Respiratory Syncytial Virus–Associated Hospitalization Rates among US Infants: A Systematic Review and Meta-Analysis

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Background: Although global reviews of infant respiratory syncytial virus (RSV) burden exist, none have summarized data from the United States or evaluated how RSV burden estimates are influenced by variations in study design.

Methods: We performed a systematic literature review and meta-analysis of studies describing RSV-associated hospitalization rates among US infants and examined the impact of key study characteristics on these estimates.

Results: We reviewed 3328 articles through 14 August 2020 and identified 25 studies with 31 unique estimates of RSV-associated hospitalization rates. Among US infants <1 year of age, annual rates ranged from 8.4 to 40.8 per 1000 with a pooled rate of 19.4 (95% confidence interval [CI], 17.9–20.9). Study type influenced RSV-associated hospitalization rates (P = .003), with active surveillance studies having pooled rates (11.0; 95% CI, 9.8–12.2) that were half that of studies based on administrative claims (21.4; 19.5–23.3) or modeling approaches (23.2; 20.2–26.2).

Conclusions: Applying our pooled rates to the 2020 US birth cohort suggests that 79 850 (95% CI, 73 680–86 020) RSV-associated infant hospitalizations occur each year. The full range of RSV-associated hospitalization rates identified in our review can better inform future evaluations of RSV prevention strategies. More research is needed to better understand differences in estimated RSV burden across study design.

Keywords: burden of disease; epidemiology; incidence; RSV prevention; study design; United States.

Respiratory syncytial virus (RSV) is the primary cause of lower respiratory tract infection among infants and young children globally [1–5] and the main reason for infant hospitalization in the United States [3, 6]. No specific treatment or broadly available prevention options for RSV infection exist. Palivizumab, a monoclonal antibody administered monthly during the RSV season, is given prophylactically only to high-risk infants [7]. Development of additional RSV prevention options for infants is underway, and several maternal vaccines and extended half-life monoclonal antibodies are entering late-stage development [8].

With new prevention strategies on the horizon, understanding the true magnitude of RSV burden is critical for informing evaluations of the potential public health benefit these emerging prevention options may bring. A recent global review of RSV burden estimated that, worldwide, RSV causes 3.2 million hospitalizations each year among children <5 years of age, mostly in infants [1]. While this recent review summarized RSV burden across the globe [1], US-specific summary estimates were lacking. In addition, while the global review [1] provided a comprehensive qualitative summary of studies included in their analysis, it did not systematically evaluate how RSV burden estimates were influenced by variations in study design. To fill these epidemiologic gaps, we performed a systematic literature review and meta-analysis of studies describing rates of RSV-associated hospitalization among US infants. We also examined the impact of key study characteristics on estimates of RSV-associated hospitalization.

METHODS

Search Strategy and Selection Criteria
We identified all published data available in PubMed (inclusive of MEDLINE) and the Cochrane Library describing RSV-associated hospitalization rates in infants and young children. Only studies conducted in the United States and published in English were considered. Each article had to include ≥1 “RSV term” and “epidemiological measurement term” in the title (Supplementary Table 1). Search results are current through 14 August 2020.

To reduce risk of study selection bias, we adhered to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. Two independent reviewers with expertise in RSV and epidemiology (F. K. and J. M. M.) screened titles and abstracts of all references identified by the search strategy to create a master list of potentially

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relevant references for full-text review. Reference lists of studies in this master list were also reviewed. Abstracts for all references flagged for inclusion were reviewed to determine if the full report should be included in the analysis. Discrepancies between the 2 independent reviewers were resolved through discussion at each stage of the review. If a study reported >1 RSV-associated hospitalization rate based on within-study variations or sensitivity analyses in study population or design, we treated each rate as an additional, unique estimate.

We included all articles with ≥1 estimated rate of RSV hospitalization among children <5 years old. Articles had to have a clear case definition of RSV and a population-based denominator for a defined time period. We excluded studies if RSV rates were reported only as a secondary outcome in a limited population where many RSV cases were likely missed (eg, studies of childhood pneumonia only [10]) or only for specific subpopulations of infants (eg, preterm infants or those with underlying medical conditions) which were not comparable with the general infant population.

We presented results for infants <1 year and <6 months old and for all children <5 years old. In rare instances where studies did not directly report rates for infants but did report rates for another age group among children <5 years old, we calculated age-adjusted rates for infants <1 year old based on available data. We performed similar calculations to estimate rates among infants <6 months old and children <5 years old in studies where only rates for infants <1 year old were reported. For these age-adjusted rate imputations, we used methods similar to those applied by Shi et al [1]. This approach uses age-specific median rate ratios for hospitalization (Supplementary Table 2) derived from the literature to impute missing rates and has previously yielded reliable results [1]. For studies that reported rates for multiple years or for subgroups aged <5 years, <1 year, or <6 months, we calculated average age-adjusted rates for our study age groups. Where not directly reported, 95% confidence intervals (CIs) were calculated based on available data. A description of how rates were obtained or calculated for each estimate is available in Supplementary Table 3.

Study Characteristics Evaluated
We examined whether studies were prospective or retrospective, how RSV was identified, and whether studies were based on medical record review (MRR) or on administrative claims data. We also examined study time period. For claims-based studies, we evaluated data sources and which diagnosis positions were queried when identifying incident cases.

Statistical Analysis
Rates of RSV-associated hospitalization across studies were summarized using descriptive statistics. We examined variability in hospitalization rates by study type and characteristics by testing the between-group difference in means using 1-way analysis of variance. Descriptive analyses were conducted using SAS 9.4 software (SAS Institute). We performed a meta-analysis to calculate pooled rates by study type using the metan command in Stata software, version 14.0 (StataCorp). Because in-study and between-study data heterogeneity was anticipated, we used random-effects models [11–13].

