Increasing Rates of RSV Hospitalization among Preterm Infants: A Decade of Data

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Abstract

Objective In 2014, the American Academy of Pediatrics (AAP) changed its policy on the use of respiratory syncytial virus immunoprophylaxis (RSV-IP) so that RSV-IP was no longer recommended for use among infants without other medical conditions born >29 weeks of gestational age (wGA). This study examines 10-year trends in RSV-IP and RSV hospitalizations among term infants and preterm infants born at 29 to 34 wGA, including the 5 RSV seasons before and 5 RSV seasons after the AAP guidance change.

Study Design A retrospective observational cohort study of a convenience sample of infants less than 6 months of age during RSV season (November–March) born between July 1, 2008, and June 30, 2019, who were born at 29 to 34 wGA (preterm) or >37 wGA (term) in the IBM MarketScan Commercial and Multi-State Medicaid databases. We excluded infants with medical conditions that would independently qualify them for RSV-IP. We identified RSV-IP utilization along with RSV and all-cause bronchiolitis hospitalizations during each RSV season. A difference-in-difference model was used to determine if there was a significant change in the relative rate of RSV hospitalizations following the 2014 policy change.

Results There were 53,535 commercially insured and 85,099 Medicaid-insured qualifying preterm infants and 1,111,670 commercially insured and 1,492,943

Keywords
- respiratory system
- respiratory syncytial virus
- preterm infants
- hospitalization

Respiratory syncytial virus (RSV) is the most common cause of bronchiolitis and pneumonia among children younger than 1 year of age.[1] Typically occurring between October and April in most U.S. regions,[2] RSV invades the respiratory epithelial cells causing inflammation and edema.[3] RSV is the most common airway infection among children under 2 years of age,[4] and is associated with respiratory outcomes like wheezing and higher health care utilization into childhood.[5] While most children recover with limited medical intervention, severe RSV disease is a leading cause of infant

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Medicaid-insured qualifying term infants. Following the 2014 policy change, RSV-IP utilization decreased for all infants, while hospitalization rates tended to increase for preterm infants. Rate ratios comparing preterm to term infants also increased. The relative rate for RSV hospitalization for infants born at 29 to 34 wGA increased significantly for both commercially and Medicaid-insured infants (1.95, 95% CI: 1.67–2.27, p <0.001; 1.70, 95% CI: 1.55–1.86, p <0.001, respectively). Findings were similar for all-cause bronchiolitis hospitalizations.

Conclusion We found that the previously identified increase in RSV hospitalization rates among infants born at 29 to 34 wGA persisted for at least 5 years following the policy change.

Key Points

- Immunoprophylaxis rates decreased after the 2014 American Academy of Pediatrics guidelines update.
- Rate of RSV hospitalization increased among preterm infants after the 2014 AAP guidelines update.
- Increase in RSV hospitalization persisted for at least 5 years after AAP guidelines update.

hospitalization, and management can include intensive care unit admission and mechanical ventilation.[3,6]

In the United States, 2 to 3% of infants 12 months or younger visit the emergency department for bronchiolitis each year,[7] and the risk of RSV-related hospitalization appears to be greatest during the first few months of life.[4,9] Several factors associated with an increased risk of severe RSV have been identified, including preterm birth, chronological age of less than 6 months during RSV season, low birth weight, chronic lung disease, and congenital heart disease.[10,11] There are no specific therapies to treat the infection or preventative vaccine for RSV, though vaccines are in development stage[12]; however, the risk of RSV hospitalization can be reduced through passive RSV immunoprophylaxis (RSV-IP) via monthly administration during the RSV season of the monoclonal antibody palivizumab.[13,14]

Since the approval of palivizumab in 1998, the American Academy of Pediatrics (AAP) Committee on Infectious Diseases has released three revisions to its initial guidance on which infants they recommend receive RSV-IP.[15–18] While earlier versions of the AAP guidance recommended the use of RSV-IP in infants born at 29 to 34 weeks of gestational age (wGA), depending on age relative to RSV season, regardless of additional risk factors, the 2014 policy recommended against RSV-IP among infants born at 29 wGA or later unless there were other risk factors.[15,19] RSV-IP utilization subsequently decreased among infants born at 29 to 34 wGA.[20,21] The 2014 policy was reaffirmed in 2019.

