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BRIEF REPORT

Modeling the Potential Impact of the 2014 American Academy of Pediatrics Respiratory Syncytial Virus Prophylaxis Guidance on Preterm Infant RSV Outcomes

Kimmie K. McLaurin · Archana Chatterjee · Doris Makari

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ABSTRACT

Introduction: The American Academy of Pediatrics (AAP) Committee on Infectious Diseases issued updated guidance on respiratory syncytial virus (RSV) prophylaxis in 2014. This report models the potential impact of the new guidance on RSV outcomes in preterm infants 29–34 weeks' gestational age (wGA) without chronic lung disease in the United States.

Methods: The number of preterm infants was estimated using 2012 natality data. Palivizumab utilization prior to the 2014 guidance update was estimated using 2013–2014 specialty pharmacy utilization data. Low, moderate, and high RSV hospitalization (RSVH) rates as well as average hospital length of stay, intensive care unit (ICU) admissions and mechanical ventilation (MV) frequencies were derived from published observational studies. Palivizumab efficacy was derived from two randomized clinical trials. RSV events that would be attributable to the 2014 guidance change were calculated for preterm infants 29–31 and 32–34 wGA.

Results: Annual number of infants 29–34 wGA surviving the neonatal period was estimated at 123,687. Of these, an estimated 44,712 (37%) would receive palivizumab based on the 2012 guidance. The annual number of RSVH among infants 29–34 wGA would increase from 3580 under the 2012 guidance to 6166 under the 2014 guidance based on moderate rates. This would result in an additional 24,440 hospitalization days, 1162 ICU admissions, and 584 MV events among this population.

Conclusions: Based on published historical and contemporary data on RSVH rates in preterm infants 29–34 wGA, the 2014 AAP guidance is expected to result in additional burden to the healthcare system and families of preterm infants. The impact of the new guidance will be difficult to detect among the overall infant population, particularly in settings without routine testing for RSV, but the impact will be

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K. K. McLaurin (✉) · D. Makari
AstraZeneca, Gaithersburg, MD, USA
e-mail: Kimmie.McLaurin@astrazeneca.com

A. Chatterjee
University of South Dakota Sanford School of Medicine, Sioux Falls, SD, USA

substantial for the small high-risk population affected by the changes.
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INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of acute lower respiratory tract infection and a major cause of hospitalizations in young children [1]. In preterm infants, the risk for severe RSV disease may lead to hospitalization and, in some cases, intensive care unit (ICU) admissions and mechanical ventilatory support [2].

Palivizumab (MedImmune, Gaithersburg, MD, USA) is a monoclonal antibody indicated for the prevention of serious lower respiratory tract disease caused by RSV in high-risk children [3]. The American Academy of Pediatrics (AAP) first published guidance for use of palivizumab prophylaxis against RSV in 1998 and subsequently updated them in 2000, 2003, 2006, 2009, and 2012 [4]. These later iterations of the guidance narrowed the population recommended for prophylaxis with a focus on the increased risk and severity of RSV disease associated with younger gestational age and younger chronologic age [4, 5]. The 2012 Committee on Infectious Diseases (COID) guidance recommended use of palivizumab during the RSV season in preterm infants ≤28 weeks' gestational age (wGA) and <12 months of age at RSV season start, 29–31 wGA and <6 months of age at RSV season start, and 32–34 wGA and <3 months of age at RSV season start. In addition to being <3 months of age, infants 32–34 wGA were required to have additional risk factors of either day care and/or school-age siblings and could only receive prophylaxis through 90 days of age [6]. In July 2014, the AAP issued updated guidance on RSV prophylaxis that no longer recommended palivizumab for preterm infants born 29–34 wGA without chronic lung disease (CLD), asserting that "data regarding the risk of RSV hospitalization for most preterm infants do not support a benefit from prophylaxis [4]".

