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SUPPLEMENT ARTICLE

Respiratory Syncytial Virus Is the Leading Cause of United States Infant Hospitalizations, 2009–2019: A Study of the National (Nationwide) Inpatient Sample

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Background. This study describes leading causes of hospitalization, including respiratory syncytial virus (RSV), in United States infants (<1 year) from 2009 through 2019.

Methods. Within the National (Nationwide) Inpatient Sample (NIS) data, hospitalizations were determined by primary diagnosis using *International Classification of Diseases*, *Ninth* or *Tenth Revision* codes. RSV was defined as 079.6, 466.11, 480.1, B97.4, J12.1, J20.5, or J21.0. Bronchiolitis was defined as 466.19, J21.8, or J21.9. Leading causes overall and by sociodemographic variables were identified. The Kids' Inpatient Database (KID) was used for confirmatory analyses.

Results. Acute bronchiolitis due to RSV (code 466.11 or J21.0) was the leading primary diagnosis, accounting for 9.6% (95% confidence interval [CI], 9.4%–9.9%) and 9.3% (95% CI, 9.0%–9.6%) of total infant hospitalizations from January 2009 through September 2015 and October 2015 through December 2019, respectively; it was the leading primary diagnosis in every year accounting for >10% of total infant hospitalizations from December through March, reaching >15% in January–February. From 2009 through 2011, acute bronchiolitis due to RSV was the leading primary diagnosis in every birth month. Acute bronchiolitis due to RSV was the leading cause among all races/ethnicities, except Asian/Pacific Islanders, and all insurance payer groups. KID analyses confirmed these results.

Conclusions. Acute bronchiolitis due to RSV is the leading cause of US infant hospitalizations.

Keywords. bronchiolitis hospitalizations; health equity; infants; Medicaid; respiratory syncytial virus; respiratory syncytial virus hospitalizations; RSV.

Respiratory syncytial virus (RSV) is an important public health concern. Among infants and children aged <5 years in the United States (US), 58 000 annual hospitalizations with 100–500 annual deaths are due to RSV [1]. Globally, among infants aged <6 months, 1.4 million hospital admissions and 27 300 in-hospital deaths due to RSV lower respiratory tract infection (LRTI) were estimated [2].

A systematic literature review [3] of the RSV literature published between January 2000 and June 2021 recently identified 4 publications [4–7] that reported leading-cause analyses of infant hospitalizations in the US with 1 study conducted in California [7]. In these studies, RSV bronchiolitis (*International Classification of Diseases, Ninth Revision* [*ICD-9*] code 446.11) was consistently the leading cause of infant hospitalizations; however, all 4 publications [4–7] utilized data from before 2003, and only 1 study [5] provided leading-cause analyses by race/ethnicity (US general infant population and American Indian/Alaska Native [AI/AN] infants). As infant RSV hospitalization rates vary by sociodemographic variables including chronological age, sex, race/ethnicity, and insurance payer [7–9], an update of this analysis is warranted.

Currently, RSV candidates are advancing in clinical development showing safety and efficacy against RSV LRTIs in otherwise healthy, late preterm, and term infants [10, 11]. Hence, current, nationally representative data are needed to support policy discussions. In this retrospective study, the Healthcare Cost and Utilization (HCUP)'s inpatient hospital discharge datasets from the Agency for Healthcare Research and Quality were used to determine the leading causes of hospitalizations from 2009 through 2019 among US infants aged <1 year.

METHODS

Study Design and Data Source

The HCUP's inpatient hospital discharge data are the largest and most comprehensive collection of longitudinal care data available in the US, and they contain encounter-level information on >7 million inpatient stays [12, 13]. HCUP's family

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Table 1. Leading Cause of Hospitalizations and Most Frequent Hospitalizations, National (Nationwide) Inpatient Sample, 2009–2019

Diagnosis (*ICD-9* or *ICD-10* Code)	Leading Primary Diagnosis			Most Frequent Diagnosis in Any Position		
	Rank	Weighted Frequency, No.	Percentage of Total Infant Hospitalizations (95% CI)	Rank	Weighted Frequency, No.	Percentage of Total Infant Hospitalizations (95% CI)
January 2009 to September 2015 (*ICD-9*)						
Acute bronchiolitis due to RSV (466.11)	1	206 265	9.6 (9.4–9.9)	1	249 251	11.6 (11.3–11.9)
Unspecified fetal and neonatal jaundice (774.6)	2	131 126	6.1 (5.7–6.4)	3	224 337	10.4 (10.1–10.7)
Acute bronchiolitis due to other infectious organisms (466.19)	3	127 150	6.1 (5.8–6.3)	5	170 454	7.9 (7.7–8.2)
Pneumonia, organism unspecified (486)	4	64 680	3.4 (3.2–3.6)	[a]	[a]	[a]
Other specified conditions originating in the perinatal period (779.89)	5	53 044	2.4 (2.3–2.7)	6	147 596	6.9 (6.6–7.1)
October 2015 to December 2019 (*ICD-10*)						
Acute bronchiolitis due to RSV (J21.0)	1	165 930	9.3 (9.0–9.6)	1	227 860	12.8 (12.5–13.1)
Neonatal jaundice, unspecified (P59.9)	2	113 655	6.4 (6.1–6.6)	2	213 045	11.9 (11.6–12.3)
Acute bronchiolitis, unspecified (J21.9)	3	66 075	3.7 (3.5–3.9)	7	98 605	5.5 (5.3–5.7)
Acute respiratory failure with hypoxia (J96.01)	4	38 110	2.1 (1.9–2.3)	10	88 030	4.9 (4.6–5.2)
Acute bronchiolitis due to other unspecified organism (J21.8)	5	37 680	2.1 (2.0–2.2)	[a]	[a]	[a]

Abbreviations: CI, confidence interval; *ICD-9, International Classification of Diseases, Ninth Revision*; *ICD-10, International Classification of Diseases, Tenth Revision*; RSV, respiratory syncytial virus.