Multiple U.S. studies that evaluated the 2014 to 2017 RSV seasons have demonstrated an increased risk of RSV hospitalization after the 2014 AAP policy against RSV-IP for otherwise healthy infants born at 29 to 34 wGA and less than 6 months chronological age during RSV season.[20–25] The objective of this study was to extend this prior research by examining RSV-IP and RSV hospitalizations among term infants and preterm infants born at 29 to 34 wGA during a 10-year period, including the 5 RSV seasons before and 5 RSV seasons after the guidance change. We used a difference-in-difference multivariable model to measure the change in RSV hospitalization risk following the 2014 change in the APP policy. We also conducted a sensitivity analysis by evaluating all-cause bronchiolitis hospitalizations during RSV season among the same cohorts.

Materials and Methods

Study Design and Data Source

This retrospective observational cohort study of infants born in the United States used data obtained from de-identified administrative claims housed in the IBM MarketScan Commercial and Multi-State Medicaid databases. These databases capture the enrollment data, inpatient medical data, outpatient medical data, and outpatient prescription drug data for their respective covered population. The commercial database includes data for employees and their dependents covered under a variety of fee-for-service and managed care health plans. The Medicaid database contains the pooled health care experience of Medicaid enrollees from multiple, geographically dispersed states. Data from the commercial and Medicaid populations were analyzed separately.

All study data were obtained using International Classification of Diseases, 9th and 10th Revision, Clinical Modification (ICD-9-CM and ICD-10-CM) codes, Current Procedural Terminology 4th edition codes, Healthcare Common Procedure Coding System codes, National Drug Codes, and diagnosis-related group (DRG) codes. All study data were accessed with protocols compliant with U.S. patient confidentiality requirements, including the Health Insurance Portability and Accountability Act of 1996 regulations (HIPAA). All data were fully de-identified and compliant with HIPAA; thus, this study was exempted from institutional review board approval.

Patient Selection

We identified infants born between July 1, 2008, and June 30, 2019, who could be linked to a birth hospitalization record, had a valid code for wGA, and were discharged alive from birth hospitalization. Infants were excluded from the analysis if they had evidence of: (1) a complex, rare medical condition such as cystic fibrosis, immunodeficiency, congenital anomalies of the respiratory system, neuromuscular, immunological or genetic disorders, or organ transplants, (2) chronic lung disease of prematurity, (3) congenital heart disease, or (4) a DRG code of full-term with major health problems or a DRG code for preterm with unknown wGA.

From the remaining infants, those with a DRG indicating they were born at ≥37 wGA with no major health problems were classified as term. Preterm infants born at 29 to 34 wGA were classified into three cohorts (29–30 wGA, 31–32 wGA, 33–34 wGA) using ICD-9-CM and ICD-10-CM diagnosis codes. Preterm infants born at less than 29 wGA or 35 to 36 wGA were excluded from this analysis. In addition, infants were required to be less than 6 months old at some point during an RSV season (November to March). Follow-up began at the start of the first RSV season after birth if the infant was born before the season or at discharge from birth hospitalization if the infant was born during the season. Follow-up ended at the earliest of the following events: end of RSV season or when the infant turned 6 months old.

Variables

Infant sex was captured from the birth hospitalization record. We calculated the number of infant-seasons by dividing the total number of days that an infant contributed follow-up data while under 6 months of age during an RSV season by the duration of the RSV season (151 days). During each RSV season, RSV-IP use by infants under 6 months old was defined by the presence of at least one outpatient pharmacy claim for RSV-IP or outpatient service claim for the administration of RSV-IP. As inpatient administration of RSV-IP could not be captured in the source databases, this analysis could not include it.

