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

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ABSTRACT

Background

Understanding the true magnitude of infant respiratory syncytial virus (RSV) burden is critical for determining the potential public-health benefit of RSV prevention strategies. Although global reviews of infant 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. We also examined the impact of key study characteristics on these estimates.

Results

After review of 3328 articles through August 14, 2020, we 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 = 19.4 (95%CI: 17.9–20.9). Study type was associated with RSV hospitalization rates (P = .003), with active surveillance studies having pooled rates per 1000 (11.0; 95%CI: 9.8–12.2) that were half that of studies based on administrative claims (21.4; 95%CI: 19.5–23.3) or modeling approaches (23.2; 95%CI: 20.2–26.2).

Conclusions

Applying the pooled rates identified in our review to the 2020 US birth cohort suggests that 73,680 to 86,020 RSV-associated infant hospitalizations occur each year. To date, public-health officials have used conservative estimates from active surveillance as the basis for defining US infant RSV burden. The full range of RSV-associated hospitalization rates identified in our review better characterizes the true RSV burden in infants and can better inform future evaluations of RSV prevention strategies.

Note: Abstract updated to incorporate updated estimates published for Rha et al. (2020).[1]

BACKGROUND

- Respiratory syncytial virus (RSV) is the primary cause of lower respiratory tract infection among infants and young children globally[2-6] is the number one reason for infant hospitalization in the United States.[4,7]
- Although global reviews of infant RSV burden exist, none have summarized data from the United States or evaluated how RSV burden estimates are influenced by variations in study design.

OBJECTIVE

- 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.

METHODS

Search Strategy

- We identified all publications (in English) describing rates of RSV-associated hospitalization in infants, young children, or both available in PubMed (inclusive of MEDLINE) and the Cochrane Library as of August 14, 2020 **(Figure 1)**.
- We included all articles with a clear case (numerator) definition of RSV and have a population-based denominator for a defined time period.

Data Abstraction and Cleaning

- Titles and abstracts were screened by two independent reviewers.
- In instances where a study reported more than one rate based on within-study variations or sensitivity analyses in the study population or design, we treated each of these instances as an additional, unique estimated rate of RSV hospitalization.