[a]Not in the top 10 primary diagnosis or most frequent diagnosis.

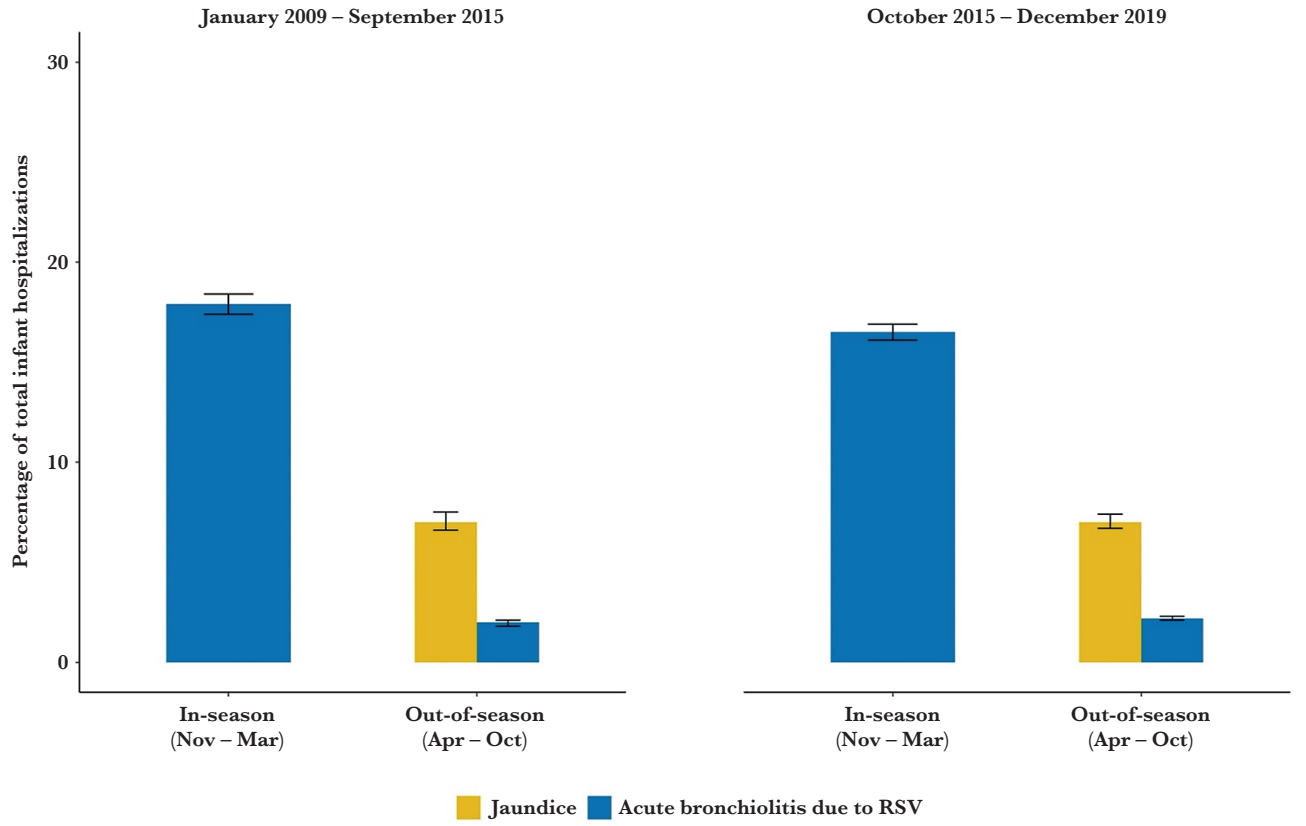

Figure 1. The leading cause of infant hospitalizations during in-season (November–March) and out-of-season (April–October) months by time period, with percentage of total infant hospitalizations and corresponding 95% confidence intervals, National (Nationwide) Inpatient Sample, 2009–2019. In-season refers to respiratory syncytial virus (RSV) seasonality. Percentage of total infant hospitalizations for acute bronchiolitis due to RSV was provided for the out-of-season months as the ninth-ranked and fourth-ranked primary diagnosis in the 2 time periods, respectively.

