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

John M. McLaughlin,[1] Farid Khan,[1] Heinz-Josef Schmitt,[1] Yasmeen Agosti,[1] Luis Jodar,[1] Eric A. F. Simões,[2,3] and David L. Swerdlow[1]

[1]Pfizer Vaccines, Collegeville, Pennsylvania, USA, [2]University of Colorado, School of Medicine, Aurora, Colorado, USA, [3]Children's Hospital Colorado, Aurora, Colorado, USA

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

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.
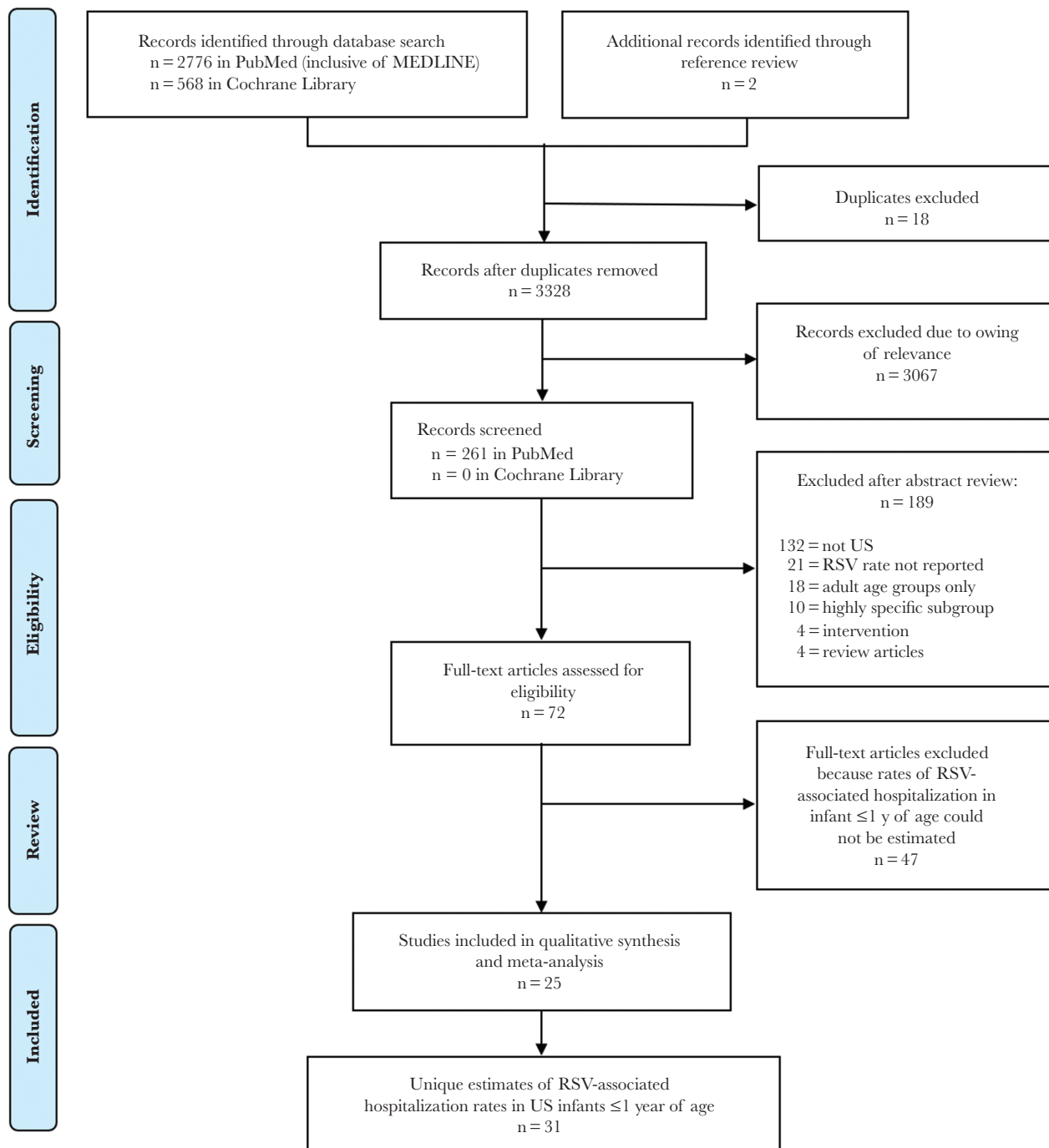
Figure 1. Flow diagram of the literature selection process. Of the 25 studies in our analysis, 5 of 25 (20%) [6, 23, 25, 31, 32] reported >1 rate based on within-study variation(s) of the definition of respiratory syncytial virus (RSV) hospitalization. Of these, 3 of 5 [6, 23, 25] were variations in 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 Projection National (Nationwide) Inpatient Sample; NHDS, National Hospital Discharge Survey.