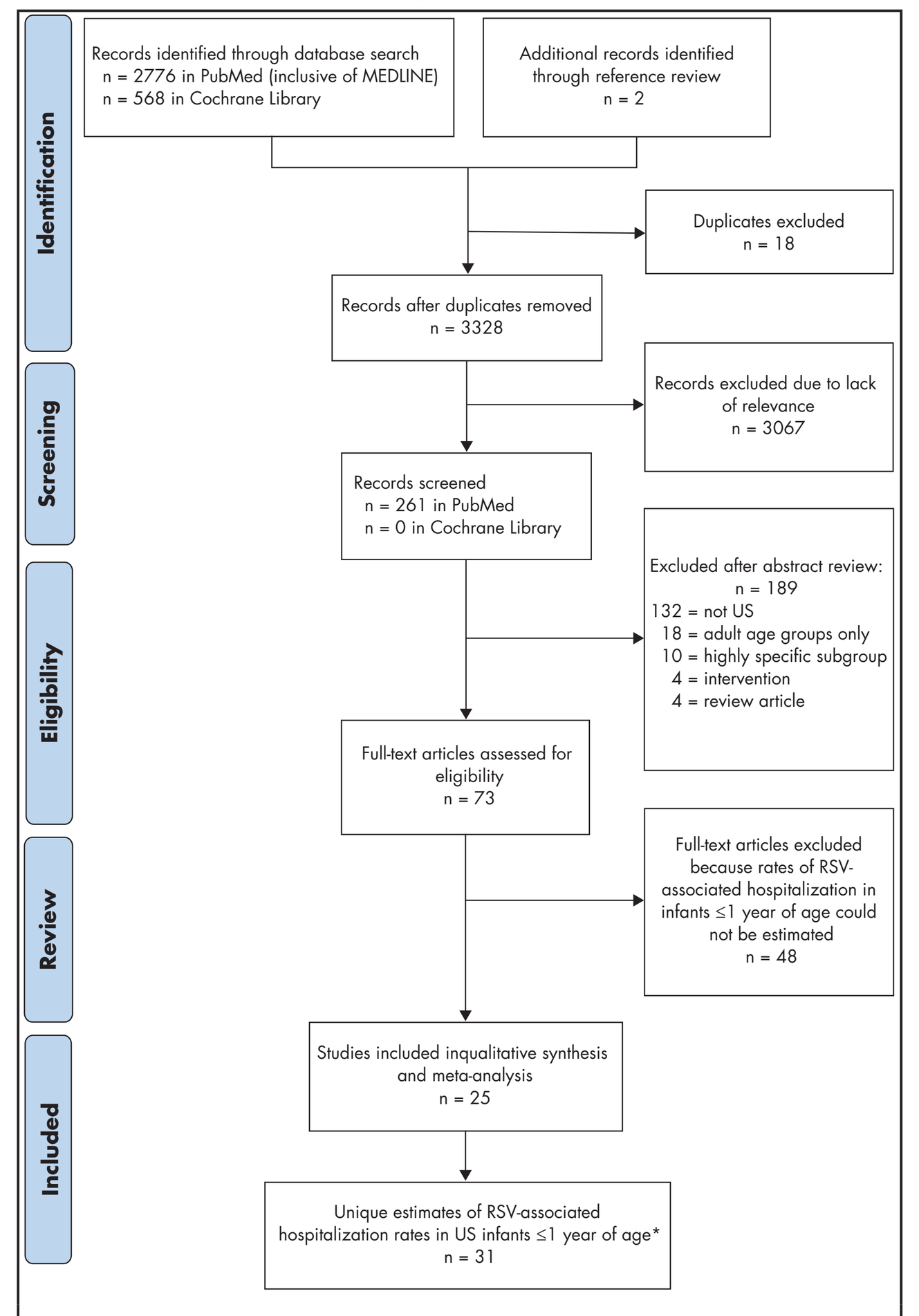
Study Characteristics Evaluated

- Incidence estimates were reported for two age groups:
  - <6 months of age
  - <1 year of age
- In rare instances where studies did not directly report rates for infants but did report rates for at least one age group among children <5 years of age, we calculated age-adjusted rates for infants <1 year based on available data.
- We performed similar calculations to estimate rates among infants <6 months of age in studies where only rates for infants <1 year were reported.
- For these age-adjusted rate imputations, we used similar methodology as applied by Shi et al.[2]

