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REVIEW

Impact of the 2014 American Academy of Pediatrics Policy on RSV Hospitalization in Preterm Infants in the United States

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ABSTRACT

Despite being a leading cause of hospitalization due to lower respiratory tract infections, the treatment of respiratory syncytial virus (RSV) infection is primarily supportive. Palivizumab is the only licensed immunoprophylaxis (IP) available for preventing severe RSV infection in high-risk populations including ≤35 weeks' gestational age (wGA) infants and children with chronic lung disease of prematurity or congenital heart disease. The American Academy of Pediatrics (AAP) has published its IP recommendations since the approval of palivizumab. In 2014, the AAP stopped recommending RSV IP in 29-34 wGA infants without comorbidities and stated that RSV hospitalization (RSVH) risk in otherwise healthy ≥29 wGA infants and term infants was similar. Since then, experts in the field have debated the appropriateness of the 2014 policy change, and several real-world evidence studies at national and regional levels in the United States have examined the impact of the AAP policy on 29-34 wGA infants. Overall, these studies showed a significant decline in RSV IP use and a concurrent increase in RSVH risk among 29-34 wGA infants relative to term infants in the seasons after the 2014 policy change. A similar decrease in IP use and increase in RSVH risk was also observed among <29 wGA infants relative to term infants after the 2014 policy change. This decrease could be an unintended consequence as <29 wGA infants are an in-policy population recommended to receive RSV IP. According to the National Perinatal Association, strong evidence exists to support the use of RSV IP in all ≤32 wGA and 32-35 wGA infants with risk factors such as attending day care, having ≥1 school-aged siblings, twin or greater multiple gestation, younger age, and exposure to parental smoking. Until new preventive and treatment options become available,

palivizumab can help prevent and mitigate RSV disease burden among high-risk preterm infants.

Keywords: American Academy of Pediatrics; Bronchopulmonary dysplasia; Chronic lung disease of prematurity; Congenital heart disease; High-risk preterm infants; Immunoprophylaxis; National Perinatal Association; Palivizumab; Respiratory syncytial virus; RSV hospitalization

Key Summary Points:

- Currently, palivizumab is the only respiratory syncytial virus (RSV) immunoprophylaxis (IP) available for use in specific high-risk pediatric populations, including premature (≤35 weeks' gestational age [wGA]) infants.
- In 2014, the American Academy of Pediatrics (AAP) stopped recommending RSV IP use in otherwise healthy 29 to 34 wGA infants without comorbidities and stated that RSV hospitalization (RSVH) risk in otherwise healthy ≥29 wGA infants and term infants was similar.
- Real-world evidence studies conducted in the United States after the 2014 policy change have reported a decrease in RSV IP use that is largely associated with an increase in RSVH risk among 29 to 34 wGA infants relative to term infants.
- In addition, RSV IP use decreased and RSVH risk increased among in-policy, <29 wGA infants; this could be an unintended consequence of the 2014 policy change.
- Revisions to the AAP recommendations are needed given the growing evidence demonstrating an increase in RSVH risk among 29 to 34 wGA infants.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.13326350

INTRODUCTION

Pediatric populations at high risk for severe respiratory syncytial virus (RSV) infection include infants born prematurely (≤35 weeks' gestational age [wGA]) and children with chronic lung disease of prematurity, congenital heart disease, Down syndrome, immunodeficiency, neuromuscular diseases, and cystic fibrosis [1-3]. Preterm infants without comorbidities have an approximately 3 times greater risk of RSV-related hospitalization (RSVH) compared with term infants [4]. Palivizumab is the only Food and Drug Administration (FDA)-approved therapy for the prevention of serious lower respiratory tract infections caused by RSV in high-risk infants [1, 5]. In 2014, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases (COID) stopped recommending RSV immunoprophylaxis (IP) for preterm infants born at ≥29 wGA without comorbidities such as chronic lung disease of prematurity and congenital heart disease [6]. The committee's rationale for the change was that the risk of RSVH in infants born at ≥29 wGA was similar to that observed in term infants [7]. However, the studies used as evidence to support the policy change were widely non-generalizable, regional studies and lacked sufficient power, unlike the well-designed, randomized clinical trials that established the safety and efficacy of palivizumab [8, 9].