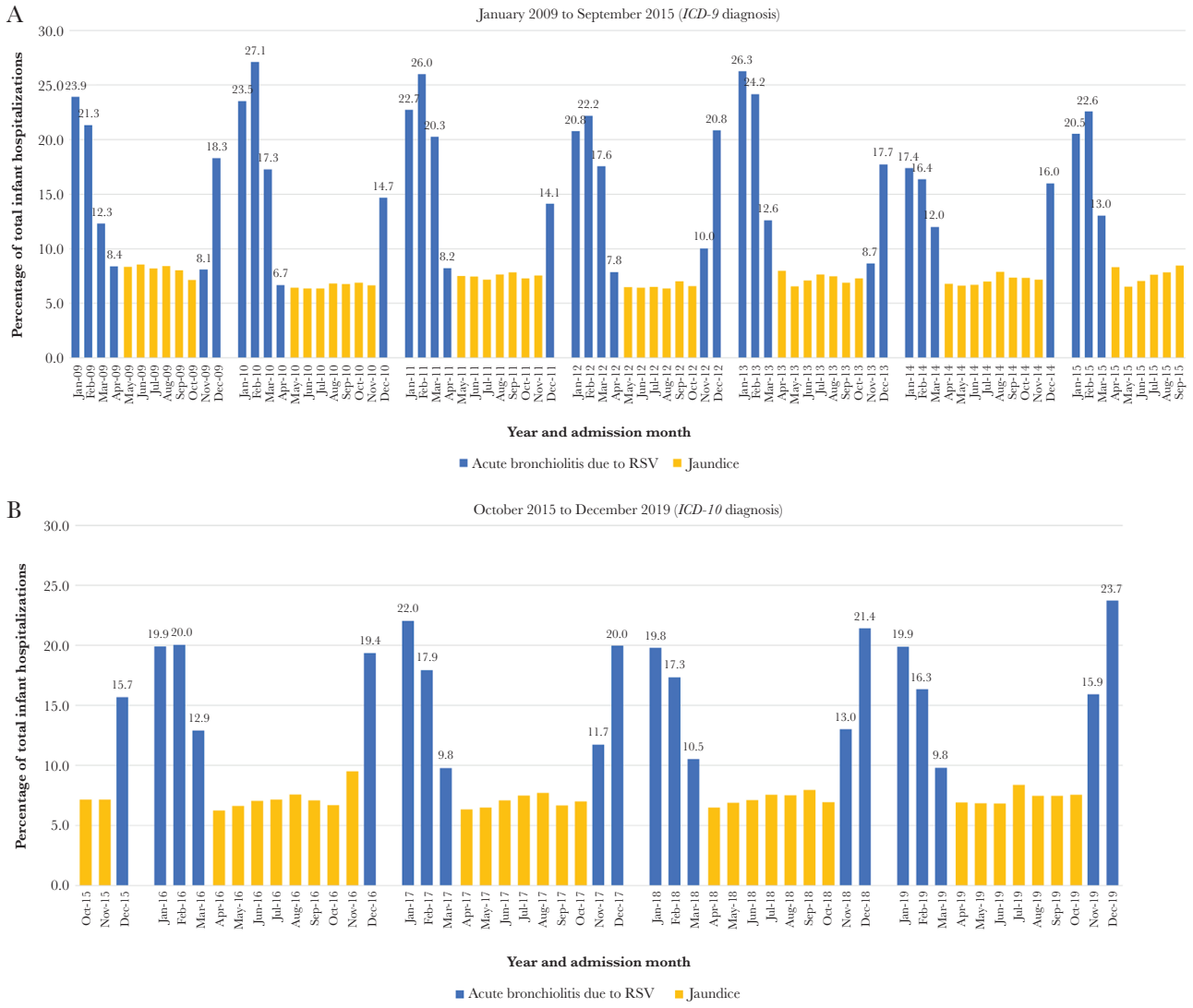

Figure 2. The leading cause of infant hospitalizations by year and admission month, with percentage of total infant hospitalizations, National (Nationwide) Inpatient Sample, 2009–2019. *A*, January 2009 to September 2015 (*ICD-9* diagnosis). *B*, October 2015 to December 2019 (*ICD-10* diagnosis). Abbreviations: *ICD-9*, *International Classification of Diseases, Ninth Revision*; *ICD-10*, *International Classification of Diseases, Tenth Revision*; RSV, respiratory syncytial virus.

of databases includes the National (Nationwide) Inpatient Sample (NIS) and Kids' Inpatient Database (KID). Released annually, NIS is the largest all-payer inpatient care database, using a 20% stratified sample of all hospital stays from US community hospitals, except rehabilitation and long-term acute care hospitals; it covers >97% of the US population [14]. Released every 3 years, KID is the largest publicly available all-payer inpatient care database for the US pediatric (<21 years of age) population, containing information on 3 million pediatric discharges each year [15]. These datasets are nationally representative and thus optimal to describe US infant hospitalizations, including RSV hospitalizations. They are also robust with sociodemographic data available at the encounter level including sex, chronological age, race/ethnicity, and insurance payer status.

The 2009–2019 NIS data were used as the primary dataset; 2019 was the latest year of data availability. As KID is released every 3 years, 2009, 2012, and 2016 data were selected to correspond with the NIS dataset timeframe. KID data were used to assess the generalizability of the NIS results. Data for birth month and chronological age in months were available only in NIS 2009–2011 and KID 2009 and thus only analyzed for those calendar years.

NIS and KID may have obtained hospitalization data from overlapping hospitals, but details of the sampling structure do not necessarily indicate the extent of overlap, if any [16]. Because NIS and KID contained de-identified discharge-level information on inpatient care [14, 15], this study was exempt from federal regulations for the protection of human research participants. Additionally, HCUP data use agreement procedures were