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.

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.

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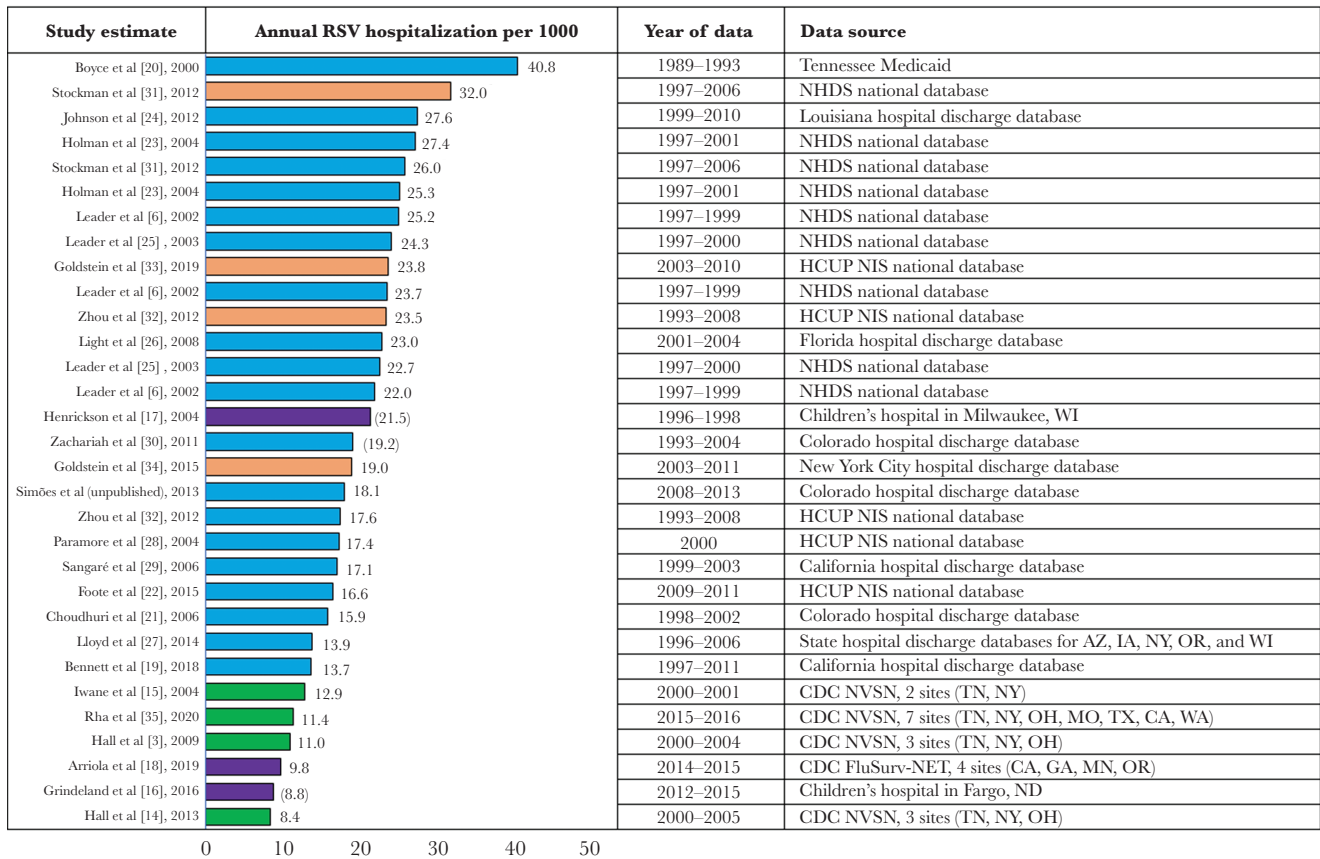
Table 2. Annual Respiratory Syncytial Virus–Associated Hospitalization rates Among US Infants