RESULTS
Search Results
We identified 3328 articles based on our initial search criteria. Review of titles and abstracts from these studies yielded 261 articles where a full review of the abstract was deemed necessary. Of these, we identified 72 to be thoroughly reviewed, of which 25 met final inclusion criteria [3, 6, 14–35]. One estimate was unpublished (Simões et al; 2013) but was included in a previous global review [1]. Of the 25 studies in our analysis, 5 (20%) [6, 23, 25, 31, 32] reported >1 rate based on within-study variations in the definition of RSV hospitalization. Of these, 3 of 5 [6, 23, 25] were variations in which diagnosis positions were queried when identifying incident cases in administrative claims data, and 2 [31, 32] were variations in how RSV was identified (ie, International Classification of Diseases, Ninth Revision [ICD-9] codes only vs modeled RSV burden). This resulted in 31 unique estimated rates of RSV-associated hospitalization for final analyses (ie, 4 studies [23, 25, 31, 32] reported 2 estimates, and 1 [6] reported 3 estimates) (Figure 1).

Study Characteristics
Studies identified were published between 2000 and 2020, and reported data collected between 1989 and 2016. Four types of estimates were identified: (1) active, prospective surveillance with etiologic confirmation of RSV (4 of 31; 13%) [3, 14, 15, 35], (2) retrospective MRR with etiologic confirmation of RSV (ie, passive surveillance of clinician-directed standard-of-care medical and laboratory records [3 of 31; 10%]) [16–18], (3) retrospective analysis of administrative claims data using RSV-specific ICD-9 codes (20 of 31; 65%) [6, 19–32], and (4) model-based estimates that combined ICD-9 claims and etiologic surveillance data (4 of 31; 13%) (Tables 1 and 2) [31–34]. All active surveillance estimates came from the Centers for Disease Control and Prevention (CDC) New Vaccine Surveillance Network (NVSN) and identified RSV via viral culture and reverse-transcription polymerase chain reaction of nasal and throat swab samples taken from children hospitalized with acute respiratory infection in study catchment sites [3, 14, 15, 35]. Two retrospective MRR studies (67%) [17, 18] adjusted RSV rates upward to account for cases that were missed based on standard-of-care diagnostic and testing practices.
All claims-based studies [6, 19–32] used the same 3 ICD-9 codes to identify RSV: 466.11 (acute bronchiolitis due to RSV), 480.1 (RSV pneumonia), and 079.6 (RSV as the cause of diseases classified elsewhere). Most (13 of 20; 65%) [6, 19–24, 27, 29–32] included RSV codes in any diagnosis position, 3 of 20 (15%) [6, 25, 26] included codes in the first or second diagnosis position, and 4 of 20 (20%) [6, 25, 28] included RSV coded in the primary diagnosis position only.

**Figure 1.** Flow diagram of the literature selection process. Of the 25 studies in our analysis, 5 of 25 (20%) [6, 23, 25, 31, 32] reported >1 rate based on within-study variation(s) of the definition of respiratory syncytial virus (RSV) hospitalization. Of these, 3 of 5 [6, 23, 25] were variations in which diagnosis positions were queried when identifying incident RSV cases in administrative claims data, and 2 of 5 [31, 32] were variations in how RSV was identified (ie, International Classification of Diseases, Ninth Revision codes only vs modeled RSV burden). This resulted in 31 unique estimated rates of RSV-associated hospitalization among US infants for final analyses (ie, 4 studies [23, 25, 31, 32] reported 2 estimates and 1 [6] reported 3 estimates). Abbreviations: HCUP NIS, Healthcare Cost and Utilization Project National (Nationwide) Inpatient Sample; NHDS, National Hospital Discharge Survey.
RSV-Associated Hospitalization Rates

Among infants <1 year, annual rates of RSV-associated hospitalization ranged from 8.4 to 40.8 per 1000 (Figure 2), with a mean of 20.0 (95% CI, 17.3–22.6) and a median of 19.2 (interquartile range [IQR], 13.9–24.3) across 31 estimates (Table 2). Only 3 of 31 (10%) came from studies that did not directly report rates for infants <1 year old or where average rates for this age group could not be calculated [16, 17, 30]. In these instances, rates for infants <1 year old were estimated from other reported age groups (2 estimates were imputed using rates reported for children <2 years old [16, 30] and 1 from rates reported for children <5 years old [17]). Excluding these 3 estimates [16, 17, 30] had little impact on study results (Supplementary Table 4).

Among infants <6 months old, rates ranged from 11.6 to 56.5 per 1000 (Figure 3), with a mean of 27.1 (95% CI, 23.5–30.7) and a median of 25.6 (IQR, 18.5–32.1) (Table 2). Rates for infants <6 months old were less commonly reported and were imputed based on rates in infants <1 year old for 22 of 31 estimates (71%) (Table 2) [6, 16, 17, 19, 21–27, 29–34]. Restricting the analysis to the 9 estimates where rates in infants <6 months old were directly reported [16, 17, 30] yielded similar results (Supplementary Table 4). In addition, the median incidence rate ratio comparing infants <6 months with those <1 year old based on these 9 studies (for which data were available for both age subgroups) (Supplementary Table 5) was comparable to the median ratio we applied based on a previous systematic review [1] (1.47 vs 1.32, respectively).

Among children <5 years old, hospitalization rates ranged from 2.3 to 11.0 per 1000 (Supplementary Figure 1), with a mean of 5.4 (95% CI, 4.7–6.1) and a median of 5.2 (IQR, 3.8–6.7) (Table 2). Rates for children <5 years old were imputed based on rates in infants <1 year old for 17 of 31 estimates (55%) (Table 2) [6, 14, 16, 18–20, 23, 25–27, 29, 30]. Restricting the analysis to the 14 estimates where rates in children <5 years old

Table 1. Study Characteristics

| Study Characteristic                  | No. or Dates |
|--------------------------------------|--------------|
| Studies identified, no.              | 25           |
| Unique estimates of RSV-associated hospitalization rates * | 31           |
| Publication dates of studies, range  | 2000–2020    |
| Data collection dates, range         | 1989–2016    |
| Studies directly reporting rates, No. (%) |             |
| In infants aged <1 y                 | 28 (90)      |
| In infants aged <6 mo                | 9 (29)       |
| In infants aged <5 y                 | 14 (45)      |

Abbreviation: RSV, respiratory syncytial virus.

