Authors' Responses In Response to the Letter From Ambrose

We appreciate the opportunity to comment on the issues raised by an AstraZeneca employee regarding the revised American Academy of Pediatrics (AAP) Guidance on the use of palivizumab for respiratory syncytial virus (RSV) prophylaxis.

First, we agree preterm infants experience an RSV hospitalization rate that increases with decreasing gestational age. The critical question is, "How great is the increase in risk for preterm infants relative to term infants?" In the prospective study of 132 000 infants by Hall et al[1] and reproduced in Table 1 of the newly published AAP Technical Report,[2] the risk of RSV hospitalization over a 6-month season for infants born at ≥37 weeks is 5.3 per 1000 (95% confidence interval [CI], 4.9–5.8). Corresponding rates for infants with gestational age ≥35, 32–34, 29–31, and <29 weeks were 5.1 (95% CI, 4.7–5.5), 6.9 (95% CI, 4.3–10.1), 6.3 (95% CI, 2.0–12.4), and 19.3 (95% CI, 8.4–34.0) per 1000, resulting in nonsignificant differences for all levels of prematurity compared with term infants, except for infants born at <29 weeks, who show a recognizable spike in hospitalization rates. In this report, the increase in risk of hospitalization is ~1 more RSV hospitalization for every 1000 preterm births. Two other studies discussed in the AAP Technical Report and performed in the preprophylaxis era show a similar very small increase in risk of RSV hospitalization among preterm infants relative to full-term infants.

Second, AAP Clinical Practice Guidelines regarding the diagnosis and management of bronchiolitis will be published in *Pediatrics* in the next few months. The new palivizumab Policy Statement and Technical Report were developed in close collaboration with the authors the Bronchiolitis Guidelines Committee so that the AAP recommendations are harmonized and identical. These Clinical Practice Guidelines will be presented in a format consistent with the Institute of Medicine Standard for Development of Trustworthy Practice Guidelines. Each Key Action Statement reviews the level of evidence, presents the benefit–harm relationships, and addresses the level of strength of the recommendation.

Third, Ambrose suggests that the discussion of the study by Hall et al in the Technical Report is "incomplete and potentially misleading." Ambrose states that "approximately 70% of eligible infants in the study were receiving palivizumab," and therefore the study results "cannot be used to describe the burden of RSV in the absence of prophylaxis." A careful reading of the publication by Hall et al finds the following statement: "Palivizumab's effect on our overall rates of RSV hospitalization was unlikely to be appreciable because only a small proportion (less than 5%) of our study population was eligible for palivizumab and administration to eligible infants was variable (30% to 70%) during most study years."[1] Thus, the results from this Centers for Disease Control and Prevention–sponsored study are valid and unlikely to be influenced by palivizumab use in a small number of participants.

Fourth, Ambrose states the report by Stevens et al "did not include hospitalizations in the community's regional hospital" and might underestimate hospitalization rates.[3] In fact, Stevens et al wrote, "We extrapolated from data collected at the university hospital to generate estimates for our entire region" (a 12-county neonatal network surrounding Rochester, New York). Thus, hospitalization rates were adjusted to account for all RSV hospitalizations in the 12 counties and not just Rochester General Hospital. This indicates the hospitalization rates reported in this study probably are precise and reliable. Stevens et al also note, "Our analysis did not demonstrate a net cost savings of RSV prophylaxis for the entire cohort of high-risk infants or for any of the subgroups analyzed," which included 1029 infants born at ≤32 weeks' gestation.

Ambrose states publications may "underestimate the true rates of (RSV hospitalization) due to the suboptimal sensitivity of antigen detection and viral culture." It is widely recognized that RSV antigen tests and other rapid detection methods have sensitivities of 80% to 99% and specificities of >95% when compared with culture. In fact, antigen detection assays were used to define the primary end point in the 2 MedImmune-sponsored clinical trials that addressed the efficacy of palivizumab prophylaxis.

Surprisingly, Ambrose suggests greater use of palivizumab prophylaxis is justified by quoting Winterstein et al.[4] This publication evaluated the age at which moderate preterm Medicaid-enrolled infants without other indications for RSV prophylaxis showed an RSV hospitalization risk similar to that of healthy term infants in Florida and Texas. Although moderately premature infants show about twice the risk of RSV hospitalization during the first month of life, this risk drops to no recognizable differences at an age of 4 months. The authors also report the effect of palivizumab prophylaxis on the odds of RSV hospitalization in preterm infants. In this population-based study, palivizumab effectiveness was smaller in Texas than in the IM-pact RSV trial and was statistically nonsignificant in Florida.