Study Type	Annual RSV-Associated Hospitalization Rate per 1000, by Age Group[a]		
	Age <1 y	Age <6 mo	Age <5 y
Overall, all study estimates (n = 31)			
Range	8.4–40.8	11.6–56.5	2.3–11.0
Mean (SD)	20.0 (7.2)	27.1 (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 (0.5)
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.

[a]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 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, *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.

Legend: ■ Active surveillance ■ Retrospective MRR ■ ICD-9 codes ■ Model based

Study estimate	Annual RSV hospitalization per 1000	Year of data	Data source
Boyce et al [20], 2000	40.8	1989–1993	Tennessee Medicaid
Stockman et al [31], 2012	32.0	1997–2006	NHDS national database
Johnson et al [24], 2012	27.6	1999–2010	Louisiana hospital discharge database
Holman et al [23], 2004	27.4	1997–2001	NHDS national database
Stockman et al [31], 2012	26.0	1997–2006	NHDS national database
Holman et al [23], 2004	25.3	1997–2001	NHDS national database
Leader et al [6], 2002	25.2	1997–1999	NHDS national database
Leader et al [25], 2003	24.3	1997–2000	NHDS national database
Goldstein et al [33], 2019	23.8	2003–2010	HCUP NIS national database
Leader et al [6], 2002	23.7	1997–1999	NHDS national database
Zhou et al [32], 2012	23.5	1993–2008	HCUP NIS national database
Light et al [26], 2008	23.0	2001–2004	Florida hospital discharge database
Leader et al [25], 2003	22.7	1997–2000	NHDS national database
Leader et al [6], 2002	22.0	1997–1999	NHDS national database
Henrickson et al [17], 2004	(21.5)	1996–1998	Children's hospital in Milwaukee, WI
Zachariah et al [30], 2011	(19.2)	1993–2004	Colorado hospital discharge database
Goldstein et al [34], 2015	19.0	2003–2011	New York City hospital discharge database
Simões et al (unpublished), 2013	18.1	2008–2013	Colorado hospital discharge database
Zhou et al [32], 2012	17.6	1993–2008	HCUP NIS national database
Paramore et al [28], 2004	17.4	2000	HCUP NIS national database
Sangaré et al [29], 2006	17.1	1999–2003	California hospital discharge database
Foote et al [22], 2015	16.6	2009–2011	HCUP NIS national database
Choudhuri et al [21], 2006	15.9	1998–2002	Colorado hospital discharge database
Lloyd et al [27], 2014	13.9	1996–2006	State hospital discharge databases for AZ, IA, NY, OR, and WI
Bennett et al [19], 2018	13.7	1997–2011	California hospital discharge database
Iwane et al [15], 2004	12.9	2000–2001	CDC NVSN, 2 sites (TN, NY)
Rha et al [35], 2020	11.4	2015–2016	CDC NVSN, 7 sites (TN, NY, OH, MO, TX, CA, WA)
Hall et al [3], 2009	11.0	2000–2004	CDC NVSN, 3 sites (TN, NY, OH)
Arriola et al [18], 2019	9.8	2014–2015	CDC FluSurv-NET, 4 sites (CA, GA, MN, OR)
Grindeland et al [16], 2016	(8.8)	2012–2015	Children's hospital in Fargo, ND
Hall et al [14], 2013	8.4	2000–2005	CDC NVSN, 3 sites (TN, NY, OH)