However, there is controversy surrounding the elimination of palivizumab use among infants 29–34 wGA. It has been argued that the recommendation is not justified by the studies cited by the COID [7, 8]. Boyce et al. noted, "as academic physician-scientists, we should carefully evaluate all of the existing data and properly study proposed changes before further restricting palivizumab use in this voiceless and vulnerable population of infants [7]". Similarly, the Institute of Medicine's Standards for Developing Trustworthy Clinical Practice Guidelines recommend that guidelines include descriptions of the potential benefits and harms [9].

The current analysis was designed to address this need to evaluate the potential impact of the AAP guidance change on RSV hospitalizations in US preterm infants. By constructing a model that elucidates the expected RSV outcomes for preterm infants per the 2012 guidance compared with the 2014 guidance, we were able to estimate the potential impact of the 2014 AAP guidance on RSV outcomes in preterm infants born 29–34 wGA without CLD during the 2014–2015 and future RSV seasons.

METHODS

This article does not contain any new studies with humans or animal subjects performed by

any of the authors. Eight steps were taken to model the potential impact of the 2014 AAP guidance on RSV outcomes in preterm infants 29–31 wGA and <6 months chronologic age at RSV season start and infants 32–34 wGA and <90 days chronologic age with ≥1 risk factor (Fig. 1). The first step involved identifying the total number of US preterm births surviving the neonatal period using the 2012 CDC Natality File and Linked Birth/Infant Death Data File [10]. In step 2, the number of preterm infants 29–31 and 32–34 wGA without CLD who would have received palivizumab on the basis of the 2012 AAP guidance were estimated using Specialty Distribution Network outpatient usage data from the 2013–2014 RSV season. For example, infants 32–34 wGA who would have received palivizumab were assumed to be less than 90 days of age during the RSV season and had at least one additional risk factor (daycare attendance or preschool-aged siblings). Step 3 involved selecting low, moderate, and high rates of RSV hospitalization (RSVH) for infants born at 29–31 and 32–34 wGA who would have received palivizumab under the 2012 guidance and for infants 29–31 and 32–34 wGA who would have not received palivizumab under the 2012 guidance. These hospitalization rates were estimated using historical and contemporary data from published studies [11–13]. The low, moderate, and high RSVH rates for infants 29–31 wGA <6 months at RSV season start who would have received palivizumab were 6.0%, 8.5%, and 12.0%, respectively. Among infants 32–34 wGA <90 days of age during the RSV season with one additional risk factor (daycare attendance or preschool-aged siblings), the low, moderate, and high RSVH rates for infants that would have received palivizumab were 5.0%, 6.5%, and 10.0%, respectively [11]. Observational studies would suggest that infants 29–31 wGA and 32–34 wGA that would have not received palivizumab (those >6 months at RSV season start for 29–31 wGA and those >90 days or those <90 days during the season without risk factors for infants 32–34 wGA) would have lower RSVH risk than infants of the same wGA group that was identified to receive palivizumab. Therefore, the low, moderate, and high RSVH rates were estimated to be 3.0%, 4.5%, and 6.0% for infants 29–31 wGA and 2.0%, 3.5%, and 5.0% for infants 32–34 wGA, respectively. From these rates and the known population sizes, the total annual number of RSVH among preterm infants 29–31 and 32–34 were calculated.

Next, the RSVH relative risk reduction rates associated with palivizumab use were applied in step 4; a relative risk reduction of 78% for preterm infants without bronchopulmonary dysplasia was obtained from the IMpact study findings, which are similar to recent results of Blanken et al. [12, 14]. In step 5, the number of hospitalizations with palivizumab use based on the 2012 AAP guidance was calculated, and in step 6, the number of hospitalizations with palivizumab use based on the 2014 AAP guidance was calculated. These estimates were then subtracted to calculate the number of additional hospitalizations expected from the change in guidances (step 7). Finally, in step 8, hospitalization length of stay, ICU rates, and mechanical ventilation rates were applied from an observational study of RSV-confirmed hospitalizations among US preterm infants 29–35 wGA that did not receive palivizumab [15–17]. The average hospitalization length of stay was 10.4 days in infants 29–31 wGA and 8.4 days in infants 32–34 wGA and <90 days chronologic age. The average ICU rates were 48.1% in infants 29–31 wGA and 41.4% in infants 32–34 wGA and <90 days chronologic

