Mortality Among US Infants and Children Under 5 Years of Age with Respiratory Syncytial Virus and Bronchiolitis: A Systematic Literature Review

Lauren C. Bylsma,[1] **Mina Suh,**[1] **Naimisha Movva,**[1] **Jon P. Fryzek,**[1] **and Christopher B. Nelson**[2]

[1]EpidStrategies, A Division of ToxStrategies, Inc, Rockville, Maryland, USA; and [2]Sanofi, Swiftwater, Pennsylvania, USA

Background. A systematic literature review was conducted to summarize the mortality (overall and by disease severity factors) of US infants and children aged <5 years with respiratory syncytial virus (RSV) or all-cause bronchiolitis (ACB).

Methods. Comprehensive, systematic literature searches were conducted; articles were screened using prespecified eligibility criteria. A standard risk of bias tool was used to evaluate studies. Mortality was extracted as the rate per 100 000 or the case fatality ratio (CFR; proportion of deaths among RSV/ACB cases).

Results. Among 42 included studies, 36 evaluated inpatient deaths; 10 used nationally representative populations updated through 2013, and only 2 included late-preterm/full-term otherwise healthy infants and children. The RSV/ACB definition varied across studies (multiple International Classification of Diseases [ICD] codes; laboratory confirmation); no study reported systematic testing for RSV. No studies reported RSV mortality rates, while 3 studies provided ACB mortality rates (0.57–9.4 per 100 000). CFRs ranged from 0% to 1.7% for RSV (n = 15) and from 0% to 0.17% for ACB (n = 6); higher CFRs were reported among premature, intensive care unit–admitted, and publicly insured infants and children.

Conclusions. RSV mortality reported among US infants and children is variable. Current, nationally representative estimates are needed for otherwise healthy, late-preterm to full-term infants and children.

Keywords. bronchiolitis; children; infants; lower respiratory tract infection; LRTI; mortality; respiratory syncytial virus; RSV; systematic literature review.

Respiratory syncytial virus (RSV) represents a substantial public health burden in children aged <5 years. In the United States, the Centers for Disease Control and Prevention (CDC) has estimated that approximately 40 000 infants are hospitalized due to RSV annually [1, 2]. A recent publication from the CDC New Vaccine Surveillance Network (NVSN) indicated that in the 2015–2016 surveillance period, RSV hospitalizations in the United States were 2.9 (95% confidence interval [CI], 2.8–3.1) per 1000 children aged <5 years and 14.7 (95% CI, 13.6–15.9) per 1000 infants aged <6 months, with the highest rate observed among 1-month-old infants (25.1 per 1000; 95% CI, 21.1–29.3) [2]. In another study based on the 2011–2019 National (Nationwide) Inpatient Sample (NIS) data, infant RSV hospitalizations were 56 927 (range, 43 945–66 155)

and infant RSV hospitalization rate in 2019 was 17.2 (95% CI, 15.5–19.0) per 1000 live births [3]. Despite the significant public health concern posed by RSV, routine laboratory testing for RSV is not recommended in the United States [4, 5]. Therefore, the true number of RSV cases among infants and children is likely to be underestimated or uncertain [6–8].

Mortality among infants and children with RSV varies in the published literature. Mortality is typically measured using either a rate per 100 000 persons in the general population or a case fatality ratio (CFR), defined as the proportion of deaths among cases of RSV [9]. A recent review of global cases of severe acute respiratory infection due to RSV reported in-hospital CFRs ranging from 0.1% among children aged 1–5 years in industrialized nations to 9.3% among infants aged 6–11 months in low-income nations [10]. In 1 CDC study, RSV mortality in US populations was modeled using the 1976–1998 National Center for Health Statistics (NCHS) mortality data and the National Respiratory and Enteric Virus Surveillance System laboratory data for RSV [6]. The estimated RSV-associated mortality rate for the 1990/1991–1998/1999 seasons for US infants aged <1 year ranged from 3.1 to 5.4 per 100 000 person-years; in US children aged 1–4 years, the estimated RSV-associated mortality rate was between 0.1 and 0.9 per 100 000 person-years. To our knowledge, a systematic

review of RSV mortality for US infants and children does not exist in the current RSV literature.

The objective of this systematic literature review (SLR) was to summarize the scientific literature regarding mortality among US infants and children aged <5 years with RSV, overall and by sociodemographic and clinical variables proposed to affect disease severity, such as chronological age, weeks' gestational age (wGA), and intensive care unit (ICU) admission. As cases of RSV are likely to be underestimated, mortality among all-cause bronchiolitis (ACB) cases was also described as an upper limit of RSV mortality.

METHODS

This SLR was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines to ensure transparency and reproducibility [11]. The SLR was conducted under a prespecified protocol.

Eligibility Criteria

The eligibility criteria were defined by population, exposure, comparison, outcomes, and study design (PECOS). As most of the studies were descriptive in nature, a comparison group was not required for inclusion. Observational studies of infants and children aged <5 years conducted in the United States and reporting RSV or ACB mortality as a primary or incidental outcome during any time period were included. Randomized controlled trials were excluded. While reviews were excluded from the SLR, the bibliographies of relevant reviews were searched for additional articles of interest. Only studies published in English were included.

Study Identification and Screening

Comprehensive literature searches were conducted in PubMed and EMBASE to identify articles of interest using terms for RSV, mortality, and United States. Search strings are presented in Supplementary Table 1. Searches were limited to articles published in 2000 and later, though any time period for study data was accepted. Articles resulting from the searches were deduplicated across databases and uploaded to DistillerSR (Evidence Partners Inc, 2021) for review tracking and management.

The deduplicated articles were screened using the eligibility criteria first at the level of title and abstract. Ten percent of the abstracts were reviewed for quality control by an independent reviewer. The full texts of all articles marked as relevant in the title/abstract review were then screened using the eligibility criteria. All articles reviewed at this level were assessed for eligibility by 2 reviewers independently, and conflicting results were resolved by senior reviewers. Articles from the same cohort or study population were reviewed and only 1 article representing the most complete and/or updated version of the cohort was included.

