



Published in final edited form as:

*Pediatr Infect Dis J.* 2012 November ; 31(11): e229–e231. doi:10.1097/INF.0b013e318266bf89.

## ADHERENCE TO GUIDELINES FOR RESPIRATORY SYNCYTIAL VIRUS IMMUNOPROPHYLAXIS AMONG INFANTS WITH PREMATURITY OR CHRONIC LUNG DISEASE IN THREE UNITED STATES COUNTIES

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### Abstract

Among infants with prematurity and/or chronic lung disease for whom respiratory syncytial virus immunoprophylaxis is recommended, we examined adherence in infants enrolled during healthcare visits for acute respiratory illness in 3 US counties from 2001 to 2007.

Immunoprophylaxis among infants who met national criteria for prophylaxis increased from 33% to 83% over the 6-year period; 17% (11/65) of infants who received immunoprophylaxis did not meet eligibility criteria.

### Keywords

respiratory syncytial virus; adherence; palivizumab

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Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infections in children,<sup>1</sup> with chronic lung disease (CLD), prematurity and congenital heart disease (CHD) conferring the highest risk for severe disease.<sup>2</sup> Palivizumab, a monoclonal antibody to the RSV F protein, reduces RSV hospitalizations among high-risk children when administered

as immunoprophylaxis.<sup>3</sup> We evaluated adherence to American Academy of Pediatrics (AAP) recommendations for palivizumab use in infants with CLD and/or prematurity from 3 US counties.<sup>4–6</sup>

## MATERIALS AND METHODS

The Centers for Disease Control and Prevention–funded New Vaccine Surveillance Network (NVSN) supported prospective, population-based surveillance among children less than 5 years of age with healthcare encounters for acute respiratory illnesses and/or fever in 3 urban counties (Davidson County [Nashville], TN; Monroe County [Rochester], NY; and Hamilton County [Cincinnati], OH).<sup>7,8</sup> Both the NVSN network and this substudy, nested within the NVSN, were approved by the Institutional Review Boards at each of the participating institutions and the Centers for Disease Control and Prevention.

### Study Population

After obtaining informed consent, research staff administered questionnaires to parents for information on high-risk conditions (CLD/bronchopulmonary dysplasia, prematurity, CHD), second-hand smoke exposure (SHS) and day-care attendance. During study years 2001 to 2007, the question “Has your child received palivizumab (Synagis) during fall/winter?” was added to the questionnaire. Nasal and throat swabs were obtained and tested for RSV using previously described reverse-transcription polymerase chain reaction methods.<sup>8</sup>

To evaluate adherence to palivizumab recommendations, only infants who met the following criteria were included in this substudy: enrolled during the 2001 to 2007 RSV seasons, less than 1 year of age at enrollment, successful linkage to birth certificate to determine estimated gestational age (EGA)<sup>9</sup> and parent reported whether the infant received palivizumab (infants whose parents gave a response of unknown were excluded). In addition, it was determined a priori that only infants with swabs testing negative for RSV would be included in the adherence estimates because RSV-positive infants are overrepresented in the study sample and would be expected to have lower rates of adherence if immunoprophylaxis was protective.

### Adherence to AAP Recommendations

Adherence to AAP recommendations released during study years 1998, 2003 and 2006 was assessed.<sup>4–6</sup> The start of the RSV season each year was defined to be November. Eligible infants were categorized into 4 mutually exclusive groups, based on AAP recommendations: (1) history of CLD (bronchopulmonary dysplasia) and age <12 months at start of RSV season; (2) EGA of <29 weeks and age <12 months at start of RSV season; (3) EGA between 29 and <32 weeks and age <6 months at start of RSV season; and (4) EGA of 32 to <35 weeks, age <6 months at start of RSV season and parental report of both SHS and day-care attendance. AAP recommendations regarding palivizumab eligibility for infants between 32 and <35 weeks EGA included more than 1 risk factor and age <6 months at the start of RSV season.<sup>4,6</sup> SHS exposure and day-care attendance were the only 2 risk factors we were able to determine for all infants. Infants with parental report of CHD were excluded because data on the specific type of heart disease were not collected and thus we were not able to determine eligibility.

### Definition of Palivizumab Administration

Children whose parents reported that their infant received palivizumab were considered recipients. We reviewed the medical records of the 7 eligible infants with complete medical records available to validate parental report of immunoprophylaxis. In addition, for the

infants whose parents reported that the child received palivizumab but did not meet the AAP criteria, medical records were also reviewed to reassess eligibility.

