. We then created the propensity scores using Proc Logistic with these covariates, followed by taking the inverse of the propensity score to derive the weight.(23) Proc GLM was run on the adjusted (IPSW) values, to ensure that the treatment and control groups were balanced. Finally, we performed an inverse propensity score-weighted multiple logistic regression model to adjust PE. In addition to significance level, we used the Hosmer and Lemeshow goodness of fit test to select the best predictive model.(24)

**Multivariate Analysis:** We compared the odds of palivizumab administration within the 30 days before disease onset between RSV cases and controls using a multiple logistic regression (SAS Proc Logistic) model, to calculate an adjusted odds ratio (aOR), using the IPSW. RSV PE (%) was estimated as  $(1 - \text{aOR}) \times 100$ .(18) Outcomes were assessed related to the PE in prevention of ICU admissions and MV after adjustment with an IPSW multiple logistic regression model. The ideal model was considered to have palivizumab treatment status as the only predictor and was weighted by the IPSW, to predict RSV outcome. However, if the IPSW adjustment was insufficient to remove all potential confounding, then other significant predictors were included in the final model. When there was co-linearity evident among significant predictors, the predictor with a lesser significant effect was removed from the model.

Sensitivity analyses included restriction to cases hospitalized within 7 days of symptom onset, to address concerns that RSV may be a concurrent infection and not the cause of LRTI in subjects with a longer duration of symptoms prior to presentation. An additional sensitivity

analysis was performed among those who tested negative for RSV but positive for HMPV to assess for the specificity of the effect of PE.

Subgroups were analyzed [preterm infants without hsCHD or CLD with separate analysis for infants <3 versus 3 to <6 months chronologic age overall, <29 wGA and 29 – 35 wGA for infants < 6 months, children with hsCHD overall (separate analyses of those with chronologic age <12 months on November 1 versus age of 12 - <24 months on November 1), children with CLD overall (separate analyses of those with chronologic age <12 months on November 1 versus 12 to <24 months on November 1)]. Interactions between subgroup and palivizumab administration were examined.

## Results

Of 1162 children enrolled in the original study, 849 (73.1%) met inclusion criteria for this analysis (Figure 1). The most common reasons for exclusion were residence in the Southern hemisphere (165, 14.2%) and enrollment outside the RSV season (93, 8.0%). Overall, 58.4% were male, 45.8% were white, 42.7% had a gestational age between 32–<36 weeks, 33.7% had CLD (without hsCHD), 18.1% had hsCHD, and 83.0% (656/790 with known data) had a previous neonatal intensive care unit admission. The subjects' baseline demographics and medical history are presented in (Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C674>).

Two subjects, one in the treatment and one in the control, missing gestational age were excluded from the GLM analysis of potential confounders and subsequent analyses (Table 1). Compared to the 414 (48.9%) participants who did not receive palivizumab, the 433 (51.1%) participants who had received palivizumab were more likely to have medical and social risk factors for RSV infection. They were more often white than Hispanic, were older (median age 6.2 versus 3.8

months,  $p < 0.0001$ ), had an earlier gestational age (median 29 versus 34 weeks,  $p < 0.0001$ ), had lower birthweight (median 1,300 versus 2,150 grams,  $p < 0.0001$ ), were more frequently admitted to the NICU at birth, had a longer stay (median 64 versus 18 days,  $p < 0.0001$ ), had more chronic medical conditions (75.6% versus 36.6%,  $p < 0.0001$ ), were less frequently breastfed (10.6% versus 17.6%,  $p = 0.0026$ ), and had older and more educated mothers. Despite these significant potential confounders, the unadjusted PE was 43.3% (95% CI 34.1 – 51.2%) and did not differ when limiting the cases to hospitalization  $< 7$  days after symptom onset (44.3% [95% CI 35.1 – 52.3%]).