Table 2. Annual Respiratory Syncytial Virus–Associated Hospitalization rates Among US Infants

| Study Type                      | Age <1 y Mean (SD) | Age <6 mo Mean (SD) | Age <5 y Mean (SD) |
|---------------------------------|--------------------|---------------------|--------------------|
| Overall, all study estimates (n = 31) |                    |                     |                    |
| Range                           | 8.4 (7.2)          | 11.6–56.5           | 2.3–11.0           |
| Mean (SD)                       | 20.0 (1.9)         | 271 (9.9)           | 5.4 (2.0)          |
| Median (IQR)                    | 19.2 (13.9–24.3)   | 25.6 (18.5–32.1)    | 5.2 (3.8–6.7)      |
| Active surveillance (n = 4)      |                    |                     |                    |
| Range                           | 8.4–12.9           | 13.0–18.5           | 2.3–3.5            |
| Mean (SD)                       | 10.9 (1.9)         | 15.8 (2.4)          | 2.9 (1.0)          |
| Median (IQR)                    | 11.2 (9.7–12.2)    | 15.8 (13.9–17.7)    | 3.0 (2.6–3.3)      |
| Retrospective MRR (n = 3)       |                    |                     |                    |
| Range                           | 8.8–21.5           | 11.6–28.4           | 2.4–5.8            |
| Mean (SD)                       | 13.4 (7.1)         | 18.1 (9.0)          | 3.6 (1.9)          |
| Median (IQR)                    | 9.8 (8.8–21.5)     | 14.3 (11.6–28.4)    | 2.7 (2.4–5.8)      |
| ICD-9 codes (n = 20)            |                    |                     |                    |
| Range                           | 13.7–40.8          | 18.1–56.5           | 3.7–11.0           |
| Mean (SD)                       | 21.9 (6.3)         | 29.6 (9.2)          | 5.9 (1.7)          |
| Median (IQR)                    | 22.4 (17.3–25.3)   | 29.5 (22.9–33.3)    | 6.0 (4.6–6.8)      |
| Model based (n = 4)             |                    |                     |                    |
| Range                           | 19.0–32.0          | 25.1–42.2           | 4.7–8.7            |
| Mean (SD)                       | 24.6 (5.4)         | 32.4 (7.1)          | 6.7 (1.8)          |
| Median (IQR)                    | 23.7 (21.3–27.9)   | 31.2 (28.1–36.8)    | 6.8 (5.3–8.1)      |

Abbreviations: ICD-9, International Classification of Diseases, Ninth Revision; IQR, interquartile range; MRR, medical record review; RSV, respiratory syncytial virus; SD, standard deviation.

*Of the 26 studies in our analysis, 5 of 25 (20%) [6, 23, 25, 31, 32] reported >1 rate based on within-study variation(s) of the definition of RSV hospitalization. Of these, 3 of 5 [6, 23, 25] were variations in which diagnosis positions were queried when identifying incident RSV cases in administrative claims data, and 2 of 5 [21, 32] were variations in how RSV was identified (ie, ICD-9 codes only vs modeled RSV burden). This resulted in 31 unique estimated rates of RSV-associated hospitalization among US infants for final analyses (ie, 4 studies [23, 25, 31, 32] reported 2 estimates, and 1 study [6] reported 3). All active prospective surveillance study estimates came from the Centers for Disease Control and Prevention New Vaccines Surveillance Network program and identified RSV via culture and reverse-transcription polymerase-chain reaction of nasal and throat swab samples taken from children hospitalized with acute respiratory infection in 1 of the study catchment sites. Retrospective MRR studies were based on passive surveillance of available standard-of-care medical and laboratory records. Two retrospective MRR studies (17, 18) adjusted their estimated RSV incidence rates upward to account for the estimated number of cases that were missed based on standard-of-care diagnostic and testing practices (ie, missed case ascertainment in passive surveillance). ICD-9 code studies were retrospective analyses of administrative claims data based on RSV-specific ICD-9 codes (466.11, 480.1, and 079.6). Model-based estimates supplemented RSV-specific ICD-9 claims data with etiologic surveillance data.
to-season variation occurred in studies that reported data over all children <5 years old (\(P = .003\); Table 2). Although seasonality was reported in studies of children 

| Study estimate                  | Annual RSV hospitalization per 1000 | Year of data | Data source                  |
|--------------------------------|-------------------------------------|--------------|------------------------------|
| [Boyce et al, 2010]            | 11.2                                | 1989–1995    | Tennessee Medicaid           |
| [Stockman et al, 2014]         | 12.0                                | 1997–2006    | NHDS national database       |
| [Johnson et al, 2004]          | 12.4                                | 1999–2010    | Louisiana hospital discharge database |
| [Holman et al, 2004]           | 12.7                                | 1997–2001    | NHDS national database       |
| [Stockman et al, 2012]         | 12.9                                | 1997–2006    | NHDS national database       |
| [Holman et al, 2005]           | 13.3                                | 1997–2001    | NHDS national database       |
| [Leader et al, 2002]           | 13.8                                | 1997–1999    | NHDS national database       |
| [Leader et al, 2003]           | 14.3                                | 1997–2000    | NHDS national database       |
| [Goldstein et al, 2019]        | 14.8                                | 2003–2010    | HCUP NIS national database   |
| [Leader et al, 2005]           | 15.3                                | 1997–1999    | NHDS national database       |
| [Zhou et al, 2012]             | 15.7                                | 1997–2000    | NHDS national database       |
| [Liget et al, 2006]            | 16.0                                | 1997–1999    | NHDS national database       |
| [Leader et al, 2003]           | 16.6                                | 1997–1998    | Children’s hospital in Milwaukee, WI |
| [Leader et al, 2002]           | 17.1                                | 1997–1999    | HCUP NIS national database   |
| [Heinrich et al, 2004]         | 17.6                                | 2000–2005    | New York City hospital discharge database |
| [Zachariah et al, 2006]        | 17.7                                | 2000–2004    | Colorado hospital discharge database |
| [Goldstein et al, 2015]        | 18.6                                | 2000–2003    | California hospital discharge database |
| [Simões et al [unpublished]]   | 19.0                                | 2000–2004    | California hospital discharge database |
| [Zhao et al, 2012]             | 19.3                                | 2000–2005    | California hospital discharge database |
| [Pomier et al, 2004]           | 20.0                                | 2000–2004    | California hospital discharge database |
| [Santer et al, 2004]           | 20.1                                | 2000–2003    | California hospital discharge database |
| [Foste et al, 2015]            | 20.3                                | 2000–2004    | California hospital discharge database |
| [Choudhari et al, 2006]        | 20.6                                | 2000–2003    | California hospital discharge database |
| [Lloyd et al, 2014]            | 20.8                                | 2000–2003    | California hospital discharge database |
| [Bennett et al, 2018]          | 21.0                                | 2000–2004    | California hospital discharge database |
| [Ishii et al, 2004]            | 21.3                                | 2000–2004    | California hospital discharge database |
| [Raba et al, 2011]             | 21.4                                | 2000–2004    | California hospital discharge database |
| [Hall et al, 2013]             | 21.7                                | 2000–2004    | California hospital discharge database |
| [Hall et al, 2014]             | 21.9                                | 2000–2004    | California hospital discharge database |