In another manuscript, Winterstein and colleagues[5] wrote, "The cost of immunoprophylaxis with palivizumab far exceeded the economic benefit of preventing hospitalizations, even in infants at highest risk of RSV infection." This study evaluated Florida Medicaid

claim forms during the 2004 to 2005 season. For the most cost-effective subgroup, a mean of $302 103 would be spent to prevent 1 RSV hospitalization costing a mean of $8910. Furthermore, as noted in the Technical Report, palivizumab prophylaxis has not been shown to prevent intensive care admission or reduce mortality, and prophylaxis has only a limited impact on long-term morbidity. We acknowledge the presence of a slightly elevated risk of RSV hospitalization for moderate premature infants in the first months of life but judge the small baseline incidence coupled with high palivizumab cost to not justify the expenditures. Although the impact of RSV hospitalization on a family is more than just financial cost, administration of palivizumab to a large number of children to prevent 1 RSV hospitalization exacts a cost on a number of families each month in terms of time and exposure of an infant to infected patients in a physician's office.

Finally, Ambrose cites a publication by Hasegawa et al.[6] Data in this publication indicate that in the United States the hospitalization incidence for all-cause bronchiolitis between 2000 and 2009 has fallen from 17.9 to 14.9 per 1000 among children <24 months of age. Ambrose states that no corresponding decrease among infants at high risk for bronchiolitis was noted during this time frame. This finding probably reflects an increase in prevalence of children with chronic medical conditions in the general population, in whom the efficacy of prophylaxis is unknown.[7]

If the references Ambrose cites are read carefully, the results support the recommendations in the updated AAP Policy Statement.[8] Many authorities question whether the benefit from RSV prophylaxis has become so limited and the cost has become so high that prophylaxis cannot be justified. At this time, it is the considered opinion of 21 committees and sections within the AAP that prophylaxis still may be considered for infants at greatest risk, as recommended in the updated Policy Statement. In the absence of robust new data demonstrating a clear benefit for preterm infants born at <29 weeks' gestation, future guidance may determine whether is impractical to recommend prophylaxis for this group of extremely premature infants.

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Conflict of Interest:

None declared.

REFERENCES

1. Hall CA, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus–associated hospitalizations among children less than 24 months of age. *Pediatrics*. 2013;132(2). Available at: www.pediatrics.org/cgi/content/full/132/2/e341
2. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134(2). Available at: www.pediatrics.org/cgi/content/full/134/2/e620
3. Stevens TP, Sinkin RA, Hall CB, Maniscalco WM, McConnochie KM. Respiratory syncytial virus and premature infants born at 32 weeks' gestation or earlier: hospitalization and economic implications of prophylaxis. *Arch Pediatr Adolesc Med*. 2000;154(1):55–61
4. Winterstein AG, Knox CA, Kubilis P, Hampp C. Appropriateness of age thresholds for respiratory syncytial virus immunoprophylaxis in moderate-preterm infants. A cohort study. *JAMA Pediatr*. 2013;167(12):1118–1124
5. Hampp C, Kauf TL, Saidi AS, Winterstein AG. Cost-effectiveness of respiratory syncytial virus prophylaxis in various indications. *Arch Pediatr Adolesc Med*. 2011;165(6):498–505
6. Hasegawa K, Tsugawa Y, Brown DFM, Mansbach JM, Camargo CA Jr. Trends in bronchiolitis hospitalizations in the United States, 2000–2009. *Pediatrics*. 2013;132(1):28–36
7. Feudtner C, Hays RM, Haynes G, Geyer JR, Neff JM, Koepsell TD. Deaths attributed to pediatric complex chronic conditions: national trends and implications for supportive care services. *Pediatrics*. 2001;107(6). Available at: www.pediatrics.org/cgi/content/full/107/6/e99
8. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134(2):415–420

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In Response to the Letter From Braden

Dr Braden raises an important consideration regarding dispensing palivizumab from the pharmacy. The statement in the recent American Academy of Pediatrics Technical Report states "a vial sharing scheme is important to minimize wastage."[1] The Package Insert notes, "Synagis is supplied as a single-dose vial and does not contain preservatives. Do not re-enter the vial after withdrawal of drug; discard unused portion. Only administer one dose per vial."[2] The answer to Dr Braden involves 2 issues.

First is the length of time a vial can be stored once it is accessed. As directed in the *United States Pharmacopeia,* Chapter 797, the contents of a single-dose vial of a sterile product may be used ≤6 hours after initial needle puncture if the procedure is carried out in a hood with International Organization for Standardization Class 5 air quality.[3] However, if a single-dose vial is penetrated in a setting where the air quality is less than International Organization for Standardization Class 5, the contents must be used within 1 hour.

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