After IPSW adjustment, the differences between the groups resolved except for the percentage of children who were  $> 6$  months of age (Table 2). PE was determined to be 58% (95% CI 43.1 – 69%) with a Hosmer & Lemeshow Goodness of Fit  $p$ -value of 0.34 (Table 2), indicating an adequate fit of the data to the model. Subgroup analyses of PE are shown in Figure 2. The point estimates and 95% CI in many of the subgroups were wide due to small numbers, particularly in those  $< 29$  wGA and in children with hsCHD. The PE for prevention of ICU admissions was 62.1% (95% CI 35.1 – 77.9%) (Figure 2) but PE was not observed in the mechanical ventilation subgroup (31.5%, 95% CI -41.2 – 66.8%). PE for children born at 29 – 35 wGA and  $< 6$  months of chronologic age was statistically significant at 74.1% (95% CI 56.2 – 84.7%) but not in those  $< 29$  wGA and  $< 6$  months of chronologic age. Palivizumab had no significant effectiveness against HMPV hospitalization (34.7% [95% CI -12.9 – 62.2%]).

## **Discussion**

Children who receive palivizumab have more medical and social risk factors for RSV-related hospitalization than those who do not, (25, 26) an expected bias amply illustrated in our study (see Table 1 and Table, Supplemental Digital Content 1, <http://links.lww.com/INF/C674>).

Without any attempt to adjust for these potential confounders, the unadjusted PE was 43.3% (95% CI 34.1 – 51.2%) in the prevention of RSV-related hospitalizations. Given the expected imbalance in risk factors in the group receiving palivizumab prophylaxis, we planned *a priori* to adjust for potential biases between the groups, in PE estimates using inverse propensity score-weighted multiple logistic regression. The final model accounted for these potential confounders except for a residual chronologic age-related difference (Table 2), and showed a PE of 58% (95% CI 43 – 69%). Three prior clinical trials have evaluated palivizumab efficacy. The Impact-RSV trial demonstrated an RSV hospitalization rate of 10.6% in those who received placebo versus 4.8% among high-risk infants who received palivizumab (55% relative reduction,  $P < 0.001$ ); in this trial, efficacy estimates were higher (78%) in preterm infants (32-35 wGA) without CLD (8.1% vs. 1.8%).(11) Gestational age did not predict RSV hospitalization in the logistic regression analysis and the palivizumab effect remained significant ( $P < 0.001$ ). A second randomized, double-blind, placebo controlled trial in 1287 children with hemodynamically significant CHD demonstrated an RSV hospitalization rate of 9.7% in those who received placebo versus 5.3% among recipients of palivizumab (45% relative reduction,  $P < 0.003$ ). (12) Finally, a Dutch randomized trial in preterm infants 33-35 weeks gestational age demonstrated 82% efficacy against RSV hospitalization (5.1% placebo vs. 0.9% palivizumab,  $P = 0.01$ ) as well as 80% efficacy against non-hospitalized medically-attended RSV disease (4.7% placebo vs. 0.9% palivizumab,  $P = 0.02$ ). (7) Our estimated PE of 58% (95% CI 43.1 – 69%) closely approximated that observed in prospective clinical trials of palivizumab efficacy in prevention of RSV-related hospitalizations. This assuages concerns of the generalizability of randomized controlled trial findings to the real world of palivizumab use.(13)

A recent retrospective analysis using Medicaid administrative claims data in children 29-32 wGA found reduced RSV hospitalization rates in subjects who received palivizumab (3.1% versus 5.0%,  $p = 0.04$ ).<sup>(27)</sup> Of interest, in children that received palivizumab had increased hospitalizations for bronchiolitis without a RSV diagnosis (3.3% versus 1.9%,  $p = 0.05$ ). These findings are similar to our original, unadjusted data in which the unadjusted PE was 43.3% (95% CI 34.1 – 51.2%) and children infected with hMPV were more likely to have received palivizumab in the month before admission ( $p < 0.001$ ).<sup>(20)</sup> This study was a database analysis that did not account for known RSV risk factors (e.g., demographic, medical, social data) differences between children that receive palivizumab and those that do not (indication bias). Given the very low rate of palivizumab use in the 33-36 wGA group (3.7%) presumably those recipients would have been those most likely to be hospitalized. Not correcting for these biases was a serious flaw in the study analysis.