We identified RSV hospitalizations among infants under 6 months old during follow-up by the presence of ICD-9-CM (079.6, 466.11, or 480.1) and ICD-10-CM (B974, J121, J205, or J210) diagnosis codes for RSV on inpatient claims, and we report hospitalization rates per 100 infant-seasons due to variable infant follow-up. We calculated unadjusted rate ratios for preterm infants relative to term infants to account for seasonal variation in virus circulation, impacting absolute RSV hospitalization rates.

We conducted a sensitivity analysis by evaluating all-cause bronchiolitis hospitalizations during RSV season, including RSV bronchiolitis hospitalizations and other bronchiolitis hospitalizations that may have been due to RSV despite lacking the ICD-9-CM or ICD-10-CM diagnosis code. We identified bronchiolitis hospitalizations by the presence of ICD-9-CM (466.11 or 466.19) and ICD-10-CM (J210, J211, J218, or J219) diagnosis codes for bronchiolitis on inpatient claims.

Multivariable Analysis

We fit difference-in-difference models using Poisson family generalized linear models (GLMs) with a log link to determine if there was a change in relative rates of RSV hospitalizations and all-cause bronchiolitis hospitalizations for preterm infants compared with term infants after the guidance change by comparing the five seasons before the guidance change combined with the five seasons after the guidance change combined. Next, we evaluated trends over 10 years using Poisson family GLMs including a linear b-spline term for the year, to determine if trends in relative risk for preterm infants versus term infants were consistent or changed after 2014. *p*-Values less than 0.05 were considered statistically significant.

Data extraction and descriptive analyses were conducted using WPS version 4.2 (World Programming, United Kingdom). Multivariable models were generated with R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Main Analysis

We identified 2,438,623 infants with commercial insurance and 3,064,180 infants with Medicaid insurance born between July 1, 2008, and June 30, 2019, and discharged alive from the hospital (►**Supplementary Table S1**, available in the online version only). After applying all exclusion criteria, we identified 52,535 commercially insured and 85,099 Medicaid-insured infants born at 29 to 34 wGA who contributed 25,218 and 42,553 RSV seasons, respectively, at less than 6 months of age (►**Table 1**). These preterm infants were compared with 1,111,670 commercially insured and 1,492,943 Medicaid-insured term infants who contributed 568,474 and 796,746 RSV seasons, respectively, at less than 6 months of age. During the 10 RSV seasons included in this study, there were 722 RSV hospitalizations among commercially insured preterm infants, 6,486 RSV hospitalizations among commercially insured term infants, 2,181 RSV hospitalizations among Medicaid-preterm infants, and 13,962 RSV hospitalizations among Medicaid-insured term infants.

RSV-IP use decreased among all study populations between the 2009 to 2014 RSV seasons and the 2014 to 2019 RSV seasons (►**Table 2**). Overall, between the 2009 to 2014 and 2014 to 2019 RSV seasons, RSV-IP use among preterm infants born at 29 to 34 wGA decreased 88.9%, from 26.5 to 2.9% among commercially insured infants and from 24.8 to 2.8% among Medicaid-insured infants. The absolute decrease was most prominent among preterm infants born at 29 to 30 wGA, and the relative decrease (percentage decrease) was largest among preterm infants born at 33 to 34 wGA (►**Table 2**). Among commercially and Medicaid-insured healthy term infants, RSV-IP use was less than 0.1% in the 2009 to 2014 and 2014 to 2019 RSV seasons.

Across the 10 seasons, RSV hospitalization rates per 100 infant-seasons in the commercially insured population ranged from 1.6 to 4.3 for infants born at 29 to 34 wGA

Table 1 Number of infants and infant-seasons contributed at less than six months old

	Infants, *N*	Infant seasons, *N*	RSVH[a], *N*
Commercial			
Preterm infants 29–34 wGA	52,535	25,218	722
Preterm infants 29–30 wGA	5,924	2,644	79
Preterm infants 31–32 wGA	12,305	5,816	203
Preterm infants 33–34 wGA	34,306	16,758	440
Term infants	1,111,670	568,474	6,486
Medicaid			
Preterm infants 29–34 wGA	85,099	42,553	2,181
Preterm infants 29–30 wGA	10,680	4,934	323
Preterm infants 31–32 wGA	21,298	10,429	609
Preterm infants 33–34 wGA	53,121	27,190	1,249
Term infants	1,492,943	796,746	13,962

Abbreviations: RSVH, respiratory syncytial virus hospitalization; wGA, weeks gestational age.
[a]RSVH during RSV season.