Data Extraction

All articles deemed relevant by both reviewers during full-text review were included for data extraction. A standardized form was used to extract data from the included studies. Extracted data elements included study location, study population variables, RSV or ACB definitions (eg, International Classification of Diseases [ICD] codes, laboratory confirmation), and mortality. Outcomes included RSV mortality overall and by individual and parent-level sociodemographic and clinical variables such as chronological age, wGA, sex, race/ethnicity, insurance payer, underlying health conditions, and ICU admission. Mortality was extracted from the studies as either a rate per 100 000 live births or a CFR.

Risk of Bias

Risk of bias in individual studies was evaluated using modified versions of the Newcastle Ottawa Scale (NOS) for cohort and for case-control studies [12]. Surveillance studies were evaluated using a modified version of the NOS for cohort studies. The NOS evaluates 3 domains of bias: selection of cohorts or cases/controls, comparability of cohorts or cases/controls, and assessment of outcome (cohort studies) or exposure (case-control studies). The tool was modified by excluding 1 question from the selection domain for case-control studies ("definition of controls") and 2 questions from the selection domain for cohort studies ("selection of the nonexposed cohort" and "demonstration that outcome of interest was not present at start of study"). Studies could score a maximum of 7 (cohort studies) or 8 (case-control studies) points: 2 (cohort studies) or 3 (case-control studies) points for the selection domain, 2 points for the comparability domain, and 3 points for the outcome/exposure domain. The domain scores for each study were then converted to the Agency for Health Research and Quality (AHRQ) standards (good, fair, or poor quality; definitions provided in Supplementary Table 2).

RESULTS

Article Identification

Literature searches were conducted in PubMed and EMBASE on 11 June 2021. After deduplication, 1568 articles were screened against the eligibility criteria during the title and abstract review. After excluding irrelevant articles, 128 articles remained and were screened at the level of full text. A total of 103 articles were excluded at this stage, and 23 were included in the review. The most common reason for exclusion was the study population being older than age 5 years (n = 40; 38.8%), followed by not including any outcomes of interest (n = 25; 24.3%). An additional 41 studies were evaluated after searching
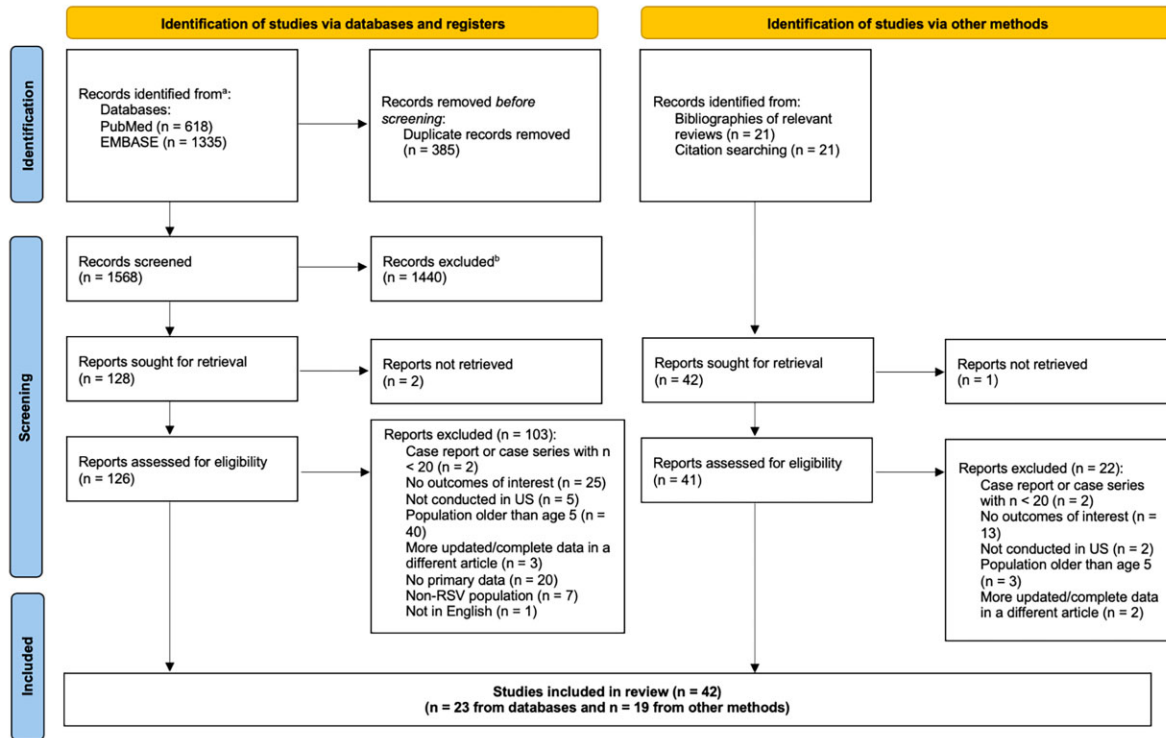
Figure 1. PRISMA flow diagram of the study selection process. Abbreviations: PECOS, population, exposure, comparator, outcomes, and study design; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RSV, respiratory syncytial virus. [a]PubMed, EMBASE databases. [b]Excluded for not meeting PECOS criteria.

the bibliographies of relevant reviews and other citations; 22 were excluded, most frequently due to not including any outcomes of interest (n = 13; 59.1%), and 19 were included in the review. Thus, a total of 42 studies were included in the SLR. A PRISMA flow diagram of the study selection process is provided in Figure 1.

Characteristics of Included Studies

Among the 42 included studies, the time periods covered ranged from 1979 to 2019 (Table 1). Thirty-six were retrospective cohort studies [13–48], 3 were surveillance studies [1, 2, 49], 2 were case-control studies [50, 51], and 1 was a prospective cohort study [52]. Study locations were varied: 20 were located within a single state [14, 16, 18, 22, 23, 28, 30, 31, 34, 35, 38–42, 44, 45, 47, 48, 50, 51], 8 used nationally representative databases [17, 19–21, 29, 33, 36, 53], and 4 used nationwide death certificate data [25–27, 37]. Six other studies [1, 2, 32, 46, 49, 52] were conducted in multiple states and 3 used large datasets that were not location specific (eg, MarketScan, Vizient [15, 24, 28]). The number of infants and children included with RSV or ACB in the studies ranged from 47 in a single-institution study [16] to 1 435 110 in a study evaluating 5 years of emergency department (ED) visits due to RSV in the Nationwide Emergency Department Sample (NEDS) database [36]. The case definition of RSV and/or ACB varied among

the included studies with different ICD codes and laboratory tests. Additional details about the included studies are presented in the Supplementary Materials.