(x-axis: 0 10 20 30 40 50)

Figure 2. Annual respiratory syncytial virus (RSV)–associated hospitalization rates per 1000 among US infants <1 year 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 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). ICD-9 code studies were retrospective analyses of administrative claims data based on RSV-specific International Classification of Diseases, Ninth Revision (ICD-9) codes (466.11, 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.

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
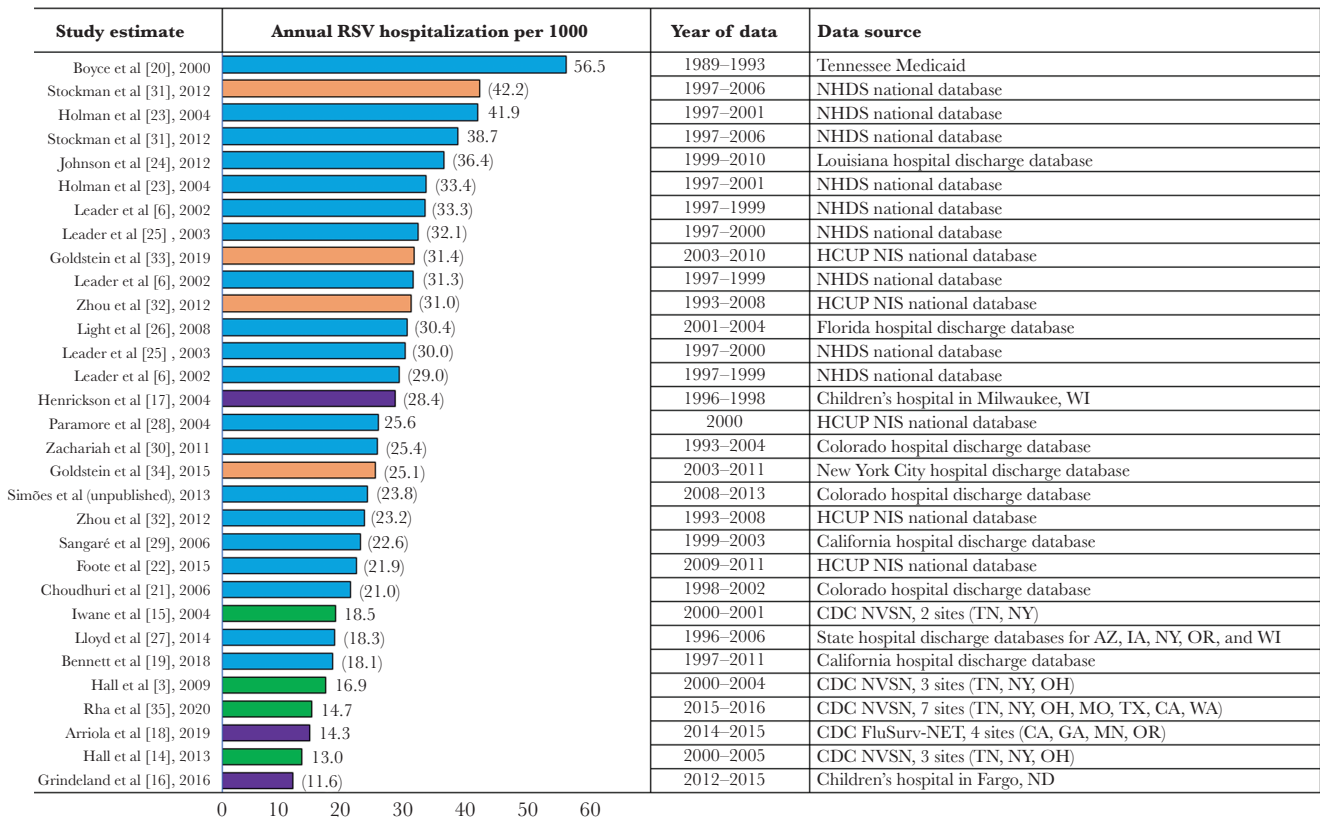
Figure 3. Annual respiratory syncytial virus (RSV)–associated hospitalization rates per 1000 among US infants <6 months of age (n = 31). Estimates in parentheses were imputed using RSV-associated hospitalization rates reported for a different age group. Active surveillance studies were prospective and 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 (466.11, 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.