Table 2 Proportion of infants less than 6 months old during the respiratory syncytial virus (RSV) season with outpatient RSV immunoprophylaxis (RSV-IP) utilization

	2009–2014			2014–2019				
	Infants, *N*	With RSV IP use, *N*	With RSV IP use, %	Infants, *N*	With RSV IP use, *N*	With RSV IP use, %	Percentage decrease, %	Absolute decrease, %
Commercial								
Preterm infants 29–34 wGA	31,231	8,274	26.5%	21,304	625	2.9%	88.9%	23.6%
Preterm infants 29–30 wGA	3,560	1,760	49.4%	2,364	314	13.3%	73.1%	36.2%
Preterm infants 31–32 wGA	7,494	2,774	37.0%	4,811	212	4.4%	88.1%	32.6%
Preterm infants 33–34 wGA	20,177	3,740	18.5%	14,129	99	0.7%	96.2%	17.8%
Term infants	714,280	114	0.02%	397,390	21	0.01%	66.9%	0.0%
Medicaid								
Preterm infants 29–34 wGA	41,216	10,201	24.8%	43,883	1,211	2.8%	88.9%	22.0%
Preterm infants 29–30 wGA	5,230	2,616	50.0%	5,450	549	10.1%	79.9%	39.9%
Preterm infants 31–32 wGA	10,421	3,538	34.0%	10,877	339	3.1%	90.8%	30.8%
Preterm infants 33–34 wGA	25,565	4,047	15.8%	27,556	323	1.2%	92.6%	14.7%
Term infants	813,899	131	0.02%	679,044	24	0.00%	78.0%	0.0%

Abbreviation: IP, immunoprophylaxis; RSV, respiratory syncytial virus; wGA, weeks of gestational age.

and from 0.9 to 1.4 for term infants (►Fig. 1A). In the Medicaid population, RSV hospitalization rates per 100 infant-seasons across the ten seasons ranged from 3.6 to 6.6 for infants born at 29 to 34 wGA and from 1.4 to 2.4 for term infants (►Fig. 1B). In every wGA cohort and at every time point, the RSV hospitalization rate was higher among preterm infants than among term infants leading to unadjusted rate ratios greater than 1 (►Fig. 2A and B).

Unadjusted rate ratios comparing preterm to term infants increased after the 2014 guidance change for commercially insured and Medicaid-insured infants. In the commercially insured population, unadjusted rate ratios for infants born at 29 to 34 wGA versus term infants ranged from 1.8 to 2.0 in the 2009 to 2014 RSV seasons and from 3.2 to 4.2 in the 2014 to 2019 RSV seasons depending on the season (►Fig. 2A). Similarly, unadjusted rate ratios in the Medicaid-insured