Statistical Analysis

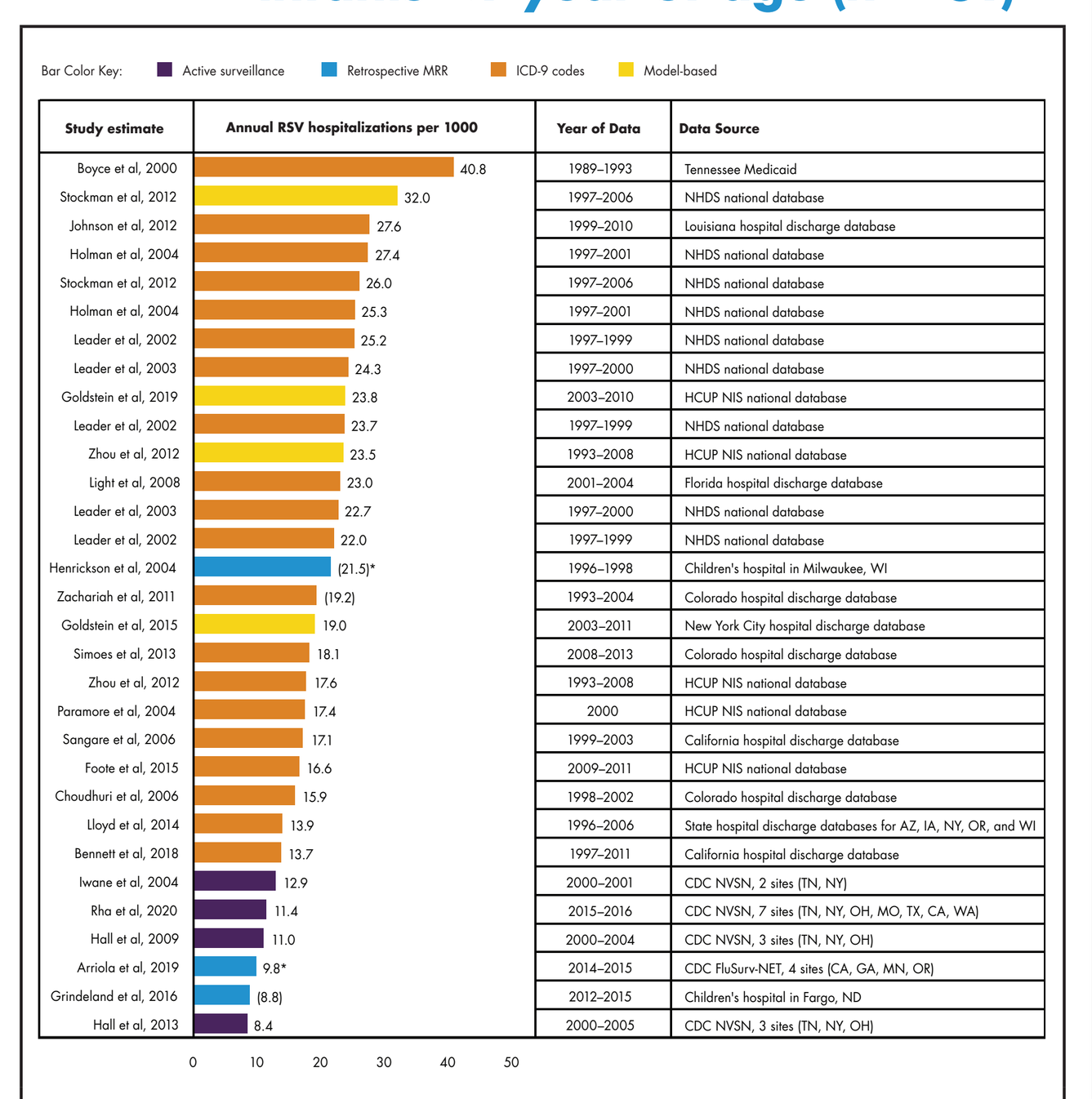
- The number of, and variability in, estimates of the rates of RSV-associated hospitalization among US infants by various study characteristics were examined using descriptive statistics with SAS 9.4 (SAS Institute, Inc., Cary, NC).
- We performed a random-effects meta-analysis to calculate pooled rates by study type using the metan command in Stata version 14.0 (StataCorp LLC, College Station, TX).