## Analysis

Infants included in the 4 eligibility groups and receiving palivizumab and those not included in the 4 eligibility groups but still receiving palivizumab were determined. The Wilson method was used to calculate 95% confidence intervals (CIs) assuming a binomial distribution. Fisher exact test was used to compare the percentage of infants included in the 4 eligibility groups that received palivizumab. Chi-square test was used to evaluate the trend in the proportions of eligible infants who received palivizumab.

## RESULTS

Overall, 1557 infants were enrolled from the 3 study sites (946, 197 and 414 from Davidson, Monroe and Hamilton counties, respectively; Fig. 1). There were 736, 396 and 425 infants enrolled in hospitals, emergency departments and clinics, respectively. More infants from Davidson County were included because Monroe County was unable to link to birth certificate data in the early study years, and Hamilton County did not participate in the NVSN until 2003. In addition, birth certificate linkage was higher in Davidson County (96%) than the other sites (61% Monroe, 76% Hamilton).

In total, 57 of 1557 infants (3.7%) were determined to be in the AAP-defined eligibility groups: 20 infants with parental report of CLD, 14 infants with EGA of <29 weeks and 23 infants with EGA between 29 and <32 weeks and aged <6 months at start of RSV season. No infant with EGA between 32 and <35 weeks, age <6 months at start of RSV season and both SHS and day-care exposure was identified. Among the 57 eligible infants (ranging from 3 to 13 annually), 70% had public insurance, 58% were male and 58% were African American.

Overall, 40 of 57 (70%; 95% CI: 56.6–81.6) infants in the eligibility groups received palivizumab by parental report. Comprehensive medical records were available on 7 of these 57 infants, and palivizumab administration was confirmed in 6 (86%). Of the 20 infants with CLD (ranging from 1 to 5 annually), 90% (95% CI: 69.9–97.2) received palivizumab, compared with 59% (95% CI: 43.5–73.7) receiving palivizumab in the other eligibility groups. Among infants included in the AAP-defined eligibility groups, there was a significant increase in the proportion who received palivizumab, from 33% (2001–2002) to 83% (2006–2007),  $P = 0.008$ .

Overall, 1500 infants did not fall into any of the 4 eligibility groups. However, 29 of these infants were reported to have received palivizumab. Comprehensive medical record review in 26 of these 29 infants was completed. Eleven were classified into one of the eligibility groups and should have received palivizumab. In addition, 15 infants did not meet eligibility criteria and should not have received palivizumab, including 9 infants in the 32 to <35 weeks EGA group who did not meet national eligibility criteria because they had only a single risk factor (7 infants) or were older than 6 months at the start of the RSV season (2 infants). Finally, parental report of palivizumab was likely inaccurate in 4 term or near-term infants as medical records did not indicate immunoprophylaxis. Overall, 14 of the 26 records reviewed contained the child's medication administration history with 11 (79%) having documentation of palivizumab administration, and 10 of 11 receiving it throughout the RSV season. Thus, of the 26 infants who did not meet eligibility criteria and were reported by the parents to receive palivizumab, medical record review indicated that 11 of these infants received palivizumab without appropriate indications, accounting for 17% (11/65) of all treated infants.

## DISCUSSION

In infants enrolled in the NVSN with acute respiratory illness or fever residing in 3 US counties, adherence to palivizumab recommendations for infants with CLD and/or prematurity increased from 33% in 2001 to 2002 to over 80% in 2005 to 2007. Differences in study methodology, adherence definitions and study periods limit direct comparisons of this population to earlier published reports; however, adherence was similar to the approximately 70% adherence reported in Florida Medicaid recipients in 2004 to 2005.<sup>10</sup> We also found that 17% of infants receiving palivizumab did not meet eligibility criteria, a percentage lower than some earlier reports, but higher than percentages found in some studies after intervention programs.<sup>10,11</sup>

Our study had limitations. First, infants were enrolled in different healthcare settings, and although most hospitalizations in study counties were included, only selected outpatient visits were captured. Second, 2 sites contributed only 4 years of data. Next, verification of palivizumab administration in each infant, complete medical record review to document type of CHD and documentation of medication use to classify infants with CLD were not included. However, our limited review of medical records found that parental report of palivizumab administration had a positive predictive value of 86% among infants who met eligibility criteria. We included all infants in the <28 weeks EGA group who were less than 1 year of age at enrollment and did not limit inclusion to only their first RSV season, as per the recommendations starting in December 2003.<sup>6</sup> Other limitations included that some infants in the 32 to <35 weeks EGA group may have been misclassified as ineligible because we did not have complete information on all risk factors and the small number of cases each year. Finally, we did not assess interventions that might have increased or modified palivizumab adherence.<sup>10-12</sup>

In this real-world assessment of adherence to palivizumab, we found increasing adherence to AAP recommendations during the 6-year period in our study population, but still 17% of treated infants did not meet AAP eligibility criteria.