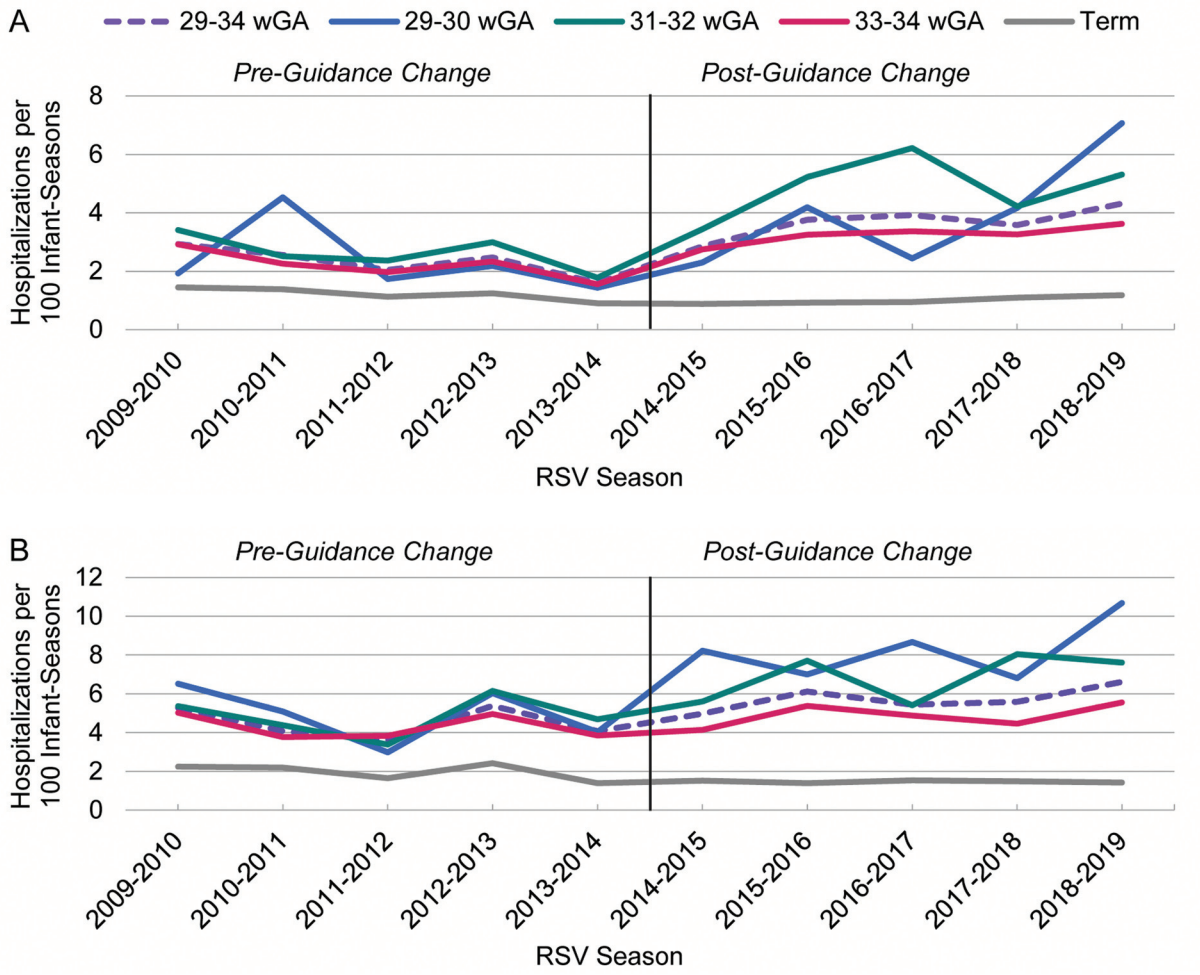

Fig. 1 Respiratory syncytial virus (RSV) hospitalization[a] rates for (**A**) commercially-insured and (**B**) Medicaid-insured infants less than 6 months old. [a]RSV-specific hospitalizations are identified by ICD-9-CM diagnosis codes 079.6, 466.11, or 480.1 or ICD-10-CM diagnosis codes B97.4, J20.5, J21.0, or J12.1 in any position on a claim. wGA, weeks gestational age.

population ranged from 1.9 to 2.9 in the 2009 to 2014 RSV seasons and from 3.3 to 4.7 in the 2014 to 2019 RSV seasons (►**Fig. 2B**).

Based on the difference-in-difference models, the relative rate of RSV hospitalization for preterm infants versus term infants was significantly higher in the five seasons after the guidance change than in the five seasons before the guidance change (►**Table 3**). The relative rate for RSV hospitalization for infants born at 29 to 34 wGA versus term infants nearly doubled (1.95, 95% CI: 1.67–2.27, $p < 0.001$) after the guidance change for commercially insured infants and increased by 70% (1.70, 95% CI: 1.55–1.86, $p < 0.001$) for Medicaid-insured infants. In the commercial population, the largest adjusted increase was among infants born at 31 to 32 weeks (2.27, 95% CI: 1.71–3.01, $p < 0.001$), whereas, in the Medicaid population, the largest adjusted increase was among infants born at 29 to 30 weeks (2.23, 95% CI: 1.78–2.80, $p < 0.001$)