In contrast, we used several techniques to try and minimize bias, such as limiting the population to "at-risk" children with indications for palivizumab prophylaxis, having a very specific outcome (lab-confirmed RSV hospitalizations), limiting analyses to the "RSV season" (Nov-April), limiting the data to US and Canada, and using inverse propensity score weighted adjustment and multivariable logistic regression modeling in an attempt to adjust for the inevitable confounding by indication. We also performed two sensitivity analyses to test for potential biases: 1) restricting the definition of a "case" to those children with symptoms of <8 days duration and 2) limiting the analysis to children who tested negative for RSV, but positive for hMPV to assess for the specificity of the effect of PE.

Test-negative controls have been used to estimate vaccine effectiveness theoretically and also through retrospective reanalysis of prospectively collected data of vaccine efficacy from

randomized controlled trials.(16-19) Importantly, a retrospective reanalysis of data from IMpact-RSV and the congenital heart disease trial of palivizumab found that PE with a test negative design (with censoring) approximated the vaccine efficacy identified by the randomized controlled trial.(19) Application of this methodology to PE is thus reasonable. Details on the verification of palivizumab administration are limited, which could result in exposure misclassification, but this likely would result in a bias towards the null (e.g., parents remembering palivizumab receipt but this having occurred >30 days prior to hospitalization, or parents not remembering palivizumab receipt). Importantly, children were enrolled into this study from 2002 – 2006 and molecular results were not available to study teams enrolling these children. Since clinical diagnostics at the time were primarily rapid antigen tests, shell vial culture, and viral culture, it is unlikely that bias was introduced by clinical test results due to the lack of availability in real time.

We also found that palivizumab was 62.1% effective in prevention of RSV-related ICU admission (95% CI 35.1 – 77.9%), confirming the 57% efficacy observed in the IMpact-RSV trial ( $p=0.026$ ).<sup>(11)</sup> Notably, PE was similar among important subgroups such as the 29 – 35 wGA infants <6 months of chronologic age without underlying hsCHD or CLD and all infants <6 months of chronologic age without underlying hsCHD or CLD. To assess for study bias, we evaluated PE against HMPV since palivizumab should have no activity against HMPV. We did not identify statistically significant PE against HMPV in either the unadjusted or the adjusted analyses. The inclusion of an analysis of PE versus HMPV was done to help provide reassurance that residual confounding was not overlooked, and that the effect we measured was specific for RSV. Had the effect we demonstrated been due to uncorrected residual confounding, one would have expected to see the same or slightly lower efficacy against a nonspecific endpoint (in this

case HMPV hospitalization). With the sample size (N = 437: 84 HMVP+ and 353 HMPV-) used in the HMPV analysis, we would have nearly 100% power to detect the 58% efficacy against RSV hospitalization using an alpha = 0.05. Further, we would have 83% power to detect an efficacy of 37%. This suggests that the PE that we found was specific to RSV, and not due to study biases.

Our study has some limitations. Although we attempted to control during the analysis for the substantial baseline differences that existed in those who received versus those who did not receive palivizumab, residual confounding still exists. Data on some potential risk factors (e.g., birthweight, prior NICU admission, breastfeeding) were not collected on children initially enrolled into the study. Point estimates for many of the subgroups (e.g., CLD, hsCHD, <29 wGA and <6 months chronologic age) were imprecise with wide confidence intervals due to small numbers of children. Since limited data were collected on CLD and hsCHD severity, additional unresolved bias in palivizumab administration might exist within these cohorts. It is also possible that some infants were misclassified as having hsCHD due to lack of a standard definition. Due to concerns about differences in use of palivizumab, differences in hospitalization, and due to the small number of children enrolled from non-US and non-Canada sites, we limited our analysis to only US and Canadian sites. This could reduce the generalizability of these data. Finally, we could not assess for impact of palivizumab administration beyond the hospitalization (e.g., recurrent wheezing) that others have described.(7)

Our data should be seriously considered by the US and global decision makers as they consider the role of palivizumab in the prevention of RSV-related hospitalizations in premature and other high risk infants and young children. The AAP now recommends against universal palivizumab administration in prematures born at  $\geq 29$  weeks of gestation unless they have CHD,