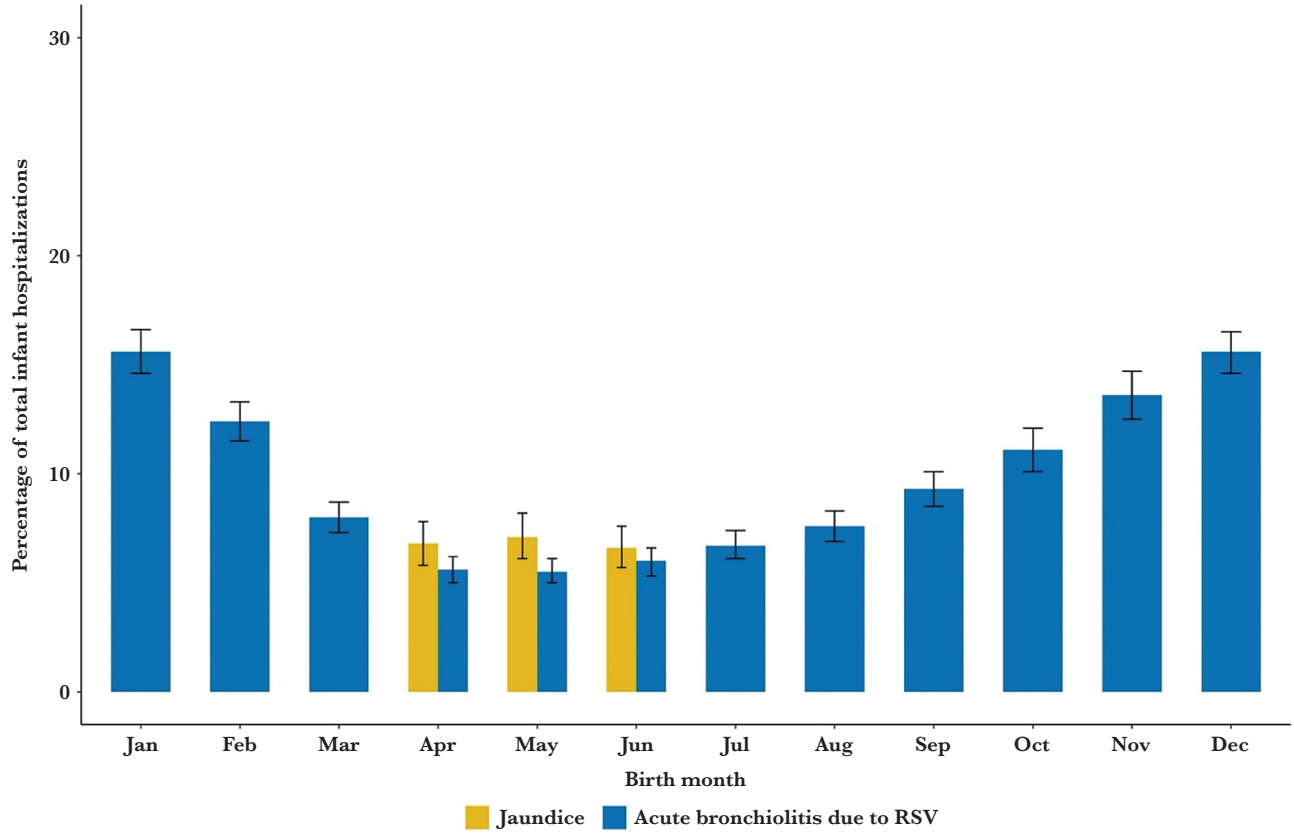

Figure 3. The leading cause of infant hospitalizations by birth month with percentage of total infant hospitalizations and corresponding 95% confidence intervals, National (Nationwide) Inpatient Sample, 2009–2011. Percentage of total infant hospitalizations for acute bronchiolitis due to respiratory syncytial virus (RSV) was provided for April, May, and June as the second-ranked primary diagnosis during those birth months.

followed to safeguard the confidentiality of patients, physicians, and healthcare institutions in the US.

Study Population

The unit of analysis in this study was infant (<1 year) hospitalizations from January 2009 to December 2019. All newborn birth hospitalizations, the most common reason for inpatient hospital stays among infants [17], were excluded by *ICD-9* (V30.XX–V39.XX) and *International Classification of Diseases, Tenth Revision* (*ICD-10*) (Z38.XX) codes. RSV hospitalization was identified by a primary diagnosis of RSV (*ICD-9*: 079.6 or *ICD-10*: B97.4); pneumonia due to RSV (*ICD-9*: 480.1 or *ICD-10*: J12.1); acute bronchiolitis due to RSV (*ICD-9*: 466.11 or *ICD-10*: J21.0); or acute bronchitis due to RSV (*ICD-10*: J20.5). Bronchiolitis hospitalization was identified by a primary diagnosis of acute bronchiolitis due to other specified organisms (*ICD-9*: 466.19 or *ICD-10*: J21.8) or acute bronchiolitis, unspecified (*ICD-10*: J21.9).

Variables and Statistical Analysis

The leading causes by percentage and corresponding 95% confidence intervals (CIs) of total infant hospitalizations were reported. In the analyses by sociodemographic variables, the denominator was the percentage of total infant hospitalizations in each group (eg, the leading cause among all Medicaid-insured infant hospitalizations). With the transition of *ICD-9* to *ICD-10* in 2015, 2 distinct time periods were evaluated for the overall analysis: (1) January 2009–September 2015; and (2) October 2015–December 2019. The leading causes of infant hospitalizations were presented in each calendar year and by admission month. In the US, the RSV season is typically from November through March for many areas [18]. Hence, leading causes of infant hospitalizations were also evaluated by in-season months (November–March) and out-of-season months (April–October) in 2009–2019. In addition, the leading cause of infant hospitalizations were presented by birth month.

Because the NIS and KID databases provided chronological age in months, sex (male and female), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, AI/AN, Asian Pacific Islander, and other), and insurance payer (Medicaid, private, other/unknown), the leading causes of infant hospitalizations were also reported within categories of these sociodemographic variables. The leading causes of infant