The longitudinal 10-year models indicated that after the increase in relative rates in the 2014 to 2015 season immediately after the policy change, the increased relative rate for preterm versus term infants persisted for each of the five seasons after the guidance changed (►**Supplementary Table S2**, available in the online version only). The increase was stable, meaning that the difference between preterm and term infants did not increase or decrease in the seasons after the guidance change (all *p*-values were not statistically significant).

The findings were similar when a similar analysis was conducted evaluating all-cause bronchiolitis hospitalizations in the study population. As with RSV hospitalizations, in every wGA cohort and at every time point, the all-cause bronchiolitis hospitalization rate was higher among preterm infants than among term infants (►**Supplementary Fig. S1A** and **S1B**, available in the online version only). Trends in unadjusted all-cause bronchiolitis hospitalization rate ratios comparing preterm to term infants after the 2014 recommendation change differed by wGA for both commercially insured and Medicaid-insured infants. For infants born at 29 to 34 wGA, the rate ratios appeared to increase over the 10-year period (►**Supplementary Fig. S2A** and **S2B**, available in the online version only). This was confirmed by the difference-in-difference models, which found that the relative rate for all-cause bronchiolitis hospitalization for infants born at 29 to 34 wGA versus

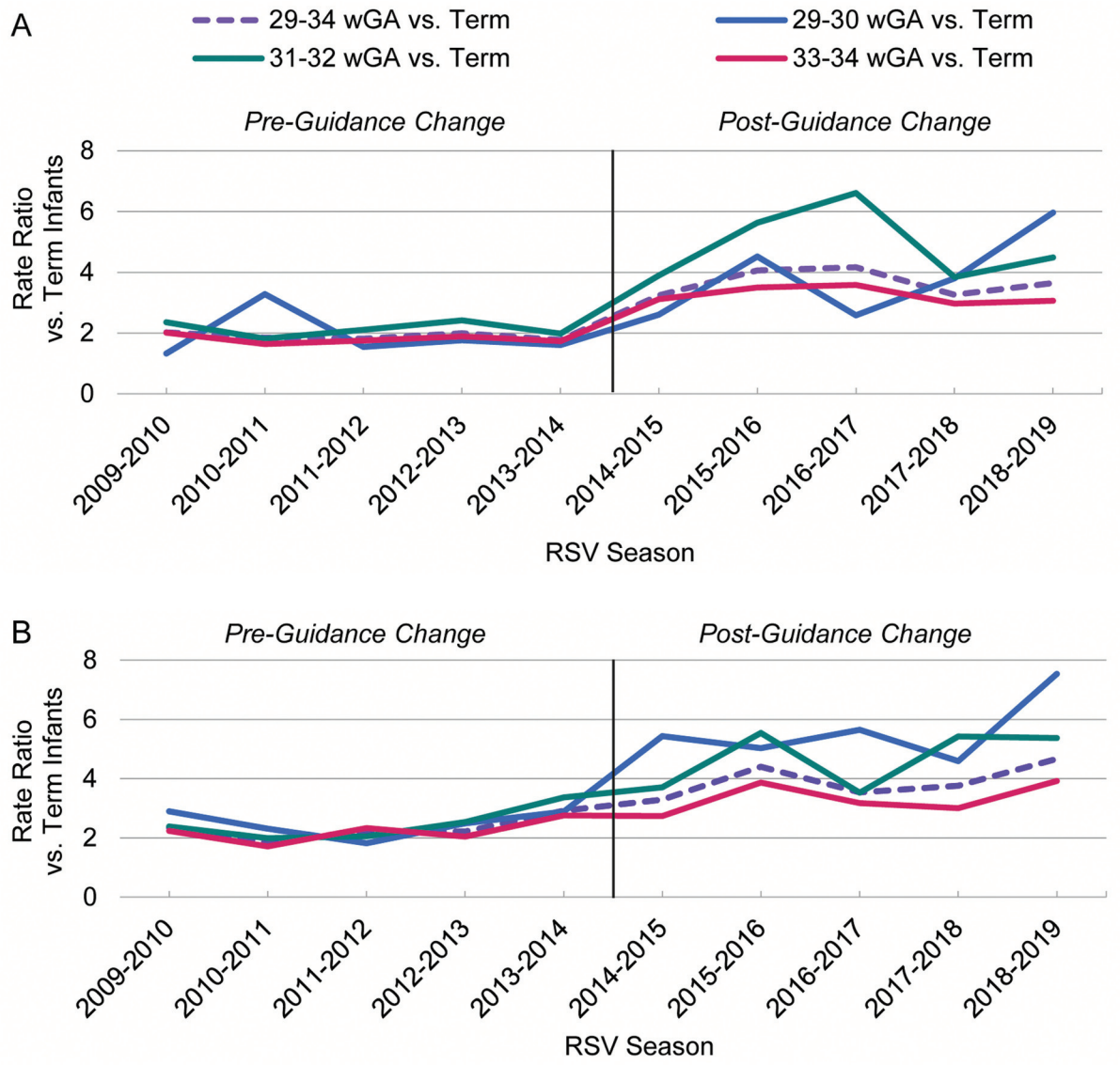

Fig. 2 Rate ratios for the respiratory syncytial virus (RSV) hospitalization[a] rates for (**A**) commercially insured and (**B**) Medicaid-insured infants less than 6 months old. [a]RSV-specific hospitalizations are identified by ICD-9-CM diagnosis codes 079.6, 466.11, or 480.1 or ICD-10-CM diagnosis codes B97.4, J20.5, J21.0, or J12.1 in any position on a claim. wGA, weeks gestational age.