Following the 2014 AAP policy change, several real-world evidence studies examined the impact of these updates on RSV IP use and RSVH among infants 29 to 34 wGA. This article will provide a comprehensive review of RSVH data from the 2011-2017 RSV seasons in the United States obtained from single-center, regional, and sizeable national database studies conducted after the 2014 AAP policy change **(Table 1)**. Although the AAP policy may be adapted by countries outside the United States, this

article is aimed at discussing the implications of the policy change in the United States only. There may be significant effects from the use of a policy that is beyond the scope of practice and clinical experience of much of the rest of the world. Indeed, there is significant morbidity and increased mortality from RSV in many resource-poor countries[10, 11]. However, the discussion of the guidelines and policies followed in countries outside the United States and their implications are beyond the scope of this review. Please also note that the pricing of RSV IP, insurance coverage, and medical practice vary between countries; thus, generalizing is difficult. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

IMPACT OF THE 2014 AAP POLICY ON RSVH IN PRETERM INFANTS FROM SINGLE-CENTER AND REGIONAL STUDIES

Data from regional studies that assessed the risk of RSVH before and after the 2014 policy change have demonstrated mixed results. In a pooled analysis of data from 8 Medicaid plans, Farber reported that RSVH (N=2031) among 29 to 32 wGA infants did not change significantly in the 3 seasons examined (4.65%, 2012-2013; 3.06%, 2013-2014; 5.41%, 2014-2015) [12]. However, the Texas Medicaid plan had not adopted the 2014 AAP policy for the 2014-2015 season, and infants who received inpatient IP were not captured. [6, 13, 14]. Additionally, the group receiving IP was younger than those not receiving IP, suggesting the groups may not be comparable [14, 15]. In another retrospective analysis, Grindeland et al. reported that RSV IP use decreased significantly in 2014-2015 compared with 2012-2014 (P<0.0001) among hospitalized children aged <2 years in North Dakota. The total number of RSVH during the study

period was 194, and no significant change was observed in RSVH rates per 1000 children in the 2012-2014 vs. 2014-2015 seasons (*P*=0.622) [16]. However, this study did not specifically examine high-risk preterm infants nor did it have the optimal statistical power to detect significant differences, if present [16, 17].

Rajah et al. conducted a retrospective analysis at Nationwide Children's Hospital in Ohio (N=2476) and showed that the proportion of RSVH among 29 to 34 wGA infants aged <6 months increased significantly in 2014-2015 (7.1%) compared with 2013-2014 (3.5%; *P*=0.01) [18]. Similarly, in a single-center analysis of 173 infants, Blake et al. reported that RSV IP prescriptions decreased (*P*=0.01), and RSVH increased significantly in 2014-2016 vs. 2012-2014 among infants born at 29 to <32 wGA (*P*=0.04) [19].

In a recent study, Zembles et al. analyzed 91 RSVH in ≥29 and <35 wGA infants aged <1 year during the 2012-2017 seasons. The authors observed no significant increase in RSVH during the three seasons after the AAP policy change (2014-2017), but the number of RSVH in the first season after the policy change (n=30, 2014-2015) was greater than in the previous seasons (n=14, 2012-2013; n=16, 2013-2014) [20]. Also, an analysis comparing RSVH in the seasons before and after 2014 showed that the proportion of RSVH among ≥29 to <35 wGA infants in 2014-2017 was about two times higher than in 2012-2014 (17.2% vs. 9.7%, respectively; *P*=0.0047; unpublished data).

Overall, some regional studies that examined the impact of the 2014 AAP policy either did not fully adopt the policy or did not stratify based on the gestational age group. A limitation of the above-mentioned single-center studies was that they were not

controlled for seasonal variations that may have occurred [12, 19]. National studies that analyzed large databases have helped address this limitation by calculating rate ratios to standardize for seasonal variations [21, 22].