Figure 1: Flow diagram of the literature selection process



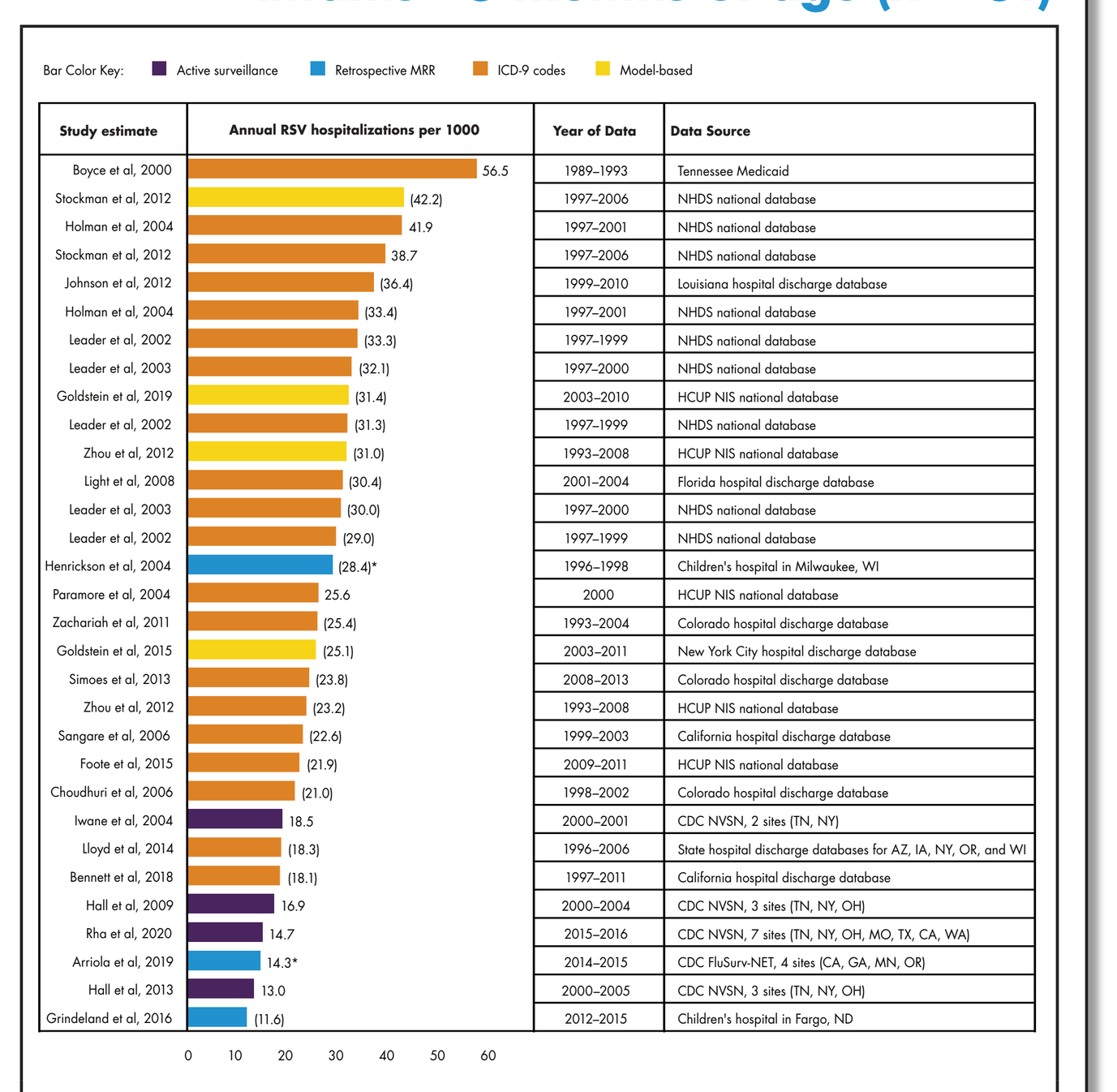
RSV = respiratory syncytial virus; US = United States.
*Of the 25 studies, five studies reported more than one incidence rate of RSV hospitalization for infants based on within-study variations or sensitivity analyses for a total of 31 unique published incidence estimates in our analysis population (ie, four studies reported two estimates, one study reported three estimates).

Figure 2: Annual RSV-associated hospitalization rates among US infants <1 year of age (n = 31)