Health Care Setting

Thirty-four studies only evaluated inpatient hospitalization due to RSV and/or ACB; 1 study [13] included inpatient and outpatient RSV cases confirmed by laboratory test, and another [43] incorporated inpatient, outpatient, and ED visits. Four studies included death certificate data [25–27, 37], which were not specific to setting, and 2 were specific to ED visit data [36, 40].

Study Population Characteristics

Variations were observed in the chronological age of the study populations, ranging from infants aged <3 months [39] to all infants and children aged <5 years [2, 33, 37, 42, 47, 48]. While 22 studies did not restrict the study eligibility to specific groups by wGA, race, or comorbidities [1, 2, 13, 19–29, 33, 35–37, 39–42], 4 studies were restricted to only premature (<37 wGA) infants and 2 to full-term infants [43, 51]. Insurance status was reported in 2 studies [1, 24] and ICU admission status in 10 [1, 13, 16, 18, 24, 30, 31, 45, 46, 51]. Two studies were conducted in late-preterm (35–36 wGA) or full-term otherwise healthy infants [43, 51].

Table 1. Characteristics of Included Studies (n = 42)

Author (Year)	Study Design	Data Source and Location	Time Period	Age	Gestational Age	Type of Respiratory Infection Reported	RSV Definition	ACB Definition	Total No. With RSV	Total No. With ACB	AHRQ Quality Score
Populations not restricted by demographic factors (wGA, sex, race), ICU admission status, or comorbidities (CHD, CLD)											
Bender (2014) [39]	Retrospective cohort (EHR)	Southern California Kaiser Permanente Network	2010–2011	<3 mo	NR	NR	Laboratory-confirmed	NR	79	NR	Good
Lalani (2019) [13]	Retrospective cohort (EHR)	Children's Healthcare of Atlanta, GA	2010–2015	<6 mo	NR	NR	Laboratory-confirmed	NR	161	NR	Good
Akenroye (2014) [40]	Retrospective cohort (EHR)	Boston Children's Hospital, Boston, MA	2007–2013	<1 y	NR	LRTI	NR	ICD-9 codes 466.11, 466.19	NR	2929	Good
Doucette (2016) [20]	Retrospective cohort (discharge data)	KID	1997–2012	<1 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1	NR	NR	NR	Good
Holman (2003) [26]	Retrospective cohort (death certificates)	NCHS data	1996–1998	<1 y	NR	LRTI	NR	ICD-9 code 466.1	NR	229	Good
Leader (2003) [25]	Retrospective cohort (death certificates)	Perinatal Linked Mortality Files	1999	<1 y	NR	LRTI	ICD-10 codes J12.1, J20.5, J21.0	ICD-10 codes J12.9, J18.X, J20.9, J21.9	NR	372	Good
Smithgall (2020) [41]	Retrospective cohort (EHR)	3 New York Presbyterian Hospitals, New York, NY	2013–2015	<1 y	NR	ARI	Laboratory-confirmed	NR	411[a]	NR	Good
Willson (2001) [28]	Retrospective cohort (EHR)	10 Children's Medical Centers (locations not specified)	1995–1996	<1 y	NR	LRTI	ICD-9 code 480.1	ICD-9 code 466.1	NR	601[b]	Good
Friedman (2017) [21]	Retrospective cohort (discharge data)	NIS	1997–2013	1–2 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1	ICD-9 code 466.19, 466.1 without RSV codes	228 857	NR[c]	Good
Arriola (2020) [1]	Surveillance	FluSurv-NET (20 hospitals in CA, GA, OR, MN)	2014–2015	<2 y	NR	ARI	Laboratory-confirmed	NR	1554	NR	Good
Byington (2015) [19]	Retrospective cohort (discharge data; claims)	KID; PHIS	2000–2011	<2 y	NR	LRTI	ICD-9 codes 480.1, 466.11	ICD-9 code 466.19[d]	872 658	NR	Good
Chang (2010) [35]	Retrospective cohort (discharge data)	CA Statewide Hospital Discharge Data	2000–2002; 2004–2006	<2 y	NR	LRTI	ICD-9 codes 466.1, 480.1, 079.6	NR	53 207	NR	Good
García (2010) [23]	Retrospective cohort (EHR)	Children's Medical Center in Dallas, TX	2002–2007	<2 y	NR	LRTI	ICD-9 code 466.11	ICD-9 code 466.19	2840	4285	Good
Hasegawa (2014) [36]	Retrospective cohort (discharge data)	NEDS	2006–2010	<2 y	NR	LRTI	NR	ICD-9 code 466.1	NR	1 435 110	Good