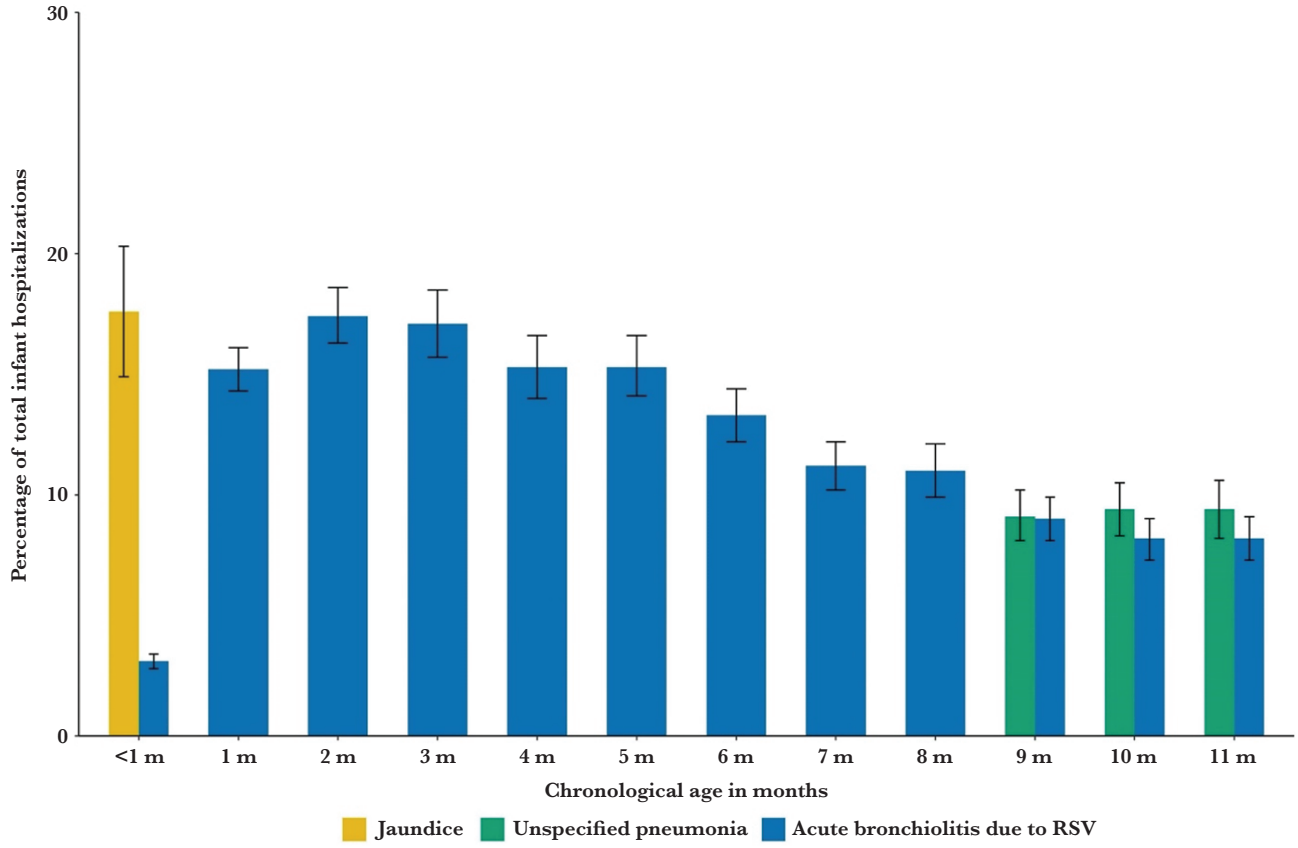

Figure 4. The leading cause of infant hospitalizations by chronological age in months, with percentage of total infant hospitalizations and corresponding 95% confidence intervals, National (Nationwide) Inpatient Sample, 2009–2011. Percentage of total infant hospitalizations for acute bronchiolitis due to respiratory syncytial virus (RSV) was provided for age <1 month, 9 months, 10 months, and 11 months when it was not the leading cause. Among age <1 month, acute bronchiolitis due to RSV was the ninth-ranked primary diagnosis. For ages 9, 10, and 11 months, acute bronchiolitis due to RSV was the second-ranked primary diagnosis but was not statistically different from the first-ranked primary diagnosis.

hospitalizations by birth month and by chronological age in months were identified in 2009–2011 only, because of data availability.

Sensitivity analyses were conducted by examining the most frequent diagnosis with the *ICD* code in any position because up to 30 codes (*ICD-9*) or 40 codes (*ICD-10*) can be listed as the diagnosis reason for a hospitalization. All analyses were conducted using SAS/STAT for Windows version 9.4 software, with statistical procedures that incorporated the sampling design features of the HCUP data. Data were visualized using R 1.4.1717 [19] and Microsoft Excel for Mac version 16.54 software.

RESULTS

Leading Cause of Infant Hospitalizations Overall, by RSV Season, by Calendar Year, by Admission Month, and by Birth Month

Between January 2009 and December 2019, 4 595 215 total infant (<1 year) hospitalizations were recorded in NIS. Acute bronchiolitis due to RSV (*ICD-9*: 466.11 or *ICD-10*: J21.0) was the leading primary diagnosis, accounting for 9.6% (95% CI, 9.4%–9.9%) of the total infant hospitalizations from January 2009 to September 2015 (*ICD-9*: 466.11), and 9.3% (95% CI, 9.0%–9.6%) from October 2015 to December 2019 (*ICD-10*: J12.0) (Table 1). In any diagnostic position, acute bronchiolitis due to RSV was the most frequent diagnosis (Table 1).

Acute bronchiolitis due to other infectious organisms (*ICD-9*: 466.19) and acute bronchiolitis, unspecified (*ICD-10*: J21.9) were both the third-ranked primary diagnoses, accounting for 6.1% (95% CI, 5.7%–6.4%) of the total infant hospitalizations from January 2009 through September 2015, and 3.7% (95% CI, 3.5%–3.9%) from October 2015 through December 2019, respectively (Table 1). Acute bronchiolitis due to other specified organisms (*ICD-10*: J21.8) was the fifth-ranked primary diagnosis from October 2015 through December 2019 (Table 1). In any diagnostic position, 2 bronchiolitis codes (*ICD-9*: 466.19 and *ICD-10*: J21.9) were within the top 10 most frequent diagnoses (Table 1).