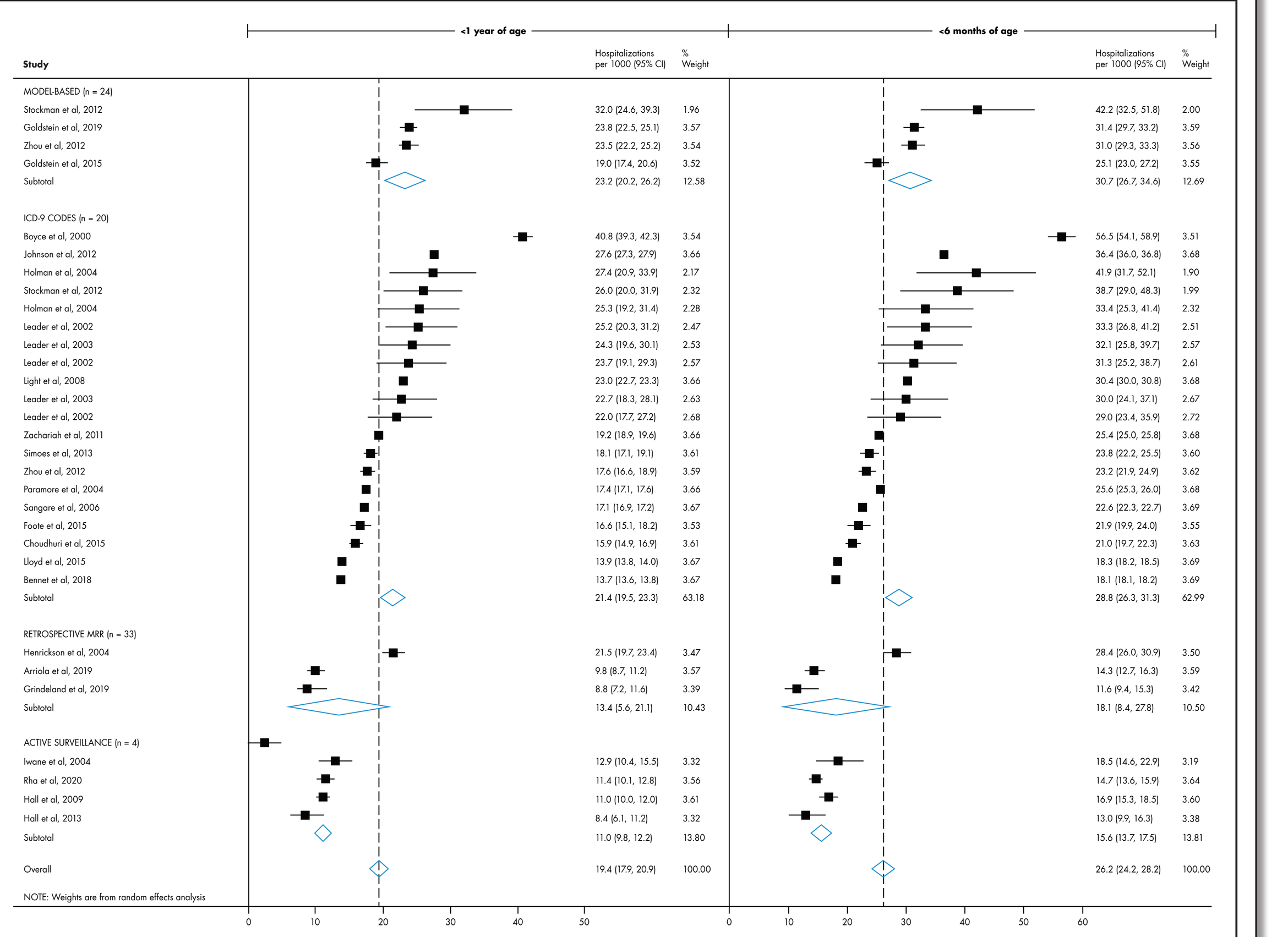
CDC NVSN = Centers for Disease Control and Prevention New Vaccines Surveillance Network; HCUP NIS = Healthcare Cost and Utilization Projection National (Nationwide) Inpatient Sample; ICD-9 = International Classification of Diseases, 9th revision; MRR = medical record review; NHDS = National Hospital Discharge Survey; RSV = respiratory syncytial virus; US = United States. 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 CDC NVSN program and identified RSV via culture and reverse transcription polymerase-chain reaction (RT-PCR) of nasal and throat swabs taken from children hospitalized with acute respiratory infection in one 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 (*) 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.