CLD, or another condition.(13) The rationale for this recommendation was partly related to an assessment that palivizumab had limited effect on RSV hospitalizations on a population basis. Pediatric societies in several other countries have similarly revised recommendations towards more restrictive use of palivizumab in preterm children.(28-30) In contrast, we found that palivizumab had a 58% (CI 43.1 – 69%) effectiveness in the prevention of RSV-related hospitalizations after adjusting PE for underlying differences that exist in those who receive palivizumab. Importantly, the point estimate of PE for those 29 – 35 wGA and  $\leq 6$  months of chronologic age without hsCHD or CLD was 74.1% (95% CI 56.2 – 84.7%). We also identified that palivizumab provided protection against ICU admissions. Recent data suggest that 29 – 32 wGA infants who have not received palivizumab prophylaxis are at particularly heightened risk of RSV-related hospitalizations, ICU admissions, and mechanical ventilation in comparison to 35wGA infants, particularly at younger chronologic ages.(31) In addition, the median cost of hospitalization was \$27,461 US dollars, but was substantially higher in those requiring ICU admission and mechanical ventilation.(31) Since we were able to demonstrate the effectiveness of palivizumab in the prevention of RSV-related hospitalizations in premature infants without CLD or hsCHD of these gestational ages, we urge that groups reconsider implementation of restrictive policies on palivizumab use in these infants, particularly given the substantial morbidity associated with RSV hospitalizations.

In conclusion, we analyzed PE against PCR-diagnosed RSV LRTI hospitalizations using a test-negative case-controlled study, the preferred design for such studies.(16-18) We found an unadjusted PE of 43.3% (95% CI 34.1 – 51.2%) in the prevention of RSV-related hospitalizations in these high risk infants. Performing inverse propensity score weighted adjustment and multivariable logistic regression modeling achieved balancing between the



groups on all risk factors (except for chronologic age). This resulted in an estimated PE of 58% (CI 43.1 – 69%). We also identified PE in several important subgroups (e.g., 29 – 35 wGA and  $\leq 6$  months of chronologic age without underlying hsCHD or CLD) and in prevention of ICU admissions. Our data suggest that PE in real life is similar to the efficacy observed in prospective clinical trials.

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The original hMPV study was conducted between December 2002 and June 2006 and sponsored by MedImmune. As investigators in the hMPV study, the authors received access to the original study data. The study was designed, data were analyzed and interpreted by the authors. The protocol, analysis, results, and conclusions presented here are solely those of the named authors. No assistance was provided by MedImmune.

**Disclosures:** EJA, EAFS, and RY received financial remuneration to their institutions for the original conduct of this study and for ongoing clinical trial work on other studies from MedImmune and/or AstraZeneca. EJA has served as a consultant for Abbvie regarding RSV. This work was unfunded.

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**Table 1:** Unadjusted and Adjusted Demographic and Baseline Measure Results for General Lineal Model (GLM) of Potential Confounding Factors Association with Palivizumab Treatment