based on *ICD-9* codes in the primary diagnosis position only, in the first or second diagnosis position, or any diagnosis position, average rates among infants <1 year (*P* = .87) and <6 months (*P* = .95) old were 21.9 and 29.5 (n = 4), 23.7 and 31.2 (n = 3), and 21.5 and 29.3 (n = 13), respectively. Results were similar for children <5 years old (data not shown). Only 3 studies [6, 23, 25] analyzed the impact of diagnosis position within the same study population. All 3 reported relatively little impact (<10% to 15% relative change) of broadening claims definitions beyond the primary diagnosis position [6, 23, 25].

Meta-analysis

Among infants <1 year and <6 months old, pooled rates of RSV-associated hospitalization per 1000 were 19.4 (95% CI, 17.9–20.9) and 26.2 (24.2–28.2), respectively (Figure 5). Among children <5 years old, the pooled rate was 5.2 (95% CI, 4.8–5.6)

(Supplementary Figure 3). Similar to descriptive analyses, rates in pooled subgroup meta-analyses stemming from active surveillance studies (11.0 [95% CI, 9.8-12.2] in infants <1 year old and 15.6 [13.7-17.5] in those <6 months old) were roughly half those from *ICD-9* claims-based studies (21.4 [19.5-23.3] and 28.8 [26.3-31.3], respectively) or modeling approaches (23.2 [20.2-26.2] and 30.7 [26.7-34.6], respectively) (Figure 5). Findings were similar for all children <5 years old (Supplementary Figure 3). In sensitivity analyses, results were essentially identical when we included estimates only from nonoverlapping data sets (n = 20; ie, excluding estimates from the same data source and time period as another larger study) (Supplementary Figures 4 and 5).