Step 1: Identify total number of US preterm births surviving the neonatal period
(Using 2012 CDC Natality File and Linked Birth/Infant Death Data [10])
Step 2: Estimate number of preterm infants 29–34 wGA without CLD who would have been eligible for and receive palivizumab on the basis of the 2012 AAP guidance
(Using 2013-14 RSV-season specialty pharmacy utilization data)

Infant Group	Number of births	Eligible and received palivizumab	Number of infants
29–31 wGA	29,106	Yes	20,474
		No	8,632
32–34 wGA	94,581	Yes	24,238
		No	70,343

Step 3: Provide low, moderate, and high estimates for the RSV hospitalization rates in infants 29–34 wGA who would have received palivizumab based on the 2012 AAP guidance
(Using hospitalization rates from previously published studies [12,13])

	Low	Moderate	High
29–31 wGA received palivizumab	6.0%	8.5%	12.0%
29–31 wGA did not receive palivizumab	3.0%	4.5%	6.0%
32–34 wGA received palivizumab	5.0%	6.5%	10.0%
32–34 wGA did not receive palivizumab	2.0%	3.5%	5.0%

Step 4: Apply RSV hospitalization relative risk-reduction rates from use of palivizumab
(Using 78% obtained from the IMpact study findings [14])

Step 5: Calculate the number of hospitalizations expected on the basis of the 2012 AAP guidance with palivizumab use

Step 6: Calculate the number of hospitalizations expected on the basis of the 2014 AAP guidance without palivizumab use

Step 7: Calculate the number of additional hospitalizations expected from the change in guidances
Number of hospitalizations in step 6–number of hospitalizations in step 5

Step 8: Apply estimated average hospitalization length of study, ICU rates, and mechanical ventilation rates (Using data from an observational study of RSV-confirmed hospitalizations [15])

	Hospitalization Length of Stay	ICU Rates	Mechanical Ventilation Rates
29–31 wGA	10.4	48.1%	25.9%
32–34 wGA	8.4	41.4%	18.9%

◀**Fig. 1** Modeling the potential impact of the 2014 AAP guidance on RSV outcomes in preterm infants. *AAP* American Academy of Pediatrics, *CDC* Centers for Disease Control and Prevention, *CLD* chronic lung disease, *ICU* intensive care unit, *RSV* respiratory syncytial virus, *wGA* weeks' gestational age

age. The average mechanical ventilation rates were 25.9% in infants 29–31 wGA and 18.9% in infants 32–34 wGA and <90 days chronologic age.

The model was created using Excel 2013 (Microsoft Corporation).

RESULTS

The annual number of infants 29–34 wGA surviving the neonatal period was estimated at 123,687 (29,106 infants 29–31 wGA and 94,581 infants 32–34 wGA; Fig. 2); this is approximately 3% of the total annual number of US births, 3,937,686. Of these infants, an estimated 44,712 (37%) would have received palivizumab based on the 2012 AAP guidance, including 20,474 (70%) infants 29–31 wGA and 24,238 (26%) infants 32–34 wGA.

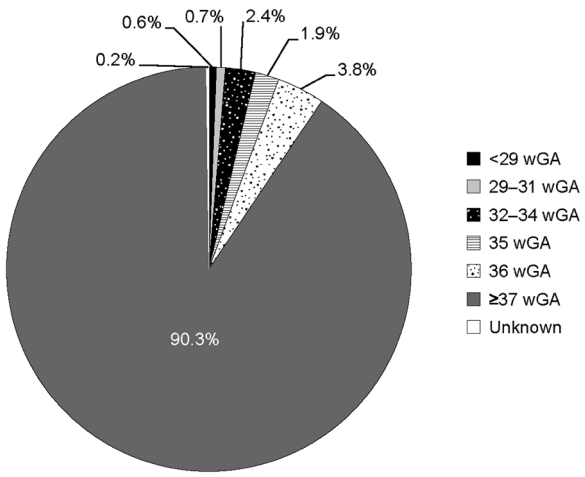

Fig. 2 US births by gestational age after adjusting for neonatal deaths. *wGA* weeks' gestational age

The low, moderate, and high estimates for the total number of RSVH expected post-2014 guidance in infants 29–31 wGA were 1487, 2129, and 2975, respectively. The low, moderate, and high estimates for the total number of RSVH expected in infants 32–34 wGA were 2619, 4037, and 5941, respectively.