Characteristic or Risk Factor		Unadjusted			Propensity Score Weighted Adjustment			
		Palivizumab (N=434)	Control (N=415)	P value	Palivizumab (N=433)	Control (N=414)	P value	
Age < 3 months	%	18.0	41.7	<0.0001	%	25.5	33.9	0.0046
Age > 6 months	%	51.8	32.1	<0.0001	%	47.9	36.1	0.0068
White Race	%	49.3	42.2	0.0369	%	45.2	46.4	0.7292
Hispanic Race	%	21.4	30.8	0.0018	%	26.5	25.6	0.7651
Birth Weight	Mean	1500.0	2096.8	<0.0001	Mean	1667	1889	<0.0001
	SD	837.7	813.2		SD	642	643	
Multiple Birth <sup>1</sup>	%	24.0	18.6	0.0545	%	21.8	20.9	0.7533
Birth ICU Admission	%	91.4	74.2	<0.0001	%	83.8	82.8	0.6336
Duration of Birth ICU Admission <sup>2</sup>	Mean	73.9	37.1	<0.0001				
	SD	54.4	43.6					
<29 wGA <sup>3</sup>	%	45.6	16.6	<0.0001	%	39.4	23.3	<0.0001
hsCHD <sup>1</sup>	%	19.6	16.6	0.2637				
CLD	%	55.1	17.8	<0.0001	%	47.1	26.3	<0.0001
No Sibs <6y in home	%	34.1	28.0	0.0531	%	32.0	30.3	0.7311
Breastfed	%	10.6	17.6	0.0025	%	13.8	16.4	0.3432
Maternal Education <sup>4</sup>	Mean	12.7	12.2	0.0412				
	SD	2.7	2.8					
Maternal Age	Mean	29.4	27.7	0.0009	Mean	28.6	28.1	0.3762
	SD	7.3	7.3		SD	7.1	7.2	
Timing of admission in relation to illness onset <sup>1</sup>	Mean	2.3	2.4	0.2157				
	SD	0.7	0.7					
Immunosuppressive meds within 1 month	%	59.0	39.5	<0.0001	%	54.0	44.5	0.0074
RSV Season 2003/04	%	43.8	35.7	0.0157	%	41.4	38.3	0.3868
RSV Season 2005/06	%	25.1	33.2	0.0090	%	27.6	30.7	0.3360

ICU = intensive care unit; RSV = respiratory syncytial virus; GLM = general linear model; wGA = weeks gestational age; hsCHD = hemodynamically significant congenital heart disease; CLD = chronic lung disease of prematurity; <6y = less than 6 years of age. NSS = not statistically significant

<sup>1</sup> The following variables were not included in the derivation of the propensity scores and the reasons thereof: multiple birth was excluded because this variable was highly correlated with birth weight, a stronger predictor of treatment group; the variables 1) timing of admission in relation to illness and 2) hsCHD were not statistically significant (NSS) predictors in the univariate GLM, and thus were excluded.

<sup>2</sup> Duration of Birth ICU Admission was not included in derivation of the propensity scores due to the number of missing values (N missing = 163).

<sup>3</sup> <29 weeks GA categorical yes/no variable was included in derivation of propensity scores in lieu of the wGA continuous variable, due to the higher significance of the categorical variable and the collinearity of these two variables.

<sup>4</sup> Maternal Educational level was NSS ( $P > 0.8$ ) in the multivariate logistic regression used to derive propensity scores; therefore it was not included in final model used to develop the propensity scores.

**Table 2:** Propensity Score Weighted Logistic Regression Models to Compute Adjusted Palivizumab Effectiveness (PE) for RSV Outcome\*

Predictor	Odds Ratio (OR)	OR 95% CI	<i>P</i> -value	PE	95% CI	Hosmer & Lemeshow <sup>2</sup> Goodness of Fit P-value
Model <sup>1</sup> Palivizumab	0.42	0.31 – 0.57	<0.0001	58.0	43.1 - 69.0	0.34103
Age > 6 months	0.7	0.5 -0.96	0.0265			
wGA < 29	0.76	0.5 -1.2	0.2623			
CLD	0.72	0.4 -1.2	0.2084			

PE = Palivizumab effectiveness; RSV = respiratory syncytial virus; wGA = weeks gestational age; CLD = chronic lung disease of prematurity; OR = odds ratio; CI: Confidence interval; NSS = Not statistically significant