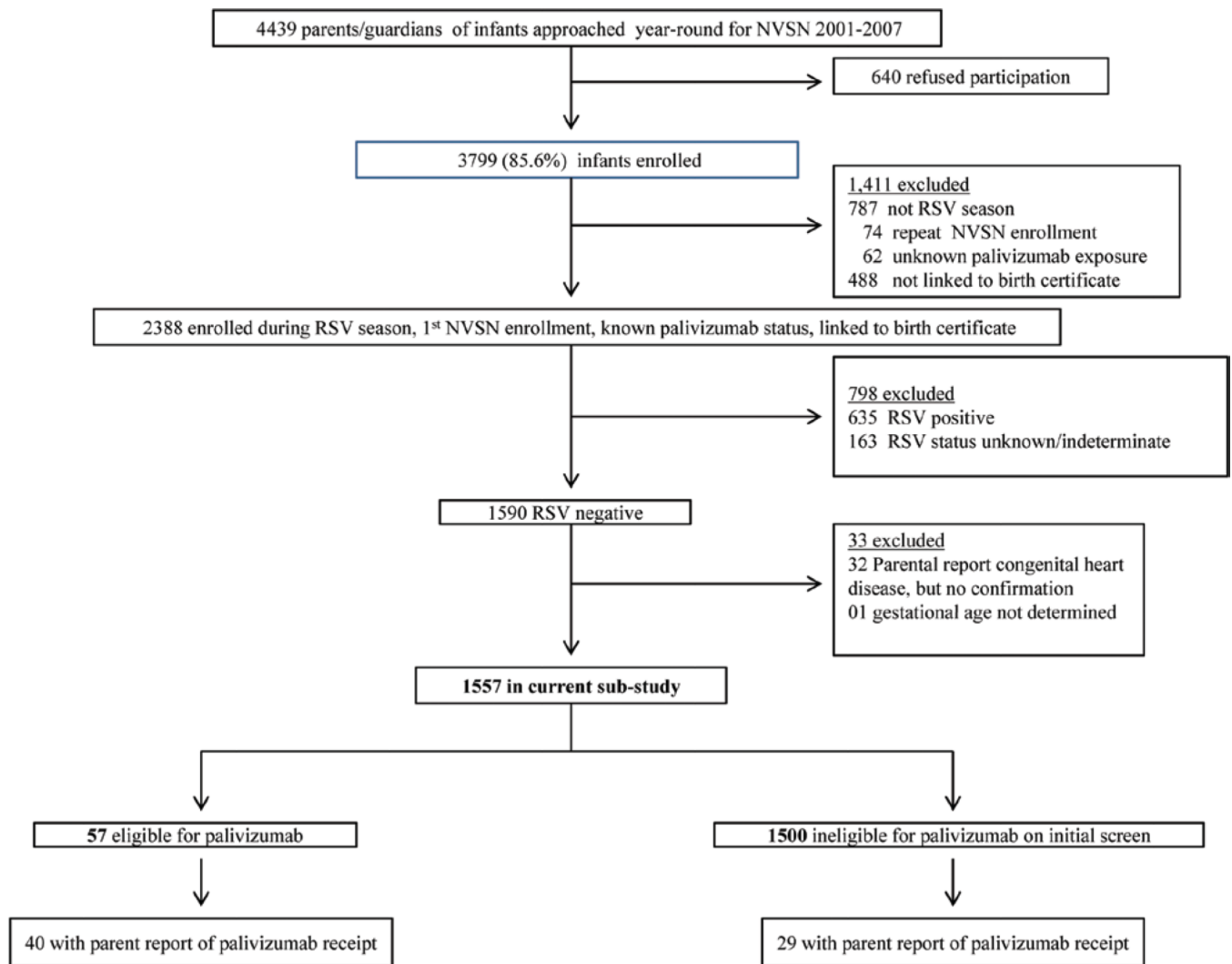
## Acknowledgments

This study was supported by the US Centers for Disease Control and Prevention [Cooperative agreement numbers U38/CCU217969, U01/IP000017, U38/CCU417958, U01/IP000022, U38/CCU522352, U01/IP000147]. AA received investigator-initiated research funding from MedImmune. MAS is a consultant for MedImmune, receives research funding from GlaxoSmith-Kline and is on the speaker's bureau for GlaxoSmithKline and Merck. CBH is a consultant for MedImmune and GlaxoSmithKline. JVW serves on the Scientific Advisory Board of Quidel. TVH has previously received grant funding from MedImmune.

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**FIGURE 1.** The number of infants enrolled in the New Vaccine Surveillance Network (NVSN) in Davidson, Rochester and Hamilton counties during 2001 to 2007, the reasons for and number of exclusions and the final number of infants included in current substudy population.