DISCUSSION

Our study confirms the high burden of RSV-associated hospitalization in infants and underscores the need for novel
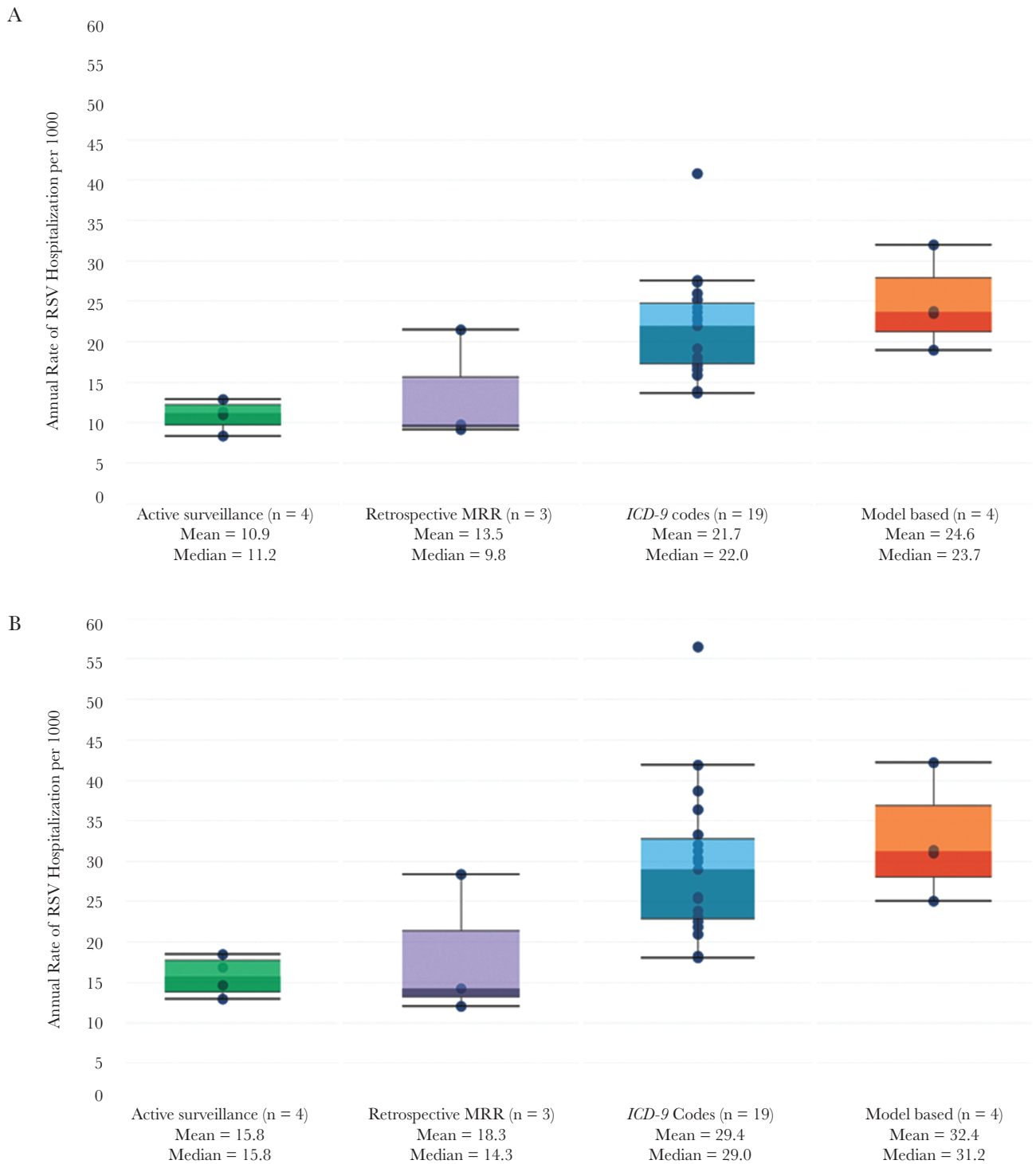
Figure 4. Box-and-whisker plot of annual respiratory syncytial virus (RSV)–associated hospitalization rate per 1000 among US infants aged <1 year (*A*) or <6 months (*B*), by study type (n = 31). In this Tukey box-and-whisker plot, individual studies are represented by dots, medians by the line separating 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.