were directly reported \([3, 15, 17, 21, 22, 24, 28, 31–35]\) yielded similar summary results (Supplementary Table 4).

Study type influenced RSV hospitalization rates \((P = .003\) for infants <1 year and \(P = .01\) for those <6 months old), with model-based estimates being the highest \((n = 4;\) means of 24.6 and 32.4 per 1000 among infants <1 year and <6 months old, respectively), followed by estimates from claims-based analyses \((n = 20;\) means of 21.9 and 29.6 per 1000, respectively), retrospective MRR studies \((n = 3;\) means of 13.4 and 18.1 per 1000), and NVSN active surveillance \((n = 4;\) means of 10.9 and 15.8 per 1000) (Table 2 and Figure 4). Findings were similar for all children <5 years old \((P = .003;\) Table 2). Although season-to-season variation occurred in studies that reported data over multiple years \([3, 19, 31–34]\), no time-related trends in RSV hospitalization rates were seen in studies that evaluated rates over time (Supplementary Figure 2).

Among claims-based estimates \((n = 20)\) \([6, 19–32]\), the data source was associated with RSV hospitalization rates \((P < .001)\) for both infants <1 year and those <6 months old. The highest estimate was from a study of Tennessee Medicaid data, with rates of 40.8 and 56.5 per 1000 among infants <1 year and <6 months old, respectively \([20]\). This was followed by estimates from the National Hospital Discharge Survey \((n = 8;\) means of 24.6 and 33.7 per 1000, respectively, among infants <1 year and <6 months old) \([6, 23, 25, 31]\), state-specific hospital discharge databases \((n = 8;\) means of 18.6 and 24.5 per 1000, respectively) \([19, 21, 24, 26, 27, 29, 30]\), and the National Inpatient Sample database \((n = 3;\) means of 17.2 and 23.6 per 1000) \([22, 28, 32]\).

Broadening claims-based definitions of RSV beyond the primary diagnosis position did not significantly influence hospitalization rates. For studies that defined RSV hospitalization...
Our study confirms the high burden of RSV-associated hospitalization in infants and underscores the need for novel

**DISCUSSION**

**Figure 3.** Annual respiratory syncytial virus (RSV)–associated hospitalization rates per 1000 among US infants <6 months of age (n = 31). Estimates in parentheses were imputed using RSV-associated hospitalization rates reported for a different age group. Active surveillance studies were prospective and required etiologic testing and confirmation of RSV. All active prospective surveillance study estimates came from the Centers for Disease Control and Prevention New Vaccines Surveillance Network (CDC NVSN) program and identified RSV via culture and reverse-transcription polymerase-chain reaction of nasal and throat swab samples taken from children hospitalized with acute respiratory infection in 1 of the study catchment sites. Retrospective MRR studies were based on passive surveillance of available standard-of-care medical and laboratory records. Two retrospective medical record review (MRR) studies [17, 18] adjusted their estimated RSV incidence rates upward to account for the estimated number of cases that were missed based on standard-of-care diagnostic and testing practices (ie, missed case ascertainment in passive surveillance).

**International Classification of Diseases, Ninth Revision (ICD-9) code studies were retrospective analyses of administrative claims data based on RSV-specific ICD-9 codes (486.11, 480.1, and 079.6). Model-based estimates supplemented RSV-specific ICD-9 claims data with etiologic surveillance data. Abbreviations: HCUP NIS, Healthcare Cost and Utilization Projection National ( Nationwide) Inpatient Sample; NHDS, National Hospital Discharge Survey.

### Table: Annual RSV hospitalization per 1000

| Study estimate | Annual RSV hospitalization per 1000 |
|---------------|-----------------------------------|
| Boyce et al [20], 2000 | 20.5 (18.9–22.2) |
| Stockman et al [31], 2012 | 33.4 (31.4–35.5) |
| Holman et al [23], 2004 | 28.8 (26.3–31.3) |
| Stockman et al [31], 2012 | 28.6 (26.6–30.5) |
| Johnson et al [24], 2012 | 21.0 (19.0–23.0) |
| Holman et al [25], 2004 | 25.6 (23.6–27.6) |
| Leader et al [6], 2002 | 25.4 (23.4–27.4) |
| Leader et al [6], 2003 | 21.6 (19.6–23.6) |
| Goldstein et al [34], 2015 | 21.6 (19.6–23.6) |
| Zauber et al [39], 2011 | 21.0 (19.0–23.0) |
| Letticko et al [17], 2004 | 21.0 (19.0–23.0) |
| Paramore et al [20], 2004 | 21.0 (19.0–23.0) |
| Zou et al [32], 2012 | 21.0 (19.0–23.0) |
| Light et al [26], 2008 | 21.0 (19.0–23.0) |
| Leader et al [25], 2003 | 21.0 (19.0–23.0) |
| Leader et al [6], 2002 | 21.0 (19.0–23.0) |
| Henttickeno et al [17], 2004 | 21.0 (19.0–23.0) |
| Sargee et al [29], 2006 | 21.0 (19.0–23.0) |
| Foutz et al [27], 2015 | 21.0 (19.0–23.0) |
| Costello et al [21], 2006 | 21.0 (19.0–23.0) |
| Iwane et al [15], 2004 | 21.0 (19.0–23.0) |
| Lloyd et al [27], 2014 | 21.0 (19.0–23.0) |
| Bremont et al [5], 2018 | 21.0 (19.0–23.0) |
| Hall et al [3], 2009 | 21.0 (19.0–23.0) |
| Ria et al [15], 2020 | 21.0 (19.0–23.0) |
| Arvola et al [18], 2019 | 21.0 (19.0–23.0) |
| Hall et al [14], 2015 | 21.0 (19.0–23.0) |
| Grindeland et al [16], 2016 | 21.0 (19.0–23.0) |