Figure 3: Annual RSV-associated hospitalization rates among US infants <6 months of age (n = 31)



CDC NVSN = Centers for Disease Control and Prevention New Vaccines Surveillance Network; HCUP NIS = Healthcare Cost and Utilization Projection National (Nationwide) Inpatient Sample; ICD-9 = International Classification of Diseases, 9th revision; MRR = medical record review; NHDS = National Hospital Discharge Survey; RSV = respiratory syncytial virus; US = United States. 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 CDC NVSN program and identified RSV via culture and reverse transcription polymerase-chain reaction (RT-PCR) of nasal and throat swabs taken from children hospitalized with acute respiratory infection in one 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 (*) 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.

Figure 4: Forest plot of annual RSV-associated hospitalization rates among US infants by study type and age group (n = 31)



ICD-9 = International Classification of Diseases, 9th revision; MRR = medical record review; RSV = respiratory syncytial virus; US = United States. The x-axis represents the annual rates of RSV-associated hospitalization per 1000. 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 (RT-PCR) of nasal and throat swabs taken from children hospitalized with acute respiratory infection in one 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 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.

Table 1: Study/estimate characteristics and annual RSV-associated hospitalization rates among US infants

Study/estimate characteristic	Estimate	
Studies identified	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 in infants age <1 y, No. (%)	28 (90)	
Studies directly reporting rates in infants age <6 mo, No. (%)	9 (29)	
RSV-associated hospitalization rates per 1000, annually	**Among <1 y**	**Among < 6 mo**
Overall, all study estimates (n = 31)		
Range	8.4–40.8	11.6–56.5
Mean (SD)	20.0 (7.2)	27.1 (9.9)
Median (IQR)	19.2 (13.9–24.3)	25.6 (18.5–32.1)
By study type†		
Active surveillance, n = 4		
Range	8.4–12.9	13.0–18.5
Mean (SD)	10.9 (1.9)	15.8 (2.4)
Median (IQR)	11.2 (9.7–12.2)	15.8 (13.9–17.7)
Retrospective MRR, n = 3		
Range	8.8–21.5	11.6–28.4
Mean (SD)	13.4 (7.1)	18.1 (9.0)
Median (IQR)	9.8 (8.8–21.5)	14.3 (11.6–28.4)
ICD-9 codes, n = 20		
Range	13.7–40.8	18.1–56.5
Mean (SD)	21.9 (6.3)	29.6 (9.2)
Median (IQR)	22.4 (17.3–25.3)	29.5 (22.9–33.3)
Model-based, n = 4		
Range	19.0–32.0	25.1–42.2
Mean (SD)	24.6 (5.4)	32.4 (7.1)
Median (IQR)	23.7 (21.3–27.9)	31.2 (28.1–36.8)

ICD-9 = International Classification of Diseases, 9th revision; IQR = interquartile range; MRR = medical record review; RSV = respiratory syncytial virus; SD = standard deviation; US = United States.
*Of the 25 studies, five studies reported more than one incidence rate of RSV hospitalization for infants based on within-study variations or sensitivity analyses for a total of 31 unique published incidence estimates in our analysis population (ie, four studies reported two estimates, one study reported three 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 (RT-PCR) of nasal and throat swabs taken from children hospitalized with acute respiratory infection in one 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 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.

RESULTS

Study Population

- Studies identified were published between 2000 and 2020, and reported data collected between 1989 and 2016.
- Nearly all (28/31, 90%) published RSV-associated hospitalization rate estimates directly reported rates for infants <1 year of age or where average rates for this age group could be calculated.
- Rates for children <6 months of age were less commonly directly reported and had to be imputed based on rates in infants <1 year for most estimates (22/31; 71%) **(Table 1)**.[7-23]