Table 1. Continued

Author (Year)	Study Design	Data Source and Location	Time Period	Age	Gestational Age	Type of Respiratory Infection Reported	RSV Definition	ACB Definition	Total No. With RSV	Total No. With ACB	AHRQ Quality Score
Prill (2016) [27]	Retrospective cohort (death certificates)	NCHS data	2004–2007	<2 y	NR	LRTI	ICD-10 codes J12.1, J20.5, J21.0	NR	170	NR	Good
Howard (2000) [29]	Retrospective cohort (discharge data)	NIS	1993–1995	<4 y	NR	LRTI	ICD-9 code 480.1	NR	57 000	NR	Good
Paramore (2004) [33]	Retrospective cohort (discharge data)	NIS	2000	<5 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1	ICD-9 code 466.19[d]	85 858	NR	Good
Rha (2020) [2]	Surveillance	NVSN (NY, OH, TN, MO, TX, WA, CA)	2015–2016	<5 y	NR	ARI	Laboratory-confirmed	NR	1 043	NR	Good
Shay (2001) [37]	Retrospective cohort (death certificates)	NCHS data	1979–1997	<5 y	NR	LRTI	NR	ICD-9 code 466.1	NR	1806	Good
Tripathi (2021) [42]	Retrospective cohort (EHR)	Children's Hospital of Illinois, Peoria, IL	2015–2019	<5 y	NR	ARI	Laboratory-confirmed	NR	162	NR	Good
McLaurin (2016) [24]	Retrospective cohort (claims)	Truven Health MarketScan	2003–2013	<1 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1	NR	46 277	NR	Fair
Hoover (2018) [22]	Retrospective cohort (EHR)	Children's Memorial Hermann Hospital, Houston, TX	2012–2015	<2 y	NR	LRTI	Laboratory-confirmed	NR	299	NR	Poor
Infants born ≥37 wGA											
Walsh (2018) [43]	Retrospective cohort (EHR)	Multiple Hospitals in Rochester, NY	2012–2015	<1 y	≥37 wGA	LRTI	Laboratory-confirmed	NR	131	NR	Fair
Tsou (2020) [51]	Case-control	Driscoll Children's Hospital, Corpus Christi, TX	2015–2017	≤1 y	≥37 wGA	LRTI	Laboratory-confirmed	ICD-9/10 codes, not provided	179	270	Fair
Infants born <37 wGA											
Atkins (2000) [38]	Retrospective cohort (EHR)	Hermann Children's Hospital, Houston, TX	1994–1998	<1 y	<32 wGA	LRTI	Laboratory-confirmed	NR	52	NR	Good
Rajah (2017) [18]	Retrospective cohort (EHR)	Nationwide Children's Hospital in Columbus, OH	2013–2015	<1 y	29–34 wGA	LRTI	ICD-9 code 466.11; confirmation with laboratory testing	ICD-9 code 466.19[g]	91	NR	Good
Anderson (2019) [52]	Prospective cohort	SENTINEL-1 cohort (in AR, CA, CO, CT, FL, GA, IL, KS, KY, LA, MA, MS, NV, NJ, NY, NC, OH, OK, PA, SC, SD, TN, TX, VA, WI)	2014–2016	<1 y	29–35 wGA	NR	Laboratory-confirmed	NR	481	NR	Good

Table 1. Continued

Author (Year)	Study Design	Data Source and Location	Time Period	Age	Gestational Age	Type of Respiratory Infection Reported	RSV Definition	ACB Definition	Total No. With RSV	Total No. With ACB	AHRQ Quality Score
Zembles (2019) [14]	Retrospective cohort (EHR)	Children's Hospital of Wisconsin	2012–2017	<1 y	29–34	LRTI	ICD-9 codes 079.6, 466.11, 480.1 ICD-10 codes J21.0, B97.4, J12.1	NR	91	NR	Fair
Intensive care unit–admitted patients											
Leimanis Laurens (2020) [44]	Retrospective cohort (EHR)	Helen DeVos Children's Hospital, Grand Rapids, MI	2012–2017	<1 y	NR	LRTI	ICD-9 codes 079.6, 466.11 ICD-10 code J21.0	ICD-9 codes 465.9, 466.11, 466.19 ICD-10 codes J21.0, J21.1, J21.8, J21.9	72	187	Good
Shutes (2021) [45]	Retrospective cohort (EHR)	Nationwide Children's Hospital, Columbus, OH	2014–2017	<1 y	NR	LRTI	Laboratory-confirmed	ICD-9/10 codes, not provided	Unclear	856	Good
Buckingham (2001) [31]	Retrospective cohort (EHR)	Pediatric tertiary care facility, TN	1994–1997	<2 y	NR	NR	Laboratory-confirmed	NR	89	NR	Good
Carroll (2016) [46]	Retrospective cohort (EHR)	Four hospitals in CT and MA	2009–2011	<2 y	NR	LRTI	Laboratory-confirmed	Clinical sequelae	323	323	Good
Randolph (2004) [30]	Retrospective cohort (EHR)	Children's Hospital, Boston, MA	1990–2002	<3 y	≥36 wGA[e]	NR	Laboratory-confirmed	NR	165	NR	Good
Jorgensen (2007) [47]	Retrospective cohort (EHR)	Children's Mercy Hospital, Kansas City MO	2000–2005	<5 y	NR	LRTI	Laboratory-confirmed	Bronchiolitis, not otherwise defined	103	151	Good
Sifers (2018) [16]	Retrospective cohort (EHR)	Tertiary children's healthcare center, location NR	January–March 2017	<2 y	≥35 wGA[f]	LRTI	RSV, not further defined	NR	47	NR	Poor
Congenital heart disease patients											
Friedman (2017) [17]	Retrospective cohort (discharge data)	NIS	1997–2013	<1 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1	NR	35 634	NR	Good
Altman (2000) [48]	Retrospective cohort (EHR)	Texas Children's Hospital, Houston, TX	1994–1998	<5 y	NR	LRTI	Laboratory-confirmed	NR	63	NR	Good
Walpert (2018) [15]	Retrospective cohort (discharge data)	Vizient	2012–2016	<2 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1 ICD-10 codes J20.5, J21.0, J12.1	NR	1269	NR	Fair
American Indian/Alaska Native patients											
Holman (2004) [32]	Retrospective cohort (discharge data)	Indian Health Service Inpatient Database	2000–2001	<1 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1	NR	1258	NR	Good

Table 1. Continued

Author (Year)	Study Design	Data Source and Location	Time Period	Age	Gestational Age	Type of Respiratory Infection Reported	RSV Definition	ACB Definition	Total No. With RSV	Total No. With ACB	AHRQ Quality Score
Bockova (2002) [49]	Surveillance	Navajo and White Mountain Apache Indian Health Service Units	1997–2000	<2 y	NR	LRTI	Laboratory-confirmed	NR	876	NR	Good
Singleton (2010) [50]	Case-control	Community hospital in Alaska's Yukon-Kuskokwim Delta region	2005–2007	<3 y	NR	LRTI	Laboratory-confirmed	NR	120	NR	Poor
Other populations[h]											
Buckley (2010) [34]	Retrospective cohort (claims)	SelectHealth (UT)	2005–2008	<1 y	NR	LRTI	ICD-9 codes 079.6, 466.11, 480.1	NR	57 (42 approved for palivizumab, 15 denied)	NR	Fair

Abbreviations: ACB, all-cause bronchiolitis; AHRQ, Agency for Health Research and Quality; ARI, acute respiratory infection; CHD, congenital heart disease; EHR, electronic health record; ICD, International Classification for Diseases; KID, Kids' Inpatient Database; LRTI, lower respiratory tract infection; NCHS, National Center for Health Statistics, NEDS, Nationwide Emergency Department Sample; NIS, National Inpatient Sample; NR, not reported; NVSN, New Vaccine Surveillance Network; PHIS, Pediatric Health Information System; RSV, respiratory syncytial virus; wGA, weeks' gestational age.