During the in-season months (November–March) combined over 2009–2019, acute bronchiolitis due to RSV was the leading primary diagnosis, accounting for 17.9% (95% CI, 17.4%–18.4%) of total infant hospitalizations from

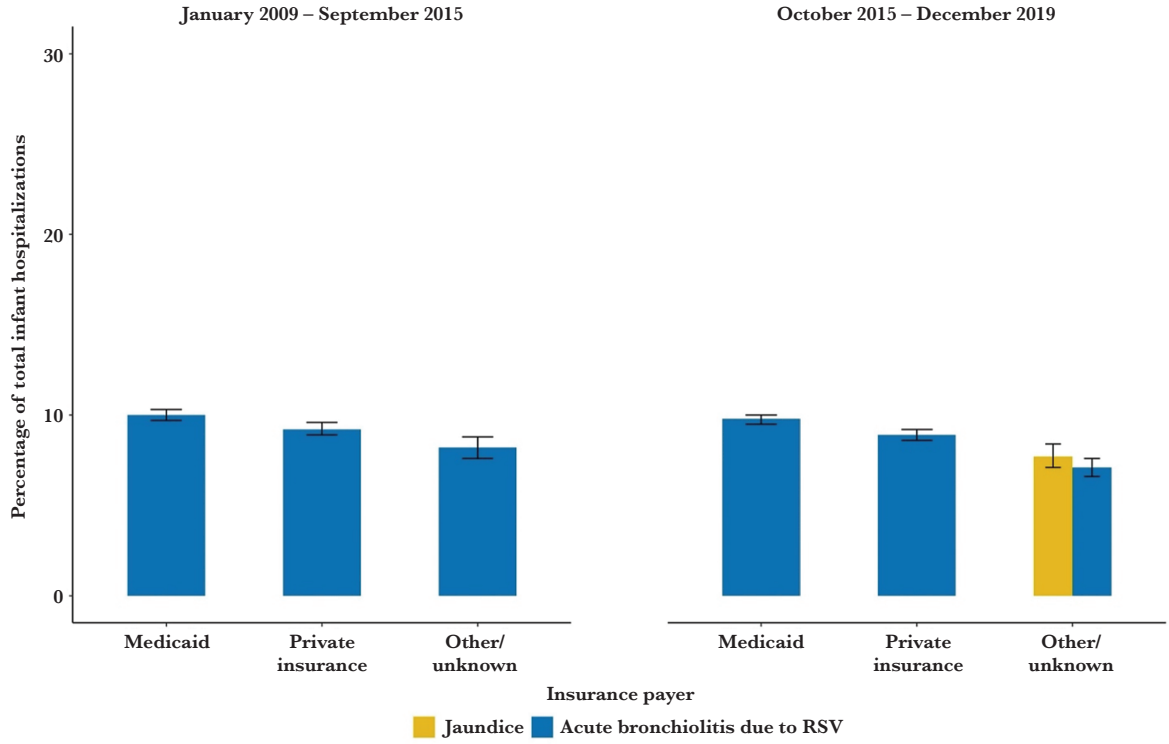

Figure 5. The leading cause of infant hospitalizations by insurance payer and time period, with percentage of total infant hospitalizations and corresponding 95% confidence intervals, National (Nationwide) Inpatient Sample, 2009–2019. Percentage of total infant hospitalizations for acute bronchiolitis due to respiratory syncytial virus (RSV) was provided for other/unknown insurance in October 2015–December 2019 and it was the second-ranked primary diagnosis.

January 2009 to September 2015 and 16.5% (95% CI, 16.1%–16.9%) from October 2015 to December 2019 (Figure 1). During the out-of-season months (April–October), acute bronchiolitis due to RSV was the ninth-ranked and fourth-ranked primary diagnosis in the 2 time periods, respectively (Figure 1).

Similarly, by individual calendar years overall and by admission months from December to March in each year, acute bronchiolitis due to RSV was the leading primary diagnosis of infant hospitalizations, accounting for >10% of total infant hospitalizations (Figure 2A and 2B; Supplementary Table 1). In January and February, acute bronchiolitis due to RSV accounted for > 15% of total infant hospitalizations.

By birth month, acute bronchiolitis due to RSV was the leading primary diagnosis in nearly every month during 2009–2011 (Figure 3). From April to June, acute bronchiolitis due to RSV was the second-ranked primary diagnosis behind jaundice, but the results were not different with overlapping percentages and 95% CIs (Figure 3). Acute bronchiolitis due to RSV accounted for >10% of total infant hospitalizations among infants born in October through February (Figure 3). Similar patterns were observed when *ICD* codes in any diagnostic position were examined by calendar year, by admission month, and by birth month (data not shown).

Leading Causes of Hospitalizations by Chronological Age and by Sex

From 2009 through 2011, acute bronchiolitis due to RSV was the leading primary diagnosis for nearly all ages except those aged <1 month (excluding newborn birth hospitalizations) and those aged ≥9 months (Figure 4). Among infants aged <1 month, jaundice was the leading cause of hospitalization, with acute bronchiolitis due to RSV as the ninth-ranked primary diagnosis (Figure 4). For infants aged 9–11 months, acute bronchiolitis due to RSV was the second-ranked primary diagnosis behind unspecified pneumonia, but the results were not different with overlapping percentages and 95% CIs (Figure 4). For ages with acute bronchiolitis due to RSV as the leading primary diagnosis, the percentage of total infant hospitalizations ranged from 11.0% (95% CI, 9.9%–12.1%) at 8 months to 17.4% (95% CI, 16.3%–18.6) at 2 months (Figure 4). In any diagnostic position, acute bronchiolitis due to RSV was the most frequent diagnosis for infants aged 1 month, 2 months, and up to 5 months (data not shown). For infants aged <1 month and those aged 6 months, 7 months, and up to 11 months, jaundice, acute bronchiolitis due to other infectious organisms, and dehydration were the most frequent diagnoses; with the exception of age <1 month, acute bronchiolitis due to RSV was still within the top 10 most frequent diagnoses in these age groups (data not shown).