Study Type

- Four major types of study estimates were identified.
  - **Active, prospective surveillance** sourced from the Centers for Disease Control and Prevention New Vaccine Surveillance Network program with required etiologic testing and confirmation of RSV (4/31; 13%)[1,4,24,25]
  - **Retrospective MRR** (ie, passive surveillance of available clinician-directed standard-of-care medical and laboratory records [3/31; 10%])[13,14,26]
    - Two of the three studies[14,26] adjusted their estimated RSV rates upward to account for the estimated number of cases that were missed based on standard-of-care diagnostic and testing practices.
  - **Retrospective analysis of administrative claims data** based on RSV-specific International Classification of Diseases, Ninth Revision (ICD-9) codes (20/31; 65%)[7-10,15-23,27,28]
  - **Model-based estimates** that combine ICD-9 claims and etiologic surveillance data (n = 4/31; 13%) **(Table 1)**.[11,12,22,23]

RSV-Associated Hospitalization Rates

- Among infants <1 year of age, annual rates of RSV-associated hospitalization ranged from 8.4 to 40.8 per 1000 **(Figure 2)**, with mean = 20.0 (SD = 7.2; 95%CI: 17.3–22.6) and median = 19.2 (IQR = 13.9 to 24.3) across the 31 study estimates **(Table 1)**.
- Among infants <6 months of age, rates ranged from 11.6 to 56.5 per 1000 annually **(Figure 3)**, with mean = 27.1 (SD = 9.9; 95%CI: 23.5–30.7) and median = 25.6 (IQR = 18.5 to 32.1) **(Table 1)**.
- Study type influenced rates of RSV hospitalization (P = .003 for infants <1 year and P = .01 for those <6 months of age) with rates from active surveillance being roughly half that of studies based on administrative claims or modeling approaches **(Table 1)**.

Meta-analysis

- Among infants <1 year and <6 months of age, pooled summary rates of RSV-associated hospitalization per 1000 were 19.4 (95%CI: 17.9–20.9) and 26.2 (95%CI: 24.2–28.2), respectively **(Figure 4)**.
  - Active surveillance studies (11.0 [95%CI: 9.8–12.2] in <1 year and 15.6 [95%CI: 13.7–17.5] in <6 months)
  - ICD-9 claims-based studies (21.4 [95%CI: 19.5–23.3] in <1 year and 28.8 [95%CI: 26.3–31.3] in <6 months)
  - Model-based studies (23.2 [95%CI: 20.2–26.2] in <1 year and 30.7 [95%CI: 26.7–34.6] in <6 months)
  - Retrospective MRR (13.4 [95%CI: 5.6–21.1] in <1 year and 18.1 [95%CI: 8.4–27.8] in <6 months)

DISCUSSION

- **Our study confirms the high burden of RSV-associated hospitalization in infants and underscores the need for novel prevention strategies.**
- **Across the 31 estimates identified in our systematic review, pooled annual rates of RSV-associated hospitalization among US infants <1 year and <6 months of age were 19 (95%CI: 18–21) and 26 (95%CI: 24–28) per 1000, respectively.**
- **When applied to the 2020 US birth cohort of just over 4.1 million,[29] this translates to an estimated 79,850 (95%CI: 73,680–86,020) RSV-associated hospitalizations among infants each year in the United States.**
- **Active surveillance studies[1,4,24,25] ensure high specificity but may have imperfect sensitivity[30] and have produced rates that are roughly half that of studies based on administrative claims databases[7-10,15-23,27,28] or modeling approaches.[11,12,22,23]**
- **To date, these more conservative estimates have been used as the basis for defining infant RSV burden by US public-health officials.[31,32]**
- **The full range of RSV burden estimates identified in our review, however, can better inform future policy evaluations of emerging RSV prevention options.**

LIMITATIONS

- Most estimates were from ICD-9 claims-based studies, and estimates from active surveillance or modeling approaches were limited. Our analysis, however, highlights the importance of stratifying by study type when interpreting RSV burden estimates.
- RSV rates for infants <6 months of age were limited, and we had to impute many of these estimates; however, our methodology was consistent with a previously published approach.[2]

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DISCLOSURES

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