[a]Only patients from hospital cohort included; mortality not reported within surveillance cohort.

[b]All patients grouped together as "viral lower respiratory illness."

[c]Number of patients with ACB not reported in study.

[d]ACB code used as proxy for RSV. All patients were described as having RSV.

[e]Patients included late preterm (36 wGA) and full-term (≥37 wGA) infants and children.

[f]Patients included late preterm (35–36 wGA) and full-term (≥37 wGA) infants and children.

[g]ACB code used to identify potential RSV cases. Records were cross-checked with virology laboratory to identify cases that tested positive for RSV.

[h]Buckley (2010) [34] includes infants whose providers requested prior authorization for palivizumab; some were approved, and others denied. The 57 patients were RSV hospitalizations.

Table 2. Respiratory Syncytial Virus and All-Cause Bronchiolitis Mortality Rates per 100 000 for US Infants and Children Aged <5 Years (n = 3; Populations Not Restricted by Demographic Factors [Weeks Gestational Age, Sex, Race], Intensive Care Unit Admission Status, or Comorbidities [Congenital Heart Disease, Chronic Lung Disease])

Author (Year)	Data Source	Study Time Period	Age	Total No. With RSV	Total No. With ACB	RSV Mortality	ACB Mortality	AHRQ Quality Score
Leader (2003) [25]	Perinatal linked mortality files	1999	<1 y[a]	NR	372	NR	<1 y: 372 deaths per y (9.4 per 100 000 live births) Males: 10.4 per 100 000 live births Females: 8.3 per 100 000 live births Black: 18.0 per 100 000 live births White: 7.7 per 100 000 live births ≤35 wGA: 39.0 per 100 000 live births ≥37 wGA: 6.8 per 100 000 live births <2500 g: 47.3 per 100 000 live births ≥2500 g: 6.3 per 100 000 live births	Good
Holman (2003) [26]	NCHS data	1996–1998	<1 y	NR	229	NR	<1 y: mean 76 deaths per y (2.0 per 100 000 live births) Male: 2.2 per 100 000 live births Female: 1.7 per 100 000 live births Black: 4.2 per 100 000 live births White: 1.5 per 100 000 live births South: 2.6 per 100 000 live births Northeast: 1.2 per 100 000 live births Midwest: 1.7 per 100 000 live births West: 1.9 per 100 000 live births	Good
Shay (2001) [37]	NCHS data	1979–1997	<5 y	NR	1806	<5 y: estimated 171–510 deaths per y	<5 y: mean 95 (range 66–127) deaths per y (0.65 per 100 000 live births in 1979; 0.57 per 100 000 live births in 1997) <1 y: mean 76 deaths per y (2.4 per 100 000 live births in 1979; 2.2 per 100 000 live births in 1997)	Good

Abbreviations: ACB, all-cause bronchiolitis; AHRQ, Agency for Health Research and Quality; RSV, respiratory syncytial virus; NCHS, National Center for Health Statistics; NR, not reported; wGA, weeks' gestational age.

[a]Perinatal linked mortality files only include deaths from 28–364 days of age (excluding newborns).

Risk of Bias

Using the AHRQ standards, 33 studies were scored as good quality [1, 2, 13, 17–21, 23, 25–33, 35–42, 44–49, 52, 54], 6 as fair quality [14, 15, 24, 34, 43, 51], and 3 as poor quality [16, 22, 50]. When evaluating risk of bias by domain, risk of bias was most apparent in the selection and comparability domains (Supplementary Figure 1). Many studies either only included 1 adjustment factor (n = 13, primarily age) or did not adjust for any factors in their analyses (n = 3).

RSV or ACB Mortality Rates

Mortality among infants and children in the United States was reported for RSV in 1 nationally representative study using the NCHS death certificate database [27] (Table 2). Using

Table 3. Overall Respiratory Syncytial Virus Case Fatality Ratios Among US Infants and Children Aged <5 Years (Populations Not Restricted by Demographic Factors [Weeks Gestational Age, Sex, Race], Intensive Care Unit Admission Status, or Comorbidities [Congenital Heart Disease, Chronic Lung Disease]) (n = 15)

Author (Year)	Data Source and Location	Time Period	Age	No. Deaths	Total No.	CFR, %	AHRQ Quality Score
Bender (2014) [39]	Southern California Kaiser Permanente Network	2010–2011	<3 mo	0	79	0.0	Good
Lalani (2019) [13]	Children's Healthcare of Atlanta, GA	2010–2015	<6 mo	0	161	0.0	Good
Doucette (2016) [20]	KID	1997–2012	<1 y	NR	NR	Non-high-risk infants: 0.04	Good
Smithgall (2020) [41]	3 New York Presbyterian Hospitals, New York, NY	2013–2015	<1 y	1	411	0.24	Good
Friedman (2017) [21]	NIS	1997–2013	1–2 y	296	228 857	0.13	Good
García (2010) [23]	Children's Medical Center in Dallas, TX	2002–2007	<2 y	3	2840	0.11	Good
Arriola (2020) [1]	FluSurv-NET (20 hospitals in CA, GA, OR, MN)	2014–2015	<2 y	5	1554	0.32	Good
Byington (2015) [19]	KID; PHIS	2000–2011	<2 y	1 221	872 658	0.14	Good
Chang (2010) [35]	CA Statewide Hospital Discharge Data	2000–2002; 2004–2006	<2 y	36	53 207	0.07	Good
Howard (2000) [29]	NIS	1993–1995	<4 y	NR	57 000	0.55	Good
Paramore (2004) [33]	NIS	2000	<5 y	11	85 858	0.14	Good
Rha (2020) [2]	NVSN (NY, OH, TN, MO, TX, WA, CA)	2015–2016	<5 y	0	1043	0.0	Good
Tripathi (2021) [42]	Children's Hospital of Illinois, Peoria, IL	2015–2019	<5 y	0	162	0.0	Good
McLaurin (2016) [24]	Truven Health MarketScan	2003–2013	<1 y	25	46 277	0.05	Fair
Hoover (2018) [22]	Children's Memorial Hermann Hospital in Houston, TX	2012–2015	<2 y	5	299	1.7	Poor