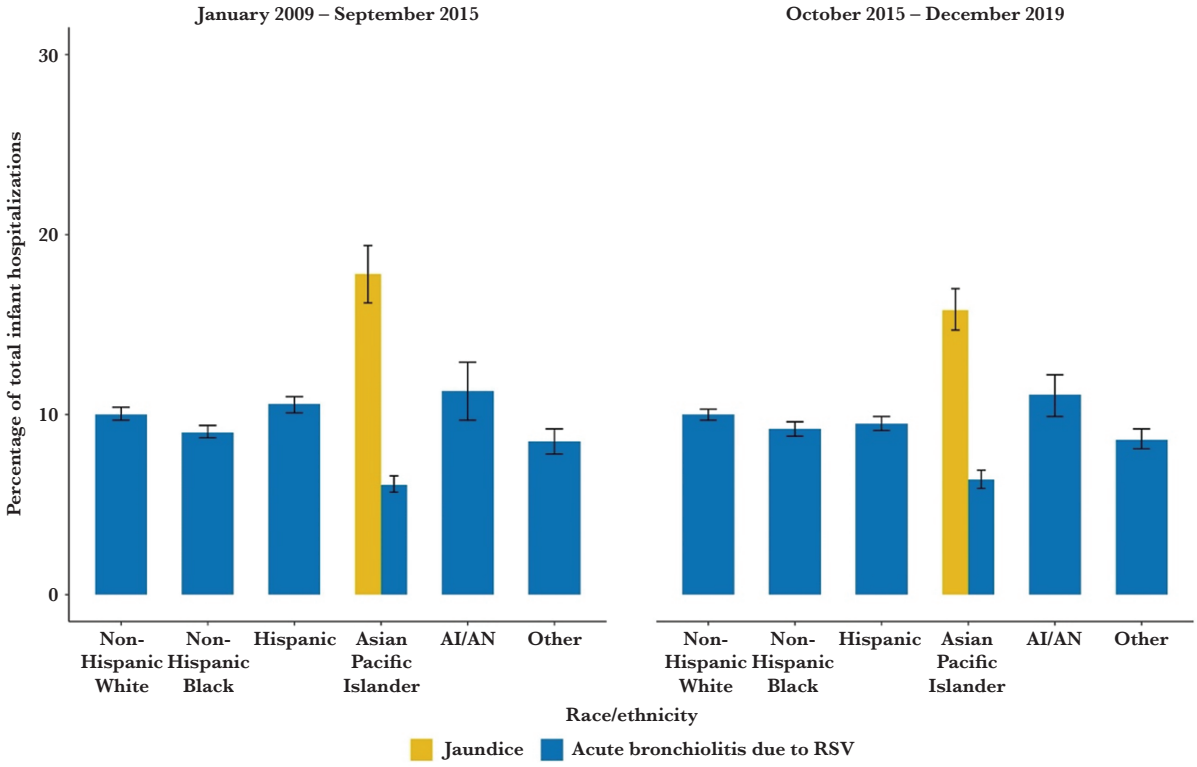

Figure 6. The leading cause of infant hospitalizations by race/ethnicity and time period, with percentage of total infant hospitalizations and corresponding 95% confidence intervals, National (Nationwide) Inpatient Sample, 2009–2019. Percentage of total infant hospitalizations for acute bronchiolitis due to respiratory syncytial virus (RSV) was provided for Asian/Pacific Islander as it was the second-ranked primary diagnosis. Abbreviation: AI/AN, American Indian/Alaska Native.

When examined by sex, acute bronchiolitis due to RSV was the leading primary diagnosis for both female and male infant hospitalizations from 2009 through 2019 (Supplementary Table 2). In any diagnostic position, similar patterns were observed (data not shown).

Leading Cause of Infant Hospitalizations by Insurance Payer and by Race/Ethnicity

From 2009 to 2019, acute bronchiolitis due to RSV was the leading primary diagnosis for all Medicaid and privately insured hospitalizations (Figure 5). Hospitalizations for acute bronchiolitis due to RSV among Medicaid infants were nearly twice those of privately insured infants (data not shown). For hospitalizations with other/unknown insurance, acute bronchiolitis due to RSV was the second-ranked primary diagnosis from October 2015 to December 2019 (Figure 5). For Medicaid-insured infants, acute bronchiolitis due to RSV accounted for 10.0% (95% CI, 9.7%–10.3%) of total infant hospitalizations from January 2009 to September 2015 and 9.8% (95% CI, 9.5%–10.0) from October 2015 to December 2019. For private insurance, acute bronchiolitis due to RSV comprised 9.2% (95% CI, 8.9%–9.6%) and 8.9% (95% CI, 8.6%–9.2%) of total infant hospitalizations in the 2 time periods, respectively. Similar patterns were observed in any diagnostic position (data not shown).