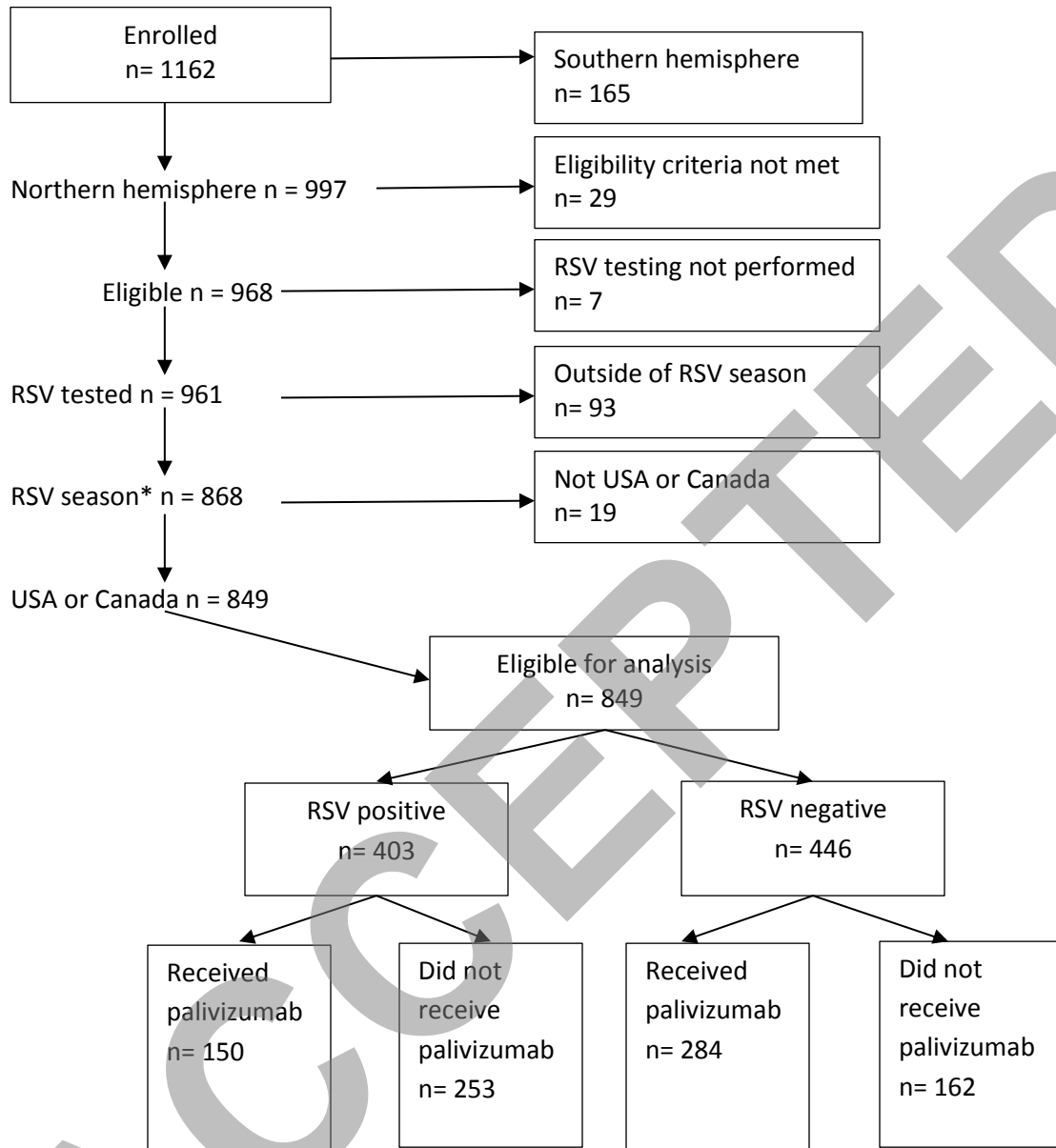
<sup>1</sup> All models tested that had included birth weight, had non-significant contributions from this predictor. The PE with inclusion of birthweight, however, was unchanged from the model presented here. Immunosuppressive medications was NSS for all models tested, and thus was excluded from the final model.

<sup>2</sup> The Hosmer & Lemeshow Goodness of Fit indicates an acceptable fit if  $P > 0.05$ .

\* Two subjects were missing data on weeks of gestational age and were not included in the propensity score weighted logistic regression model.