Abbreviations: AHRQ, Agency for Health Research and Quality; CFR, case fatality ratio; KID, Kids' Inpatient Database; NIS, National Inpatient Database; NR, not reported; NVSN, New Vaccine Surveillance Network; PHIS, Pediatric Health Information System; RSV, respiratory syncytial virus; wGA, weeks' gestational age.

state health and vital records transmitted to NCHS, Prill et al (2016) reported 170 deaths due to RSV among US children aged <2 years, 142 of which were aged <1 year, between 2004 and 2007 (mean of 43 annual deaths <2 years and 36 annual deaths <1 year) [27]. However, this study only reports death counts and not mortality rates, which are more appropriate measures for comparing mortality among populations of different sizes.

Among 3 studies reporting ACB mortality in nationally representative databases [25, 26, 37], rates ranged from 0.57 deaths per 100 000 children aged <5 years in 1997 [37] to 9.4 per 100 000 live births in 1999 [25]. However, the higher rate reported in Leader et al (2003) was likely due to the authors incorporating all deaths due to RSV as well as bronchitis, bronchiolitis, and pneumonia due to unknown causes [25], as the other ACB studies did not include unspecified bronchitis or pneumonia deaths. Shay et al (2001) [37] reported a decrease in ACB mortality deaths among children aged <5 years from 0.65 per 100 000 live births in 1979 to 0.57 per 100 000 live births in 1997. Among infants aged <1 year, ACB mortality decreased from 2.4 per 100 000 live births in 1979 [37] to 2.2 per

100 000 births in 1997 [37] in 1 study and was reported as 2.0 per 100 000 live births from 1996 to 1998 [26] in another study.

RSV Mortality CFR

Overall mortality from RSV was evaluated as CFRs among 15 publications without restrictions in wGA, race, ICU admission status, or comorbidities [1, 2, 13, 19–24, 29, 33, 35, 39, 41, 42] to allow for increased comparability between studies (Table 3). The RSV CFR among infants and children aged <5 years ranged from 0% in 2 single-institution studies (2010–2015; 2015–2019) [13, 42], 1 healthcare network study (2010–2011) [39], and 1 surveillance study (2015–2016) [2] to 1.7% in another single-institution study (2012–2015) [22]. Among the 13 good-quality studies, RSV CFRs ranged from 0% to 0.55% [1, 2, 13, 19–21, 23, 29, 33, 35, 39, 41, 42] (1993–2019) compared to 0.05% in the fair-quality study (2003–2013) [24] and 1.7% in the poor-quality study (2012–2015) [22]. The CFRs among the 6 studies using data from nationwide or large databases (eg, NIS, Kids' Inpatient Database [KID], MarketScan) ranged from 0.04% to 0.90% (1993–2013) [19–21, 24, 29, 33], compared to 0.0% to 0.32% among the 4 multiinstitutional studies

Table 4. Respiratory Syncytial Virus Case Fatality Ratios Among US Infants and Children Aged <5 Years by Chronological Age (n = 13)

Author (Year)	Data Source and Location	Time Period	<12 mo			12–23 mo			AHRQ Quality Score
			No. Deaths	Total No.	CFR, %	No. Deaths	Total No.	CFR, %	
Altman (2000) [48][a,b]	Texas Children's Hospital, Houston, TX	1994–1998	1	27	3.70	0	36	0.0	Good
Arriola (2020) [1]	FluSurv-NET (20 hospitals in CA, GA, OR, MN)	2014–2015	5	1 176	0.43	0	378	0.0	Good
Atkins (2000) [38][c]	Hermann Children's Hospital, Houston, TX	1994–1998	3	52	5.8	NR	NR	NR	Good
Bender (2014) [39]	Southern California Kaiser Permanente Network	2010–2011	0	79	0.0	NR	NR	NR	Good
Friedman (2017) [21]	NIS	1997–2013	NR	NR	NR	296	228 857	0.13	Good
Friedman (2017) [17][a]	NIS	1997–2013	428	35 634	1.2	NR	NR	NR	Good
Rajah (2017) [18][c]	Nationwide Children's Hospital in Columbus, OH	2013–2015	2	91	2.2	NR	NR	NR	Good
Rha (2020) [2]	NVSN (NY, OH, TN, MO, TX, WA, CA)	2015–2016	0	704	0.0	0	199	0.0	Good
Smithgall (2020) [41]	3 New York Presbyterian Hospitals, New York, NY	2013–2015	1	411	0.24	NR	NR	NR	Good
Tripathi (2021) [42]	Children's Hospital of Illinois, Peoria, IL	2015–2019	0	162	0.0	NR	NR	NR	Good
Tsou (2020) [51][d]	Driscoll Children's Hospital, Corpus Christi, TX	2015–2017	0	179	0.0	NR	NR	NR	Fair
Walpert (2018) [15][a]	Vizient	2012–2016	13	1 057	1.02	0	118	0.0	Fair
Walsh (2018) [43][e]	Multiple Hospitals in Rochester, NY	2012–2015	0	131	0.0	NR	NR	NR	Fair

Abbreviations: AHRQ, Agency for Health Research and Quality; CFR, case fatality ratio; National Inpatient Sample; NR, not reported; NVSN, New Vaccine Surveillance Network.