IMPACT OF THE 2014 AAP POLICY ON RSVH IN PRETERM INFANTS USING DATA FROM NATIONAL DATABASES

Although regional studies presented mixed results regarding the impact of the 2014 policy change, extensive national database studies have consistently shown a correlation between the decrease in RSV IP use after 2014 and an increase in the risk of RSVH. Kong et al. conducted a retrospective analysis using the Truven MarketScan® commercial and Medicaid insurance claims databases and compared RSV IP use and RSVH among 29 to 34 wGA infants in the 2014-2015 season vs. the 2013-2014 season. The proportion of 29 to 34 wGA infants who received at least one dose of RSV IP significantly decreased by 45% to 95% in the 2014-2015 vs. 2013-2014 seasons (P<0.01). Between 2010 and 2015, among 29 to 34 wGA infants and term infants, a total of 6,563 and 13,312 RSVH were identified in the commercial and Medicaid databases, respectively. In 2014-2015, the RSVH rate for commercially insured 29 to 34 wGA infants aged <3 months was 2.65 (P=0.0184) times higher than in 2013-2014; for Medicaid-insured infants of the same age group, the RSVH rate was 1.41 (P=0.0313) times higher (**Figure 1**). In contrast, RSVH rates were similar in 2013-2014 and 2014-2015 among term infants [22].

Goldstein et al. extended the examination of the national impact of the AAP policy change among 29 to 34 wGA infants aged <6 months in the 2014-2016 vs. 2012-2014 seasons. The analysis included commercially insured infants (29 to 34 wGA,

n=33,667 and term infants, n=668,619) and Medicaid-insured infants (29 to 34 wGA, n=51,439 and term infants, n=908,594) [21]. Similar to Kong et al., the proportion of RSV IP use decreased significantly by ≥74% for all the preterm age groups analyzed in 2014-2016 compared with 2012-2014 (*P*<0.0001, for both commercial and Medicaid databases) [21, 22]. There was no significant change in RSV IP use among term infants before and after 2014. RSVH rate ratios in 29 to 34 wGA infants relative to term infants were greater than 1 in all seasons. The risk of RSVH in 29 to 34 wGA infants vs. term infants was higher in 2014-2016 (range, 2.6-5.6) compared with 2012-2014 (range, 1.6-3.4). The difference-in-difference model that was used to control for gestational age at birth, chronologic age during the RSV season, and sex estimated that the risk of RSVH in 29 to 34 wGA infants relative to term infants increased significantly in 2014-2016 vs. 2012-2014 (**Figure 2;** rate ratio=2.00 for the commercially insured population; rate ratio=1.46 for Medicaid population; *P*<0.0001 for both) [21].

In a recent observational cohort study, Krilov et al. analyzed medical and pharmacy claims data from the Optum Research Database in the three seasons before (2011-2014) and after (2014-2017) the policy change. A total of 12,558 preterm infants and 323,216 term infants were included in the analysis. Similar to the Truven studies, the proportion of RSV IP decreased significantly in 29 to 34 wGA infants (**Figure 3**; *P*<0.001, for all wGA cohorts). This decrease was associated with a consistently higher RSVH rate ratio among preterm infants relative to term infants in 2014-2017 vs. 2011-2014. The risk of RSVH in 29 to 34 wGA infants vs. term infants increased from 1.9 in 2011-2014 to 2.9 in 2014-2017. This change represented a 55% increase in the risk of

RSVH among 29 to 34 wGA infants relative to term infants in the 2014-2017 vs. 2011-2014 RSV seasons (*P*=0.011) [23].

These large studies have some characteristic limitations: 1) RSVH may have been under-coded due to lack of a confirmatory laboratory diagnosis as the AAP does not recommend RSV testing. 2) Underestimation of RSV IP use is a possibility as inpatient IP use was not included in the analysis. 3) Relatively low n values in some gestational age groups may have masked any statistical difference between the seasons [21-23].

Overall, large national cohort studies showed that the decline in RSV IP after 2014 was associated with significant increases in RSVH rate and risk among 29 to 34 wGA infants compared with term infants. In addition, the risk of RSVH was highest among infants born at earlier gestational age and of younger chronologic age [21-23].