**Study estimate**

- Boyce et al [20], 2000
- Stockman et al [31], 2012
- Holman et al [23], 2004
- Stockman et al [31], 2012
- Johnson et al [24], 2012
- Holman et al [25], 2004
- Leader et al [6], 2002
- Leader et al [25], 2003
- Goldstein et al [34], 2019
- Leader et al [6], 2002
- Zhou et al [32], 2012
- Light et al [26], 2008
- Leader et al [25], 2003
- Leader et al [6], 2002
- Henttickeno et al [17], 2004
- Paramore et al [20], 2004
- Zauber et al [39], 2011
- Goldstein et al [34], 2015
- Simlese et al (unpublished), 2015
- Zhou et al [32], 2012
- Sargee et al [29], 2006
- Foutz et al [27], 2015
- Costello et al [21], 2006
- Iwane et al [15], 2004
- Lloyd et al [27], 2014
- Bremont et al [5], 2018
- Hall et al [3], 2009
- Ria et al [15], 2020
- Arvola et al [18], 2019
- Hall et al [14], 2015
- Grindeland et al [16], 2016

**Year of data**

- 1989–1993
- 1997–2000
- 1997–2001
- 1997–2006
- 1999–2010
- 1997–2000
- 1997–1999
- 2003–2010
- 2004–2006
- 2004–2013
- 2000
- 1993–2004
- 2003–2011
- 2008–2013
- 1999–2003
- 2009–2011
- 1998–2002
- 2000–2001
- 1996–2006
- 1997–2011
- 2004–2009
- 2015–2016
- 2003–2011
- 2014–2015
- 2000–2005
- 2012–2015

**Data source**

- Tennessee Medicaid
- NHDS national database
- NHDS national database
- NHDS national database
- Louisiana hospital discharge database
- NHDS national database
- NHDS national database
- NHDS national database
- HCUP NIS national database
- HCUP NIS national database
- HCUP NIS national database
- Florida hospital discharge database
- NHDS national database
- NHDS national database
- HCUP NIS national database
- HCUP NIS national database
- Colorado hospital discharge database
- Colorado hospital discharge database
- HCUP NIS national database
- California hospital discharge database
- HCUP NIS national database
- Colorado hospital discharge database
- State hospital discharge databases for AZ, IA, NY, OR, and WI
- California hospital discharge database
- CDC NVSN, 3 sites (TN, NY, OH)
- CDC NVSN, 3 sites (TN, NY, OH)
- CDC NVSN, 7 sites (TX, NY, OH, MO, TX, CA, WA)
- CDC FluSurv-NET, 4 sites (CA, GA, MN, OR)
- CDC NVSN, 3 sites (TN, NY, OH)
- CDC NVSN, 3 sites (TN, NY, OH)
- Children’s hospital in Fargo, ND

**ICD-9 codes**

- 486.11
- 480.1
- 079.6

**Model-based**

- IE

**Supplementary Figures 4 and 5.**
Figure 4. Box-and-whisker plot of annual respiratory syncytial virus (RSV)–associated hospitalization rate per 1000 among US infants aged <1 year (A) or <6 months (B), by study type (n = 31). In this Tukey box-and-whisker plot, individual studies are represented by dots, medians by the line separating the 2 different color shades in the shaded box, and interquartile ranges by shaded boxes. Outlying values (ie, those outside the whiskers) are studies that were beyond 1.5× the interquartile range. P = .003 and P = .01 among infants <1 year and <6 months old, respectively (1-way analysis of variance to determine differences in RSV-associated hospitalization rates by study type; degrees of freedom, 3). Active surveillance studies were prospective and required etiologic testing and confirmation of RSV. All active prospective surveillance study estimates came from the Centers for Disease Control and Prevention New Vaccines Surveillance Network program and identified RSV by means of culture and reverse-transcription polymerase-chain reaction of nasal and throat swab samples taken from children hospitalized with acute respiratory infection in 1 of the study catchment sites. Retrospective medical record review (MRR) studies were based on passive surveillance of available standard-of-care medical and laboratory records. Two retrospective MRR studies [17, 18] adjusted their estimated RSV incidence rates upward to account for the estimated number of cases that were missed based on standard-of-care diagnostic and testing practices (ie, missed case ascertainment in passive surveillance). International Classification of Diseases, Ninth Revision (ICD-9) code studies were retrospective analyses of
prevention strategies. Across 31 estimates identified in our systematic review, pooled annual rates of RSV-associated hospitalization among US infants <1 year or <6 months old were 19 (95% CI, 18–21) and 26 (24–28) per 1000, respectively. When applied to the 2020 US birth cohort of just over 4.1 million [36], this translates to an estimated 79 850 (95% CI, 73 680–86 020) RSV-associated hospitalizations among infants each year in the United States. Consistent with previous reports [3, 31], this represents roughly 75% of the total burden of RSV-associated hospitalization among all US children <5 years old—which we estimated at 106 280 (95% CI, 98 100–114 460) hospitalizations annually based on a pooled annual rate of 5 hospitalizations per 1000 in this age group. Our estimates of infant burden are in line with previous CDC estimates of annual hospitalizations among US infants ranging from 43 000 based on active surveillance [3] to 126 000 based on modeling [31]. Moreover, pooled RSV hospitalization rates in our study were nearly identical to summary rates reported for high-income countries in a recent global review (26.3 per 1000 among infants <6 months old) [1].