Table 3 Difference-in-difference (DiD) models comparing relative rates of respiratory syncytial virus hospitalization (RSVH) for preterm vs. term infants

	Commercially insured		Medicaid insured	
Gestational age	**DiD for RSVH rates 2014–2019 vs. 2009–2014, estimate (95% CI)**	***p*-Value**	**DiD for RSVH Rates 2014–2019 vs. 2009–2014, estimate (95% CI)**	***p*-Value**
29–34 wGA	1.95 (1.67, 2.27)	<0.001	1.70 (1.55, 1.86)	<0.001
29–30 wGA	2.02 (1.30, 3.15)	0.002	2.23 (1.78, 2.80)	<0.001
31–32 wGA	2.27 (1.71, 3.01)	<0.001	1.89 (1.60, 2.23)	<0.001
33–34 wGA	1.81 (1.49, 2.20)	<0.001	1.52 (1.35, 1.70)	<0.001

Abbreviations: CI, confidence interval; wGA, weeks of gestational age.

term infants increased by 78% (1.78, 95% CI 1.56–2.02, $p < 0.001$) after the policy change for commercially insured infants and increased by 64% (1.64, 95% CI 1.52–1.78, $p < 0.001$) for Medicaid-insured infants (►**Supplementary Table S3**, available in the online version only). This increase persisted in the five seasons after the guidance change (►**Supplementary Table S2**, available in the online version only).

Discussion

Utilizing a decade of data, the current study found an 88.9% decrease in outpatient use of RSV-IP in the 5 years after the policy change among infants less than 6 months of age with commercial or Medicaid insurance born at 29 to 34 wGA. Although this study did not directly assess the association between decreased use of RSV-IP and increased RSV hospitalizations, the relative rate of RSV hospitalization increased 95% for commercially insured and 70% for Medicaid-insured preterm infants who were born at 29 to 34 wGA compared with term infants in the time period after the change in policy on RSV prophylaxis. This increase in risk for RSV hospitalization for preterm versus term infants persisted over the five seasons after the policy change.