IMPACT OF THE AAP POLICY ON RSVH IN LOW-INCOME POPULATIONS

Espinosa et al. analyzed RSVH among preterm infants (<29 wGA, 29 to 35 wGA, and >35 wGA) aged <1 year in a low-income population using Kentucky Medicaid claims data from 2012-2016. The rate of RSVH among 29 to 35 wGA infants was 328 per 1000 live births in 2014-2016 compared with 172 per 1000 live births in 2012-2013. This increase accounted for a 52% higher incidence rate of RSVH than the expected rate for 2014-2016 (*P*<0.001). Of note, the highest increase in RSVH incidence rate was observed among 29 to 35 wGA infants (86%; *P*<0.001), while no significant change was observed among <29 wGA and >35 wGA infants in 2014-2016 vs. 2012-2013 [24].

These results indicate that the 2014 policy change may compound the vulnerability of high-risk infants with additional socioeconomic risk factors such as low income.

UNINTENDED CONSEQUENCES OF AAP POLICY ON RSVH IN <29 WGA INFANTS

Since 2014, studies have also assessed the potential impact of the AAP policy change on IP use and RSVH among <29 wGA infants. The AAP considers <29 wGA infants to be high risk and continues to recommend IP use for this population [1, 6]. Goldstein et al. analyzed commercial and Medicaid claims from the IBM Watson Health MarketScan® database in <29 wGA infants aged <12 months in 2014-2016 vs. 2012-2014. Outpatient RSV IP use decreased among <29 wGA infants for all chronologic age groups in 2014-2016 compared with 2012-2014. The highest decline in IP use was observed in <29 wGA infants aged <3 months (46% decline, commercial; 36% decline, Medicaid). This decline was associated with an increase in RSVH rate ratios in <29 wGA infants relative to term infants in 2014-2016 vs. 2012-2014 for each chronologic age group (both commercially insured and Medicaid-insured infants). For commercially insured <29 wGA infants aged <1 year, RSVH rate ratios ranged between 1.13 and 3.59 in 2012-2014 and 4.49 and 5.59 in 2014-2016. Similarly, in Medicaid-insured infants of the same age group, RSVH rate ratios were 1.09 to 4.88 in 2012-2014 and 3.88 to 12.48 in 2014-2016. The highest increases in RSVH rate ratios in <29 wGA infants vs. term infants were observed among infants aged <3 months [25]. Overall, these results indicate that the AAP 2014 policy change may have resulted in an unintended consequence of decreased RSV IP utilization and increased RSVH among this vulnerable <29 wGA infant population.

CONCLUSION

Taken together, data from real-world evidence studies showed that the AAP 2014 policy change resulted in a significant decrease in RSV IP use and an increase in RSVH among both outside-policy (29 to 34 wGA infants) and in-policy populations (<29 wGA infants) [18, 19, 21, 22, 25]. Despite the consequential increase in RSVH risk among 29 to 34 wGA infants, the AAP reaffirmed their 2014 policy change in 2019 [26]. Although the results discussed here are not derived from randomized controlled trials, the studies provide a real-world snapshot of the unfortunate increase in RSV disease morbidity among the affected 29 to 34 wGA infants. Moreover, conducting randomized controlled trials may be time-consuming and not always possible because of IP that occurs over and under policy intent. Based on the recent evidence demonstrating an increase in RSVH, the National Perinatal Association (NPA) published its 2018 clinical guidelines recommending RSV IP for all ≤32 wGA infants and 32 to 35 wGA infants with risk factors such as day care attendance, presence of school-aged siblings, twin or greater multiple gestation, and younger age. The NPA also highlighted that the guidance and policies should remain consistent with the FDA indication as it provides the most clarification of a clinically significant therapy based on carefully conducted, evidence-based, randomized control trials [5]. As palivizumab is the only FDA-approved intervention to prevent RSV-related complications in high-risk infants, including 29 to 35 wGA infants, the AAP policy should be revisited in light of recent evidence.