Acute bronchiolitis due to RSV was the leading primary diagnosis for all races and ethnicities except Asian/Pacific Islander (Figure 6). In this group, acute bronchiolitis due to RSV was the second-ranked primary diagnosis (Figure 6). RSV hospitalization was highest among non-Hispanic White, Hispanic, and AI/AN infants: acute bronchiolitis due to RSV comprised 10.0% (95% CI, 9.7%–10.4%) to 11.1% (95% CI, 9.9%–12.2%) of total infant hospitalizations. Hospitalizations for acute bronchiolitis due to RSV among non-Hispanic White infants were nearly 4 times higher than those of non-Hispanic Black infants (data not shown). In any diagnostic position, acute bronchiolitis due to RSV was the most frequent diagnosis among Hispanic and AI/AN infants (data not shown).

Confirmatory analyses of KID 2009, 2012, and 2016 data were consistent with those of NIS 2009–2019 data (see Supplementary Materials for details).

DISCUSSION

This study uses the largest publicly available, all-payer database in the US to describe the leading causes of infant hospitalizations. Previous studies [4–7] presented leading causes of US infant hospitalization using data from 1997 to 2003, which are now 2 decades old. This update affirms acute bronchiolitis

due to RSV as the leading cause of hospitalization in US infants aged <1 year using the most recent, comprehensive, and nationally representative data. This study is also robust and includes analyses within strata of sociodemographic variables known to impact infant RSV hospitalizations. In every birth month, all races/ethnicities, except for Asian/Pacific Islanders, and all insurance payer groups, acute bronchiolitis due to RSV was the leading cause of infant hospitalization.

In another study, we also used the 2011–2019 NIS dataset and combined all *ICD* diagnosis codes for RSV; infant RSV hospitalization mortality remained constant over time from 2011 to 2019 (0.10%; $P = .8$) while hospitalization length of stay (2019: 2.8 days [95% CI, 2.7–2.9 days]; $P < .0001$) and mean total charge during hospitalization (2019: $21 513 standardized to the 2020 US dollar; $P < .0001$) increased, elucidating that healthcare utilization associated with RSV is substantial [20]. Although palivizumab has been available since 1998, it is only recommended for preterm infants born at <29 weeks' gestational age or those with specific comorbidities including hemodynamically significant congenital heart disease or chronic lung disease of prematurity [21, 22]. These subgroups represent a very small proportion of the general population, but nearly all children are infected with RSV before 2 years of age [23]. As RSV affects all children and is the leading cause of infant hospitalizations in the US, RSV policy will likely be revisited when candidates in clinical development are licensed [21] and their potential to mitigate the effects of RSV for all infants and across the health system is discussed.

Notably, given the lack of routine laboratory testing and the utilization of *ICD* diagnosis codes to identify cases, infant hospitalizations associated with RSV are likely to be higher than those presented in the literature and our study. In much of the RSV literature, bronchiolitis hospitalizations defined by *ICD* diagnosis codes are included to represent an upper estimate of RSV hospitalizations because RSV is the most frequent cause of infant bronchiolitis and pneumonia and laboratory testing for RSV is not recommended [24]. It should be noted, however, that clinical laboratory testing and *ICD* codes do not always overlap [25]. In a study of Kaiser Permanente Northern California databases that evaluated RSV laboratory test results and bronchiolitis *ICD* diagnosis codes [25] between December and February from 2006 through 2009, 77.2% of bronchiolitis hospitalization episodes among infants aged ≤6 months as captured by *ICD-9* codes were confirmed RSV positive by laboratory testing. In our study, acute bronchiolitis due to other infectious organisms and acute bronchiolitis, unspecified were within the top 10 infant hospitalizations from 2009 through 2019. Although laboratory testing data were not available in the NIS and KID, the majority of infant bronchiolitis hospitalizations reported in these HCUP databases may be attributable to RSV considering the relationship between RSV and bronchiolitis.

One limitation of this study includes the definitions of outcomes based on *ICD-9* and *ICD-10* codes. The sensitivity and specificity of diagnosis based on *ICD-9* and *ICD-10* codes for different diseases and conditions and for different cohorts may vary and could potentially introduce information bias (eg, apart from cases of acute bronchiolitis that were not tested for RSV, within season or otherwise, laboratory-confirmed acute bronchiolitis due to RSV may not have been coded as such). Previous literature has documented that coding practice can differ by the hospitals or physicians [13, 26, 27]. Although the overall findings were not impacted, this study did show slight variations when evaluating codes as the primary diagnosis or in any diagnostic position. Second, the unit of analysis in this study was hospitalizations and not the number of infants. An infant could have contributed multiple hospitalizations for RSV and bronchiolitis. Third, chronological age data were not available for most study years, except for 2009 in KID and 2009–2011 in NIS, and therefore additional confirmatory analyses of chronological age patterns after 2011 were not possible.

The strengths of this study include the use of a cohort design and national data as NIS and KID represent a sample of discharges from all US community and pediatric hospitals participating in HCUP. Because NIS and KID are comprehensive hospitalization databases in the US, they are able to provide nationally representative estimates. Furthermore, the infant hospitalization numbers were large, which provided sufficient statistical power to detect significant trends. Moreover, with the large sample size and availability of key sociodemographic data, stratified analyses by sociodemographic variables were possible. This study provided data for current years including 2019, an enhancement to past studies that used older data.

In conclusion, these nationally representative estimates show that acute bronchiolitis due to RSV is the leading cause of US infant hospitalizations, overall and across population subgroups. Because laboratory testing for RSV is not routinely performed, the true healthcare burden of RSV is likely to be higher and its public health impact underestimated. RSV immunization strategies, currently in development for all infants, have the potential to reduce US infant hospitalizations and the burden of this disease on the healthcare system.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. M. S., N. M., X. J., L. C. B., H. R., and J. P. F. are employees of EpidStrategies. C. B. N. is an employee of Sanofi and may hold shares and/or stock options in the company. All other authors report no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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