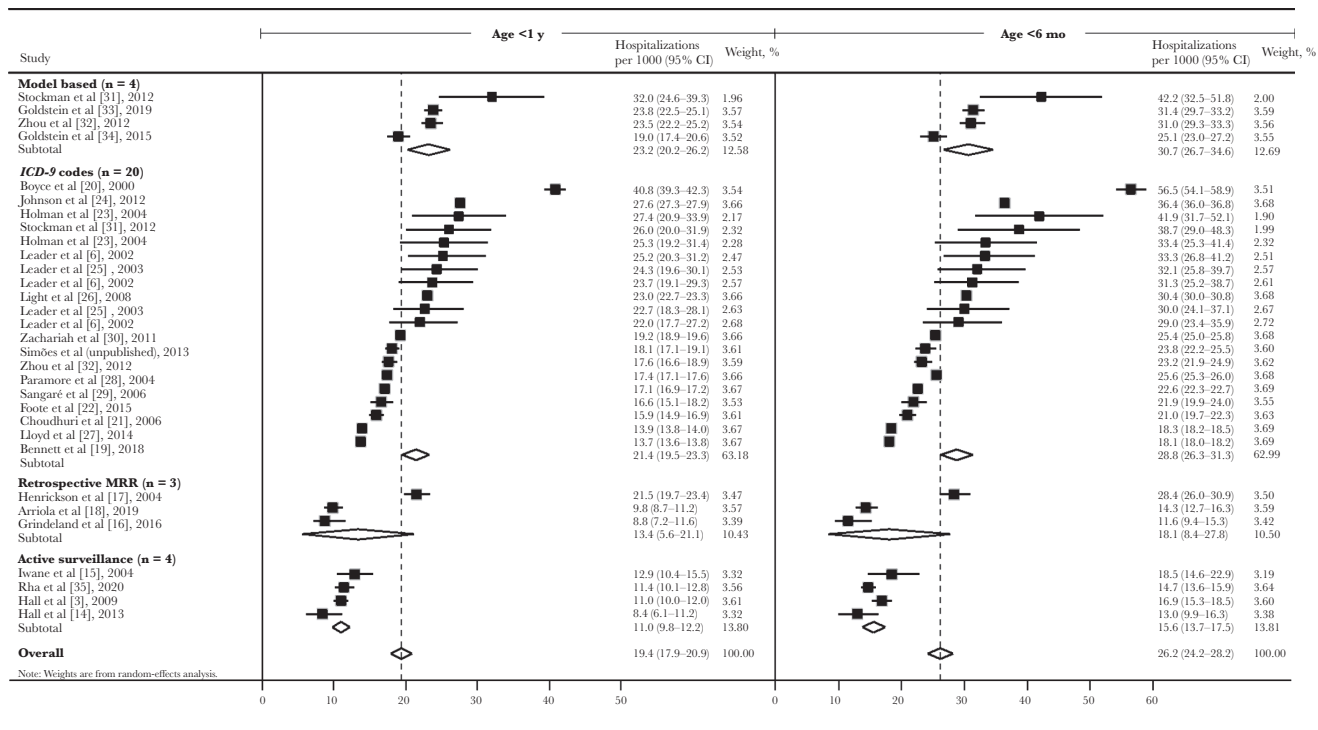
Claims-based analyses that used *ICD-9* codes were the most common study type [6, 19–32], accounting for 65% of estimates. Using broader *ICD-9* definitions (ie, more diagnosis fields) had minimal impact on RSV hospitalization rates, given that most RSV-associated illness was coded in the primary diagnosis 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