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Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

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Table 1. Summary of Evidence-Based Studies in the United States Since 2014 on RSVH

Study	RSV Seasons	Study Population	Key Outcomes
National Studies			
Kong et al. [22]	2013-2014 vs. 2014-2015	29 to 34 wGA aged <6 months	RSV IP use declined up to 95%; RSVH rate ratios among 29 to 34 wGA infants aged <3 months increased by 1.41- to 2.65-fold in 2014-2015 vs. 2013-2014 (*P*<0.05)
Goldstein et al. [21]	2012-2014 vs. 2014-2016	29 to 34 wGA aged <6 months	RSV IP use declined by ≥74%; risk of RSVH among 29 to 34 wGA infants relative to term infants aged <6 months increased in 2014-2016 vs. 2012-2014 (~1.5- to 2-fold; *P*<0.0001)
Krilov et al. [23]	2011-2014 vs. 2014-2017	29 to 34 wGA aged <6 months	A decrease in RSV IP (*P*<0.001) was associated with a 55% higher risk of RSVH for 29 to 34 wGA infants relative to term infants in 2014-2017 vs. 2011-2014 (*P*=0.011)
Goldstein et al. [25]	2012-2014 vs. 2014-2016	<29 wGA aged <12 months	RSV IP use declined by up to 46% among AAP in-policy <29 wGA infants, and this was associated with an increase in RSVH RRs in 2014-2016 vs. 2012-2014
Regional Studies			
Rajah et al. [18]	2013-2014 vs. 2014-2015	29 to 34 wGA aged <12 months	The proportion of RSVH increased in 2014-2015 (7.1%) vs. 2013-2014 (3.5%; *P*=0.01) among 29 to 34 wGA infants aged <6 months
Farber et al. [12]	2012-2014 vs. 2014-2015	29 to 32 wGA aged <6 months	There were no significant year-to-year changes in RSVH rates (4.65%, 2012-2013; 3.06%, 2013-2014; 5.41%, 2014-2015)

Grindeland et al. [16]	2012-2014 vs. 2014-2015	Children aged <2 years	RSV IP use decreased (*P*<0.0001), but there was no significant change in RSVH rate per 1000 children in 2012-2014 (5.37) vs. 2014-2015 (5.78)
Blake et al. [19]	2012-2014 vs. 2014-2016	29 to <32 wGA aged <12 months	A decrease in RSV IP use (*P*=0.01) was associated with an increase in RSVH admissions in 29 to 32 wGA infants (*P*=0.04)
Espinosa et al. [24]	2012-2013 vs. 2014-2016	Preterm infants aged <1 year	The RSVH incidence rate was 52% higher than what was predicted for 29 to 35 wGA infants in 2014-2016 (*P*<0.001)
Zembles et al. [20]	2012-2014 vs. 2014-2017	≥29 and <35 wGA aged <12 months	There was no significant change in the number of RSVH during the three seasons after the 2014 AAP policy. However, the proportion of RSVH increased in 2014-2017 vs. 2012-2014 (17.2% vs. 9.7%; *P*=0.0047; unpublished data)

AAP, American Academy of Pediatrics; IP, immunoprophylaxis; RRs, rate ratios; RSV, respiratory syncytial virus; RSVH, respiratory syncytial virus hospitalization; wGA, weeks' gestational age.

Figure Legends

Figure 1. RSVH rates increased after the 2014 policy change among 29-34 wGA infants aged <3 months [9]

CA, chronologic age; RSVH, respiratory syncytial virus hospitalization; wGA, weeks' gestational age.

Figure 2. RSVH risk increased after the 2014 policy change in 29 to 34 wGA infants relative to term infants [10]

COM, commercially insured; MED, Medicaid insured; RSVH, respiratory syncytial virus hospitalization; wGA, weeks' gestational age.

Figure 3. RSVH risk increased as RSV IP use decreased after the 2014 policy change in 29 to 34 wGA infants relative to term infants [11]

IP, immunoprophylaxis; RR, rate ratio; RSV, respiratory syncytial virus; RSVH, respiratory syncytial virus hospitalization; wGA, weeks' gestational age.