Among infants <1 year old, annual rates of RSV-associated hospitalization ranged from 8 to 41 per 1000 and among those <6 months old from 12 to 57 per 1000. This range was driven primarily by study type. Pooled rates from NVSN active surveillance studies [3, 14, 15, 35] were the lowest, at 11 and 16 per 1000 among infants <1 year and <6 months old, respectively. These estimates were roughly half those from claims-based analyses [6, 19–32], at 21 and 29 per 1000 among infants <1 year and <6 months old, respectively, and model-based estimates [31–34], at 23 and 31 per 1000, respectively. A similar pattern was seen among all children <5 years old.

The reasons for this discrepancy are not fully clear, and several factors likely contribute. It is possible that active surveillance, which tends to have strict inclusion criteria designed primarily for ensuring high specificity, underestimates RSV burden by missing some incident cases. As described by NVSN investigators previously, this includes the potential that children living in the catchment area may be hospitalized in outlying areas, that polymerase chain reaction testing may miss cases because of low viral titers or instability of RNA, or that sample collection using nasal and throat swab samples may be less sensitive than that using nasal wash or nasopharyngeal swab samples [15]. Furthermore, in these studies, RSV testing is not performed year round [3, 14, 15, 35]. Thus, cases occurring outside the respiratory season are not included. In addition, recruiting children into an active surveillance study can be challenging for research staff who are trying to balance recruitment efforts with the sensitive nature of approaching parents of hospitalized children.

There is evidence to suggest active surveillance may be underestimating RSV hospitalization rates. Based on a study that used capture-recapture methods to compare active versus passive surveillance methods, the CDC recently reported that sensitivity for active surveillance of RSV hospitalization in NVSN may only be 48% for children <5 years old [37]. This finding is noteworthy when viewed in the context of our review, where we found that rates from active surveillance were essentially half those reported in studies of RSV-specific ICD-9 codes or in modeling studies. If the sensitivity of active surveillance truly is only 48% [37], accounting for this finding would yield RSV burden results that closely mirror findings from claims-based and model-based analyses. CDC capture-recapture study results, however, are preliminary, and data came from only 1 NVSN site and were not stratified by age group (ie, infants <1 year or <6 months old) [37]. Moreover, the sensitivity of NVSN for detecting childhood influenza hospitalizations has been shown to be slightly higher, at roughly 70% [38, 39]. Thus, more research to evaluate the sensitivity of active surveillance for detecting infant RSV-associated hospitalizations is needed.

Claims-based analyses that used ICD-9 codes were the most common study type [6, 19–32], accounting for 65% of estimates. Using broader ICD-9 definitions (ie, more diagnosis fields) had minimal impact on RSV hospitalization rates, given that most RSV-associated illness was coded in the primary diagnosis field [6, 23, 25]. Most claims-based studies (65%) included RSV-coded in any diagnosis position [6, 19–24, 27, 29–32].

Studies using RSV-specific codes could overestimate rates if some cases of infant bronchiolitis or pneumonia are coded as RSV without laboratory confirmation, and thus could be due to other pathogens like influenza [40] or parainfluenza [41]. However, available evidence suggests that RSV-coded hospitalizations are specific for true RSV disease, as prior analyses have shown high concordance (87%–99%) between RSV diagnosis codes and positive RSV tests in multiple settings [23, 42–44]. Furthermore, there is no evidence to suggest that RSV-specific codes are preferentially chosen over generic bronchiolitis or pneumonia codes in the absence of laboratory data [6]. In addition, because RSV constitutes such a large proportion of all-cause bronchiolitis (50%–80%) and pneumonia (30%–60%) in infants [45], and because unspecified bronchiolitis and pneumonia remain common diagnoses in claims databases [6, 19, 23, 25, 26], it seems unlikely that inaccurate coding of generic bronchiolitis or pneumonia as
RSV-associated bronchiolitis is the second-most-common reason for hospitalization among US infants [6, 19, 25], and that the burdens of RSV-coded and unspecified bronchiolitis are similar [6, 19, 23, 25, 26]. These findings refute the notion that the burden of RSV-coded bronchiolitis is driven primarily by inaccurate coding of unspecified bronchiolitis, although more studies to evaluate the specificity of RSV diagnosis codes are needed.

Conversely, others—including reports from CDC—have suggested that RSV-specific codes lack sensitivity [6, 26, 31, 42–44] and may be underused because RSV testing is not always performed, given that virologic testing is not recommended by the American Academy of Pediatrics [46] and that virologic data rarely affect treatment decisions or reimbursement rates [6, 26, 31]. In this case, RSV rates from claims data would underestimate true RSV burden. Indeed, previous reports suggest that the sensitivity of RSV-specific codes could be <80% [6, 43, 47, 48], although more research on this topic is needed. Consequently, modeling studies [31–34] have attempted to account for potential underestimation of RSV burden in studies using only RSV-specific diagnostic codes. After applying various adjustment methods, these studies [31–34] found RSV-associated hospitalization rates that were, on average, slightly higher than those stemming from studies that relied only on RSV-specific codes.

The highest rate of RSV-associated hospitalization identified in our review (41 per 1000 infants <1 year old) [20], which was roughly twice that of our pooled summary estimate (19 per 1000 infants <1 year old), has often been characterized as an outlier because the data stemmed from a vulnerable population (i.e., Tennessee Medicaid). Two other studies, however, showed similar results, highlighting that children enrolled in the California Medicaid program have roughly twice the rate of RSV-associated hospitalization compared with children with private insurance [19, 29]. A recent report showed that ≥35 US states had ≥40% of new births financed by Medicaid programs [49]. Thus, these estimates potentially represent a significant number of US infants, and more studies in this vulnerable subpopulation are needed.
A few previous reports have suggested that RSV hospitalization rates may be declining in certain subpopulations of infants over time [19, 50, 51]. However, these reports have primarily shown reductions only in a small group of high-risk infants following palivizumab use [19, 50]. Our review confirmed that season-to-season variation in RSV hospitalization rates does exist, but most studies that examined hospitalization rates over multiple years did not report reductions in RSV hospitalization rates over time [3, 19, 24, 27, 31–34]. Moreover, RSV hospitalization rates from NVSN, where methods have remained constant year after year, have remained generally stable over the past decade and do not suggest broadly declining RSV rates [3, 14, 15, 35]. Thus, apart from the small subpopulation of high-risk infants recommended to receive palivizumab prophylaxis, there is no evidence of significantly declining RSV hospitalization rates among the broader US infant population.