[a]Congenital heart disease patients only.

[b]Categories are ≤12 months and >12 months in this study.

[c]Premature infants only.

[d]Full-term infants only; includes both ICU and general ward patients.

[e]Full-term infants only.

(2000–2016) [1, 2, 35, 39] and 0% to 1.7% among the 5 single-institution studies (2002–2019) [13, 22, 23, 41, 42].

RSV Mortality CFR by Selected Variables

Limited data were available reporting RSV mortality stratified by chronological age, wGA, ICU admission, insurance payer, race, and comorbidities. Of the 5 studies providing stratified data by chronological age groups, CFRs were generally higher among infants (0%–3.7%; 1994–2019) than children aged 1–2 years (0.0%–0.13%; 1994–2016) [1, 15, 17, 21, 48] except for the NVSN study, which reported 0% in both groups (2015–2016) [2] (Table 4). Within the first year of life, 2 studies reported higher RSV mortality among infants aged 6–11 months compared with those aged 0–5 months (2013–2015 [18]; 2014–2015 [1]).

Results by wGA were inconsistent. Among the 4 studies that stratified RSV mortality by wGA groups, 2 studies (1 surveillance [1] and 1 nationwide claims study [24]) reported that infants born <37 wGA had higher CFRs than infants born ≥37 wGA. Two other studies (both single-institutional [22, 31], although 1 was conducted among those admitted to ICU only [31]), reported similar proportions between both wGA groups (Table 5).

Eight studies reported the RSV CFR for those admitted to the ICU only and did not include general ward patients [13, 16, 18, 24, 30, 31, 45, 46] (Table 6). The CFRs among the ICU infants and children in these 8 studies ranged from 0.0% to 11.26% (1990–2017) [13, 16, 18, 24, 30, 31, 45, 46]. Only 2 studies (Arriola et al 2020, 2014–2015 and Tsou et al 2020, 2015–2017) compared stratified data for infants and children admitted to the ICU and for the general ward; mortality was higher among those in the ICU in 1 of the studies (CFR, 1.2% vs 0%, respectively) [1] and equal in the other study (both 0%) [51].

Four studies reported data on RSV mortality stratified by race [31, 32, 49, 50]. The 3 studies restricted to American Indian/Alaska Native children [32, 49, 50] reported relatively low RSV CFRs (0%–0.11%; 1997–2007) (Supplementary Table 3). One small single-institution study reported a higher CFR among white children than African American children, but numbers were small and all cases were in the ICU (5 deaths in 38 white children, 1 death in 48 African American; 1994–1997) [31].

Two studies stratified RSV mortality by insurance payer [1, 24] (Supplementary Table 4). Arriola et al [1] reported similar CFRs between publicly insured and privately insured RSV children aged <2 years (0.32% and 0.35%, respectively, 2014–2015).

Table 5. Respiratory Syncytial Virus Case Fatality Ratios Among US Infants and Children Aged <5 Years by Weeks of Gestational Age (n = 12)

| Author (Year) | Data Source and Location | Time Period | Age | <37 wGA | | | ≥37 wGA | | | AHRQ Quality Score |
				No. Deaths	Total No.	CFR, %	No. Deaths	Total No.	CFR, %	
Atkins (2000) [38][a]	Hermann Children's Hospital, Houston, TX	1994–1998	<1 y	3	52	5.8	NR	NR	NR	Good
Rajah (2017) [18]	Nationwide Children's Hospital in Columbus, OH	2013–2015	<1 y	2	91	2.2	NR	NR	NR	Good
Anderson (2019) [52]	SENTINEL-1 cohort (in AR, CA, CO, CT, FL, GA, IL, KS, KY, LA, MA, MS, NV, NJ, NY, NC, OH, OK, PA, SC, SD, TN, TX, VA, WI)	2014–2016	<1 y	2	481	0.42	NR	NR	NR	Good
Arriola (2020) [1]	FluSurv-NET (20 hospitals in CA, GA, OR, MN)	2014–2015	<2 y	3	257	1.17	2	1297	0.15	Good
Buckingham (2001) [31][b]	Pediatric tertiary care facility, TN	1994–1997	<2 y	3	49	6.12	3	40	7.5	Good
Randolph (2004) [30][c]	Children's Hospital, Boston, MA	1990–2002	<3 y	NR	NR	NR	0	165	0.0	Good
McLaurin (2016) [24]	Truven Health MarketScan	2003–2013	<1 y	13	7028	0.18	12	38 372	0.03	Fair
Zembles (2019) [14]	Children's Hospital of Wisconsin	2012–2017	<1 y	1	91	1.10	NR	NR	NR	Fair
Tsou (2020) [51][d]	Driscoll Children's Hospital, Corpus Christi, TX	2015–2017	≤1 y	NR	NR	NR	0	179	0.0	Fair
Walsh (2018) [43]	Multiple Hospitals in Rochester, NY	2012–2015	<1 y	NR	NR	NR	0	131	0.0	Fair
Hoover (2018) [22][e]	Children's Memorial Hermann Hospital, Houston, TX	2012–2015	<2 y	2	120	1.67	3	179	1.68	Poor
Sifers (2018) [16][f]	Tertiary children's healthcare center, location NR	2017	<2 y	NR	NR	NR	0	47	0.0	Poor

Abbreviations: AHRQ, Agency for Health Research and Quality; CFR, case fatality ratio; ICU, intensive care unit; NR, not reported; wGA; weeks' gestational age.

[a]Cutoff is ≤32 wGA in this study.

[b]Cutoff is >35 wGA in this study; ICU patients only.

[c]Cutoff is ≥36 wGA in this study; ICU patients only.

[d]Includes both ICU and general ward patients.

[e]Cutoff is >37 wGA in this study.

[f]Cutoff is >34 wGA in this study; ICU patients only.

In comparison, McLaurin et al [24] reported that the CFR among publicly insured RSV infants was twice as high as that of privately insured in the MarketScan database (0.07% vs 0.03%, 2003–2013).