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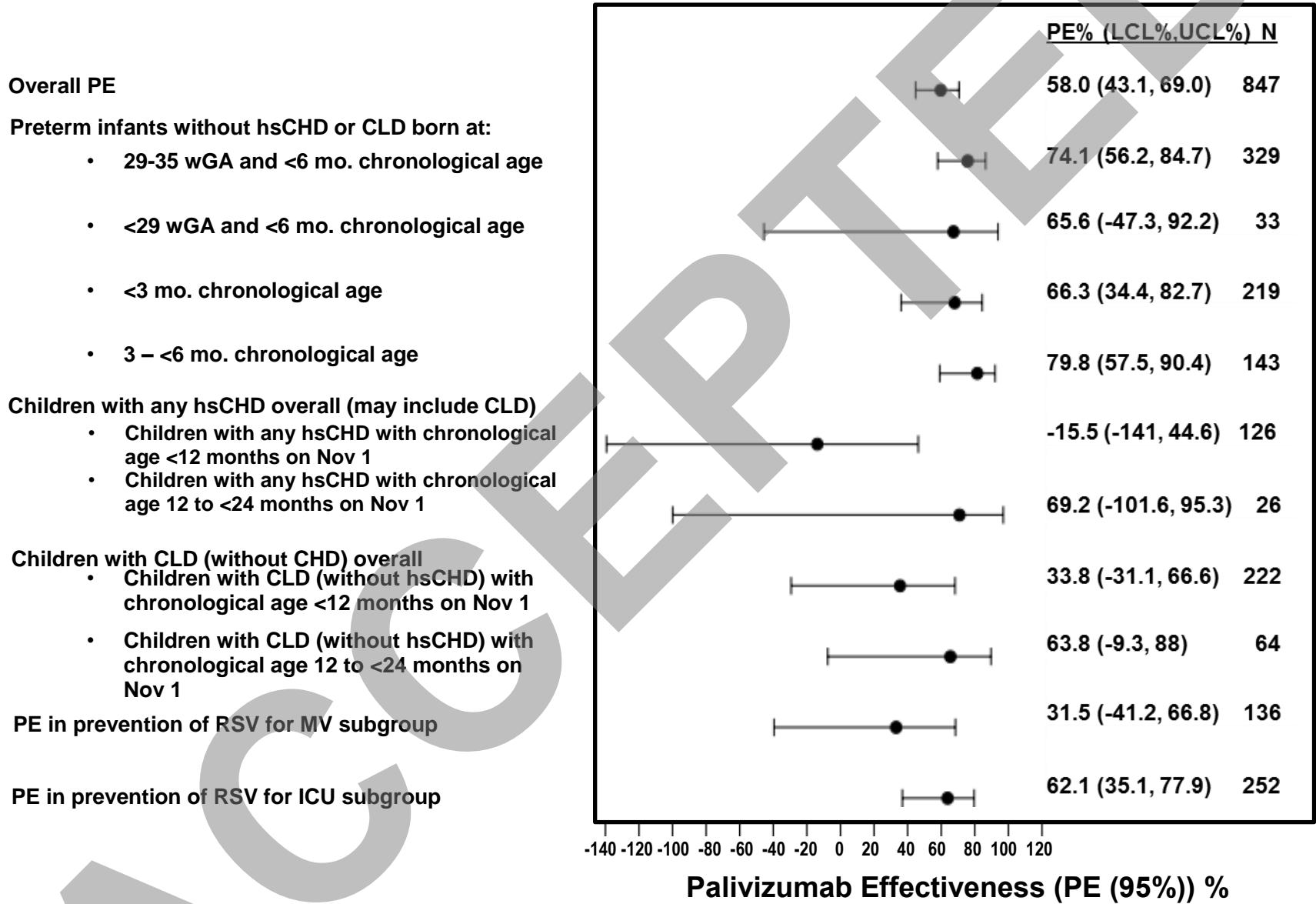
**Figure 1: Flow of study participants**



\*November 1 – April 30



Figure 2. Adjusted Palivizumab Effectiveness Derived Using the IPSW



PE = Palivizumab effectiveness; IPSW = inverse propensity score weight; hsCHD = hemodynamically significant congenital heart disease; CLD = chronic lung disease of prematurity; wGA = weeks of gestational age; mo = month; RSV = respiratory syncytial virus; MV = mechanical ventilation; ICU = intensive care unit; LCL% = lower confidence limit percent; UCL% = upper confidence limit percent

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