This study's findings are consistent with three prior studies using the MarketScan databases, which all found a decrease in RSV-IP and an increase in RSV and all-cause bronchiolitis hospitalizations following the revised AAP policy for RSV-IP.[20,22,23] Similarly, a difference-in-difference analysis of commercially insured infants in the Optum Research Database found that infants born at 29 to 34 wGA had a 55% higher RSV hospitalization risk in the 2014 to 2017 seasons compared with the 2011 to 2014 seasons.[21] In addition, hospitalization-related indicators of RSV severity, such as length of stay, intensive care unit admission, and mechanical ventilation use, were higher following the guidance change for preterm infants but not term infants.[21] Similar increases in hospitalization rates and disease severity indices were observed in a 2-year single-site study and a 7-year study of data from the Pediatric Health Information System.[24,25]

This study adds to the existing literature by examining trends over a 10-year period and demonstrating that the annually-adjusted increase in RSV hospitalizations observed among infants born at 29 to 34 wGA in the initial years following the guidance change has been persistent and stable for 5 years. The difference-in-difference method allows us to compare the periods before and after the policy change while minimizing bias from variables that change over time, such as RSV season severity, coding practices, and diagnosis or treatment practices. While this study cannot confirm a causal link between the observed increase in hospitalizations and the reduction in RSV-IP use, the timing and persistency raise concerns that this population of infants born at 29 to 34 wGA and less than 6 months old during RSV season were negatively impacted by the policy change. Of note, this study's population included infants $\geq$29 wGA without complex, rare medical conditions, chronic lung disease of prematurity, congenital heart disease, or other major health problems. Even in our population of infants without risk factors for RSV, we found increases in RSV hospitalizations following the 2014 change in AAP policy. This evidence should be considered in future policies on the administration of RSV-IP in premature infants.

Limitations

This study is subject to the limitations common to all retrospective administrative claims. First, all records are subject to coding limitations and data entry errors. Second, RSV test results are not captured in claims data; however, the AAP does not recommend routine RSV testing during RSV season as it rarely alters clinical management. For this reason, we did a sensitivity analysis on all-cause bronchiolitis hospitalizations occurring during RSV season. Third, the sample sizes were smaller for infants born at younger gestational ages, which leads to less stable trends for these cohorts over the 10-year period. Fourth, we likely underestimated the utilization of RSV-IP as inpatient administration of RSV-IP is not captured in the source databases. This underestimation may differ systematically by wGA. Fifth, the study was restricted to infants with commercial or Medicaid insurance, and the findings may not be generalizable beyond this study population.

Conclusion

After the change in AAP recommendations for RSV-IP, we found decreases in outpatient utilization of RSV-IP and increases in RSV hospitalization rates for infants born at 29 to 34 wGA compared with healthy term infants. The increase in RSV hospitalization rate persisted during the five seasons after the policy change. We observed the same trend in all-cause bronchiolitis hospitalizations during RSV season, though with a smaller effect size. Future policy on RSV-IP administration in premature infants born at 29 to 34 wGA should consider the persistently higher rate of RSV hospitalizations in these infants following the 2014 change in AAP policy.

Ethics Approval and Informed Consent

All database records are statistically deidentified and certified to be fully compliant with U.S. patient confidentiality requirements outlined in the Health Insurance Portability and Accountability Act of 1996. Because this study used only deidentified patient records and did not involve collecting, using, or transmittal of individually identifiable data, this study was exempted from Institutional Review Board approval.

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Sobi Inc. funded this study. Employees of the funding institution contributed to the design of the study; and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication

Conflict of Interest

A.B. is currently employed by Moderna, Cambridge, MA, and was employed by Sobi at the time this study was conducted. T.G. is employed by Sobi. A.M.K. is currently employed by Aetion, New York, NY, and was employed by IBM Watson Health at the time this study was conducted. I.H.W., N.M.Z., and D.D. are employed by IBM Watson Health, which received funding from Sobi to conduct this study. L.R.K. has received research funding to their institution from Pfizer and Astra Zeneca, along with consultant fees from Pfizer and Sobi. J.F. has received grant/research support from AstraZeneca/MedImmune and is a

member of the AstraZeneca and Sobi speaker's bureau. M. G. is employed at an institution that has received research funding from AstraZeneca.

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