Using low estimates, the number of additional RSVH that would be associated with the 2014 guidance relative to the 2012 guidance was 958 for infants 29–31 wGA and 945 for infants 32–34 wGA (Fig. 3a). Based on moderate estimates, the numbers of additional RSVH that would be associated with the 2014 guidance relative to the 2012 guidance were 1357 and 1229 for infants 29–31 and 32–34 wGA, respectively (Fig. 3b). The high estimates for the number of additional RSVH that would be associated with the 2014 guidance relative to the 2012 guidance were 1916 for infants 29–31 wGA and 1891 for infants 32–34 wGA (Fig. 3c).

The low estimates for the number of additional RSVH that would be associated with the 2014 guidance relative to the 2012 guidance would result in an additional 9965 and 7940 hospitalization days, 461 and 391 ICU admissions, and 248 and 179 mechanical ventilation events, in infants 29–31 wGA and 32–34 wGA, respectively. The moderate estimates for the number of additional RSVH that would be associated with the 2014 guidance relative to the 2012 guidance would result in an additional 14,117 and 10,322 hospitalization days, 653 and 509 ICU admissions, and 352 and 232 mechanical ventilation events, in infants 29–31 wGA and 32–34 wGA, respectively. Using high estimates, this would result in an additional 19,930 and 15,881 hospitalization days, 922 and 783 ICU admissions, and 496 and 357 mechanical ventilation events in infants 29–31 wGA and 32–34 wGA, respectively.