Our study has limitations. Most estimates were from claims-based studies, and estimates from active surveillance or modeling approaches were limited. Our review, however, unlike other global meta-analyses [1, 52], highlights the importance of stratifying by study type when interpreting RSV burden estimates. RSV rates for infants <6 months old were also limited, and we imputed many of these estimates. However, we used a previously published approach [1] to do so, and sensitivity analyses confirmed that this imputation had little impact on overall study findings. Looking ahead, as new RSV prevention strategies become available, evaluating reductions in all-cause lower respiratory tract infections in addition to etiologically confirmed end points in clinical trials, and conducting postlicensure vaccine probe studies may help elucidate the true burden of RSV in infants.

Our study provides a comprehensive overview of the burden of RSV-associated hospitalization among US infants. Based on our findings, RSV leads to hospitalization in 1–4 of every 100 US infants and causes approximately 80,000 infant hospitalizations each year. Our systematic review makes clear that study type greatly affects RSV hospitalization rates. Active surveillance studies [3, 14, 15, 35] ensure high specificity but may have imperfect sensitivity [37], and they have produced rates that are roughly half those of studies based on claims databases [6, 19–32] or modeling approaches [31–34]. To date, these more conservative estimates have been used as the basis for defining infant RSV burden by US public health officials [53] and for informing early models that evaluate the potential public health impact of RSV prevention strategies [54]. The full range of RSV burden estimates identified in our review can better inform future policy evaluations of emerging RSV prevention options. However, more research is needed to better understand differences in estimated RSV burden across study design.

Notes
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Author contributions: J. M. M. and F. K. performed the initial literature search and data collection, performed all data analyses, and created the study figures and tables. Y. A. aided in the initial literature search. All authors participated in data interpretation, critical review, and writing of the manuscript; approved the final manuscript as submitted and agree to be accountable for all aspects of the work; and attest that they meet the ICMJE criteria for authorship.

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References
1. Shi T, McAllister DA, O’Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017; 390:946–58.
2. Glezen P, Denny FW. Epidemiology of acute lower respiratory disease in children. N Engl J Med 1973; 288:498–505.
3. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 2009; 360:588–98.
4. Hall CB. Respiratory syncytial virus and parainfluenza virus. N Engl J Med 2001; 344:1917–28.
5. Simoes EA. Respiratory syncytial virus infection. Lancet 1999; 354:847–52.
6. Leader S, Kohlhaase K. Respiratory syncytial virus-coded pediatric hospitalizations, 1997 to 1999. Pediatr Infect Dis J 2002; 21:629–32.
7. Mac S, Sumner A, Duchesne-Belanger S, Stirling R, Tunis M, Sander B. Cost-effectiveness of palivizumab for respiratory syncytial virus: a systematic review. Pediatics 2019; 143:e20184064.
8. PATH. RSV Vaccine and mAb Snapshot. https://path.org/resources/rsv-vaccine-and-mab-snapshot/. Accessed 31 January 2020.
9. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews
and meta-analyses: the PRISMA statement. PLoS Med 2009; 6:e1000097.
10. Jain S, Williams DJ, Arnold SR, et al; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015; 372:835–45.
11. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7:177–88.
12. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. Contemp Clin Trials 2015; 45:139–45.
13. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. BMJ 2011; 342:d549.
14. Hall CB, Weinberg GA, Blumkin AK, et al. Respiratory syncytial virus-associated hospitalizations among children less than 24 months of age. Pediatrics 2013; 132:e341–8.
15. Iwane MK, Edwards KM, Szilagyi PG, et al; New Vaccine Surveillance Network. Population-based surveillance for hospitalizations associated with respiratory syncytial virus, influenza virus, and parainfluenza viruses among young children. Pediatrics 2004; 113:1758–64.
16. Grindeland CJ, Mauriello CT, Leedahl DD, Richter LM, Meyer AC. Association between updated guideline-based palivizumab administration and hospitalizations for respiratory syncytial virus infections. Pediatr Infect Dis J 2016; 35:728–32.
17. Henrickson KJ, Hoover S, Kehl KS, Hua W. National disease burden of respiratory viruses detected in children by polymerase chain reaction. Pediatr Infect Dis J 2004; 23:S11–8.
18. Arriola CS, Kim L, Langley G, et al. Estimated burden of community-onset respiratory syncytial virus-associated hospitalizations among children aged <2 years in the United States, 2014–15. J Pediatric Infect Dis Soc 2020; 9:587–95.
19. Bennett MV, McLaurin K, Ambrose C, Lee HC. Population-based trends and underlying risk factors for infant respiratory syncytial virus and bronchiolitis hospitalizations. PLoS One 2018; 13:e0205399.
20. Boyce TG, Mellen BG, Mitchel EF Jr, Wright PF, Griffin MR. Rates of hospitalization for respiratory syncytial virus infection among children in Medicaid. J Pediatr 2000; 137:865–70.
21. Choudhuri JA, Ogden LG, Ruttenber AJ, Thomas DS, Todd JK, Simoes EA. Effect of altitude on hospitalizations for respiratory syncytial virus infection. Pediatrics 2006; 117:349–56.
22. Foote EM, Singleton RJ, Holman RC, et al. Lower respiratory tract infection hospitalizations among American Indian/Alaska Native children and the general United States child population. Int J Circumpolar Health 2015; 74:29256.
23. Holman RC, Curns AT, Cheek JE, et al. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. Pediatrics 2004; 114:e437–44.
24. Johnson JJ, Ratard R. Respiratory syncytial virus-associated hospitalizations in Louisiana. J La State Med Soc 2012; 164:268–73.
25. Leader S, Kohlhase K. Recent trends in severe respiratory syncytial virus (RSV) among US infants, 1997 to 2000. J Pediatr 2003; 143:S127–32.
26. Light M, Bauman J, Mavunda K, Malinoski F, Eggleston M. Correlation between respiratory syncytial virus (RSV) test data and hospitalization of children for RSV lower respiratory tract illness in Florida. Pediatr Infect Dis J 2008; 27:512–8.
27. Lloyd PC, May L, Hoffman D, Riegelman R, Simonsen L. The effect of birth month on the risk of respiratory syncytial virus hospitalization in the first year of life in the United States. Pediatr Infect Dis J 2014; 33:e135–40.
28. Paramore LC, Ciuryla V, Ciesla G, Liu L. Economic impact of respiratory syncytial virus–related illness in the US: an analysis of national databases. PharmacoEconomics 2004; 22:275–84.
29. Sangaré L, Curtis MP, Ahmad S. Hospitalization for respiratory syncytial virus among California infants: disparities related to race, insurance, and geography. J Pediatr 2006; 149:373–7.
30. Zachariah P, Ruttenber M, Simões EA. Hospitalizations due to respiratory syncytial virus in children with congenital malformations. Pediatr Infect Dis J 2011; 30:442–5.
31. Stockman LJ, Curns AT, Anderson LJ, Fischer-Langle G. Respiratory syncytial virus-associated hospitalizations among infants and young children in the United States, 1997–2006. Pediatr Infect Dis J 2012; 31:5–9.
32. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993–2008. Clin Infect Dis 2012; 54:1427–36.
33. Goldstein E, Finelli L, O’Halloran A, et al. Hospitalizations associated with respiratory syncytial virus and influenza in children, including children diagnosed with asthma. Epidemiology 2019; 30:918–26.
34. Goldstein E, Greene SK, Olson DR, Hanage WP, Lipsitch M. Estimating the hospitalization burden associated with influenza and respiratory syncytial virus in New York City, 2003–2011. Influenza Other Respir Viruses 2015; 9:225–33.
35. Rha B, Curns AT, Lively JY, et al. Respiratory syncytial virus–associated hospitalizations among young children: 2015–2016. Pediatrics 2020; 146:e20193611.
36. US Census Bureau Population Division. Projected population size and births, deaths, and migration: main projections series for the United States, 2017–2060. Washington, DC. https://www2.census.gov/programs-surveys/popproj/
37. Rose EB, Rice M, McNeal M, Biggs H, Langley G, Staat MA. Using active and passive surveillance to estimate respiratory syncytial virus hospitalization rates—Hamilton County, Ohio, 2009–2015. Presented at: 68th Annual Epidemic Intelligence Service (EIS) Conference; April 29–May 2, 2019; Atlanta, GA.