Study	Age <1 y	Hospitalizations per 1000 (95% CI)	Weight, %	Age <6 mo	Hospitalizations per 1000 (95% CI)	Weight, %
Model based (n = 4)						
Stockman et al [31], 2012		32.0 (24.6–39.3)	1.96		42.2 (32.5–51.8)	2.00
Goldstein et al [33], 2019		23.8 (22.5–25.1)	3.57		31.4 (29.7–33.2)	3.59
Zhou et al [32], 2012		23.5 (22.2–25.2)	3.54		31.0 (29.3–33.3)	3.56
Goldstein et al [34], 2015		19.0 (17.4–20.6)	3.52		25.1 (23.0–27.2)	3.55
Subtotal		23.2 (20.2–26.2)	12.58		30.7 (26.7–34.6)	12.69
ICD-9 codes (n = 20)						
Boyce et al [20], 2000		40.8 (39.3–42.3)	3.54		56.5 (54.1–58.9)	3.51
Johnson et al [24], 2012		27.6 (27.3–27.9)	3.66		36.4 (36.0–36.8)	3.68
Holman et al [23], 2004		27.4 (20.9–33.9)	2.17		41.9 (31.7–52.1)	1.90
Stockman et al [31], 2012		26.0 (20.0–31.9)	2.32		38.7 (29.0–48.3)	1.99
Holman et al [23], 2004		25.3 (19.2–31.4)	2.28		33.4 (25.3–41.4)	2.32
Leader et al [6], 2002		25.2 (20.3–31.2)	2.47		33.3 (26.8–41.2)	2.51
Leader et al [25] , 2003		24.3 (19.6–30.1)	2.53		32.1 (25.8–39.7)	2.57
Leader et al [6], 2002		23.7 (19.1–29.3)	2.57		31.3 (25.2–38.7)	2.61
Light et al [26], 2008		23.0 (22.7–23.3)	3.66		30.4 (30.0–30.8)	3.68
Leader et al [25] , 2003		22.7 (18.3–28.1)	2.63		30.0 (24.1–37.1)	2.67
Leader et al [6], 2002		22.0 (17.7–27.2)	2.68		29.0 (23.4–35.9)	2.72
Zachariah et al [30], 2011		19.2 (18.9–19.6)	3.66		25.4 (25.0–25.8)	3.68
Simões et al (unpublished), 2013		18.1 (17.1–19.1)	3.61		23.8 (22.2–25.5)	3.60
Zhou et al [32], 2012		17.6 (16.6–18.9)	3.59		23.2 (21.9–24.9)	3.62
Paramore et al [28], 2004		17.4 (17.1–17.6)	3.66		25.6 (25.3–26.0)	3.68
Sangaré et al [29], 2006		17.1 (16.9–17.2)	3.67		22.6 (22.3–22.7)	3.69
Foote et al [22], 2015		16.6 (15.1–18.2)	3.53		21.9 (19.9–24.0)	3.55
Choudhuri et al [21], 2006		15.9 (14.9–16.9)	3.61		21.0 (19.7–22.3)	3.63
Lloyd et al [27], 2014		13.9 (13.8–14.0)	3.67		18.3 (18.2–18.5)	3.69
Bennett et al [19], 2018		13.7 (13.6–13.8)	3.67		18.1 (18.0–18.2)	3.69
Subtotal		21.4 (19.5–23.3)	63.18		28.8 (26.3–31.3)	62.99
Retrospective MRR (n = 3)						
Henrickson et al [17], 2004		21.5 (19.7–23.4)	3.47		28.4 (26.0–30.9)	3.50
Arriola et al [18], 2019		9.8 (8.7–11.2)	3.57		14.3 (12.7–16.3)	3.59
Grindeland et al [16], 2016		8.8 (7.2–11.6)	3.39		11.6 (9.4–15.3)	3.42
Subtotal		13.4 (5.6–21.1)	10.43		18.1 (8.4–27.8)	10.50
Active surveillance (n = 4)						
Iwane et al [15], 2004		12.9 (10.4–15.5)	3.32		18.5 (14.6–22.9)	3.19
Rha et al [35], 2020		11.4 (10.1–12.8)	3.56		14.7 (13.6–15.9)	3.64
Hall et al [3], 2009		11.0 (10.0–12.0)	3.61		16.9 (15.3–18.5)	3.60
Hall et al [14], 2013		8.4 (6.1–11.2)	3.32		13.0 (9.9–16.3)	3.38
Subtotal		11.0 (9.8–12.2)	13.80		15.6 (13.7–17.5)	13.81
Overall		19.4 (17.9–20.9)	100.00		26.2 (24.2–28.2)	100.00

Note: Weights are from random-effects analysis.

Figure 5. Forest plot of annual respiratory syncytial virus (RSV)–associated hospitalization rates per 1000 among US infants by study type and age group (n = 31). The x-axis represents the annual rates of RSV-associated hospitalization per 1000. Inverse-variance weighting, which weights each study on the inverse of the variance of each study effect estimate (ie, larger weights for studies with smaller standard errors), was used to combine individual study estimates. 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 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 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 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. Abbreviation: CI, confidence interval.

RSV-associated could entirely explain our findings. As evidence, previous research has shown that after RSV-coded bronchiolitis, unspecified 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 (ie, 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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