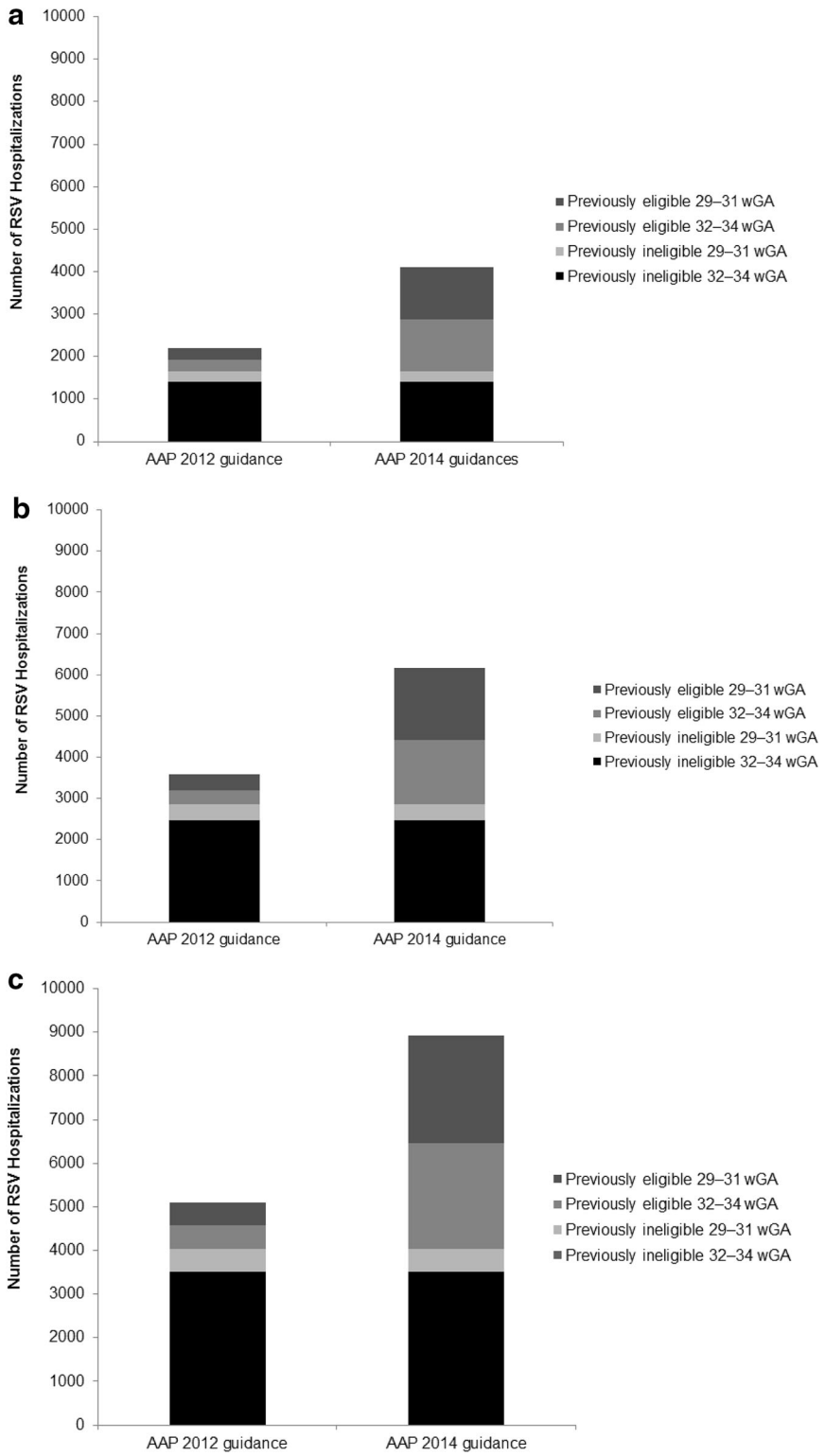

Fig. 3 Estimated number of RSV hospitalizations among infants 29–31 wGA and 32–34 wGA based on **a** low, **b** moderate, and **c** high estimates. *AAP* American Academy of Pediatrics, *RSV* respiratory syncytial virus, *wGA* weeks' gestational age

DISCUSSION

The current analysis quantifies the size of the population affected by the 2014 policy change and the range of expected additional RSV hospitalizations in that population in the absence of palivizumab use. This quantification of the negative or serious consequences of a new clinical practice guidance is a recommended best practice by the Institute of Medicine [9].

The data justifying the 2014 COID guidance on palivizumab use have been questioned, because they rely on reinterpretation of historical studies that were previously cited by AAP in support of palivizumab use, along with newer studies conducted in years in which palivizumab use was widespread [7, 11]. The 2014 AAP policy asserted, "In recent large cohort studies of moderately preterm infants, the majority of whom did not receive palivizumab, 2.5% to 4.9% required hospitalization for RSV infection during the RSV season indicating that more than 95% did not require hospitalization [4]". A review of historical and contemporary studies suggests that this range is an underestimate, consistent with the fact that the cited study did not employ active surveillance or active testing for RSV.

Similarly, without active case-finding methods to evaluate the burden of RSV disease among US preterm infants, the overall adverse outcomes and healthcare costs associated with the new 2014 AAP guidance may be easily overlooked due to the small number of infants affected by this guidance. Preterm infants born 29–34 wGA comprise 3.1% of live births, whereas those born 29–31 wGA represent only 0.7% [18]. The likelihood of an individual physician or payer recognizing the impact of the 2014 AAP guidance is low because of the small number of preterm infants in individual practices or healthcare plans. Additionally, impact assessment will be particularly difficult given that there is not routine testing for RSV, even among preterm infants [11]. Findings from the present study predict that the 2014 AAP guidance will result in additional burden to the healthcare system and families of preterm infants.

CONCLUSION

Although the impact of the new guidance is difficult to quantify among the overall infant population, the impact may be significant for this small, high-risk population, which, after having incurred high costs for birth hospitalization [19], will potentially be at risk for additional adverse outcomes such as RSV hospitalization, intensive care admission, and mechanical ventilation.

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Compliance with ethics guidelines. This article does not contain any new studies with humans or animal subjects performed by any of the authors.

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