38. Grijalva CG, Craig AS, Dupont WD, et al. Estimating influenza hospitalizations among children. Emerg Infect Dis 2006; 12:103–9.

39. Grijalva CG, Weinberg GA, Bennett NM, et al. Estimating the undetected burden of influenza hospitalizations in children. Epidemiol Infect 2007; 135:951–8.

40. Poehling KA, Edwards KM, Weinberg GA, et al; New Vaccine Surveillance Network. The underrecognized burden of influenza in young children. N Engl J Med 2006; 355:31–40.

41. Weinberg GA, Hall CB, Iwane MK, et al; New Vaccine Surveillance Network. Parainfluenza virus infection of young children: estimates of the population-based burden of hospitalization. J Pediatr 2009; 154:694–9.

42. Cai W, Tolksdorf K, Hirve S, et al. Evaluation of using ICD-10 code data for respiratory syncytial virus surveillance. Influenza Other Respir Viruses 2020; 14:630–7.

43. Makari D, Staat MA, Henrickson KJ, Wu X, Ambrose CS. The underrecognized burden of respiratory syncytial virus among infants presenting to US emergency departments. Clin Pediatr (Phila) 2015; 54:594–7.

44. Pisesky A, Benchimol EI, Wong CA, et al. Incidence of hospitalization for respiratory syncytial virus infection amongst children in Ontario, Canada: a population-based study using validated health administrative data. PLoS One 2016; 11:e0150416.

45. Shay DK, Holman RC, Newman RD, Liu LL, Stout JW, Anderson LJ. Bronchiolitis-associated hospitalizations among US children, 1980–1996. JAMA 1999; 282:1440–6.

46. Ralston SL, Lieberthal AS, Meissner HC, et al.; American Academy of Pediatrics. Clinical practice guideline: the diagnosis, management, and prevention of bronchiolitis. Pediatrics 2014; 134:e1474–502.

47. Prasad N, Newbern EC, Trenholme AA, et al. Respiratory syncytial virus hospitalisations among young children: a data linkage study. Epidemiol Infect 2019; 147:e246.

48. Atkins JT, Nasreen R, Karami P. RSV hospitalizations may be underestimated using FDX codes despite recent coding changes. Pediatr Res 2000; 47:256A.

49. Kaiser Family Foundation. Survey of Medicaid officials in 50 states and DC conducted by Health Management Associates, October 2019. https://www.kff.org/medicaid/state-indicator/births-financed-by-medicaid. Accessed 30 September 2020.

50. Singleton RJ, Bruden D, Bulkow LR, Varney G, Butler JC. Decline in respiratory syncytial virus hospitalizations in a region with high hospitalization rates and prolonged season. Pediatr Infect Dis J 2006; 25:1116–22.

51. Weinberger DM, Klugman KP, Steiner CA, Simonsen L, Viboud C. Association between respiratory syncytial virus activity and pneumococcal disease in infants: a time series analysis of US hospitalization data. PLoS Med 2015; 12:e1001776.

52. Nair H, Simões EA, Rudan I, et al. Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. Lancet 2013; 381:1380–90.

53. Centers for Disease Control and Prevention. RSV trends and surveillance. https://www.cdc.gov/rsv/research/us-surveillance.html. Accessed 31 January 2020.

54. Rainisch G, Adhikari B, Meltzer MI, Langley G. Estimating the impact of multiple immunization products on medically-attended respiratory syncytial virus (RSV) infections in infants. Vaccine 2020; 38:251–7.