Among studies that stratified RSV CFR by congenital heart disease (CHD) status, CFRs were higher among infants and children with CHD (n = 8; 0.28%–14.3%; 1993–2015) than those without CHD (0.04%–6.2%) [1, 17, 20, 21, 23, 29, 31, 35] (Supplementary Table 5); however, the upper CFR ranges were among children in ICU [31]. Similar trends were reported among 3 studies that stratified RSF CFRs by chronic lung disease (CLD) status; children with CLD had higher CFRs (0%–6.9%) than those without (0.04%–0.33%; 1993–2015) [20, 29], with the exception of 1 surveillance study that reported no deaths among a small cohort of 44 CLD infants and children compared with 5 deaths within a much larger cohort of 1510 non-CLD infants and children (2014–2015) [1]. This difference may have been due to the small sample size of CLD patients in the study (Supplementary Table 6).

ACB Mortality

Overall mortality for ACB was evaluated among 6 studies whose populations were not restricted by wGA, ICU status, or comorbidities [20, 21, 23, 28, 36, 40] (Supplementary Table 7). Among the studies using nationally representative databases (NIS, NEDS, and KID), ACB CFRs ranged from 0.01% among infants classified as non–high-risk in the KID database (1997–2012) and another study of children <2 years in the NEDS database (2006–2010) [20, 36] to 0.7% among infants classified as high-risk in the KID database (1997–2012) [20].

DISCUSSION

This SLR demonstrated that among all US infants and children aged <5 years with RSV or ACB, mortality is relatively low. Among the studies using nationally representative databases (NIS, KID, NEDS, and NCHS), RSV CFRs for otherwise healthy children ranged from 0.04% to 0.55% from 1997 to 2019 (0.01%–0.02% for ACB from 1997 to 2013). Mortality

Table 6. Respiratory Syncytial Virus Case Fatality Ratios Among US Infants and Children Aged <5 Years by Intensive Care Unit Admission Status (n = 10)

Author (Year)	Data Source and Location	Time Period	Age	ICU No. Deaths	ICU Total No.	ICU CFR, %	General Ward No. Deaths	General Ward Total No.	General Ward CFR, %	AHRQ Quality Score
Lalani (2019) [13]	Children's Healthcare of Atlanta, GA	2010–2015	<6 mo	0	50	0.0	NR	NR	NR	Good
Rajah (2017) [18][a]	Nationwide Children's Hospital in Columbus, OH	2013–2015	<1 y	2	48	4.2	NR	NR	NR	Good
Shutes (2021) [45]	Nationwide Children's Hospital, Columbus, OH	2014–2017	<1 y	1	Unclear	NR	NR	NR	NR	Good
Arriola (2020) [1]	FluSurv-NET (20 hospitals in CA, GA, OR, MN)	2014–2015	<2 y	5	416	1.2	0	1138	0.0	Good
Buckingham (2001) [31]	Pediatric tertiary care facility, TN	1994–1997	<2 y	6	89	6.7	NR	NR	NR	Good
Carroll (2016) [46]	Four hospitals in CT and MA	2009–2011	<2 y	0	323	0.0	NR	NR	NR	Good
Randolph (2004) [30]	Children's Hospital, Boston, MA	1990–2002	<3 y	0	165	0.0	NR	NR	NR	Good
McLaurin (2016) [24]	Truven Health MarketScan	2003–2013	<1 y	25	222	11.26	NR	NR	NR	Fair
Tsou (2020) [51][b]	Driscoll Children's Hospital, Corpus Christi, TX	2015–2017	≤1 y	0	100	0.0	0	79	0.0	Fair
Sifers (2018) [16][c]	Tertiary children's healthcare center, location NR	2017	<2 y	0	47	0.0	NR	NR	NR	Poor

Abbreviations: AHRQ, Agency for Health Research and Quality; CFR, case fatality ratio; ICU, intensive care unit; NR, not reported; wGA, weeks' gestational age.

[a]Preterm infants only.

[b]Full-term infants only.

[c]Only >34 wGA in this study.

was not reported as a rate for RSV but rather described as 43 and 36 deaths per year among children <2 years and <1 year, respectively; mortality rates for ACB ranged from 0.57 to 9.4 per 100 000 from 1979 to 1999. These results are comparable to reviews of RSV CFRs for infants and children in high-income countries [10, 55]. A German study of 8521 infants and children <5 years hospitalized with RSV reported an overall CFR of 0.12% [56]. However, this review also revealed that nationally representative estimates of RSV mortality for otherwise healthy, late preterm to full-term infants are limited and out of date (no available mortality rates; latest update through 2007 for mortality counts and update in 2013 for CFRs) or are not stratified by important demographic or clinical variables such as race or insurance payer. Notably, after this review was completed, Prill et al published an update of RSV mortality through 2016 using NCHS data (n = 315 total deaths among age <1 from 2005 to 2016 [mean 26 annual deaths]), although these data were not included in the current review due to the time frame [57]. Many (20%) of the included studies focused on mortality among populations eligible or formerly eligible for prophylaxis (eg, CHD, CLD, 29–34 wGA). In addition, 21% of studies were rated as fair or poor quality using the NOS and AHRQ scales; the impact of the potential biases on the results is unclear. Finally, due to the lack of systematic laboratory testing across health care settings and differences in ICD diagnosis and cause of death codes used in studies, the true burden of RSV and its associated mortality is uncertain [6–8, 25].

Among the included studies, infants and children admitted to the ICU experienced the highest mortality, an expected finding. The recent study of German infants and children hospitalized with RSV identified age <6 months, birth at 28–37 wGA, congenital defects, perinatal respiratory and cardiovascular disorders, and various other comorbidities as significant risk factors for ICU admission [56]. Another study of 734 children aged <2 years hospitalized with ACB in Connecticut reported younger age and history of premature birth as significant risk factors for ICU admission [58]. These studies suggest that preventative measures should be taken in infants and children with these risk factors to protect against severe disease and mortality.

Two studies provided inconclusive data on RSV CRF by insurance status, with increased RSV mortality reported among infants with public insurance in a claims study [24] and comparable mortality reported for public and commercial insurance children in a surveillance study [1]. However, the differences in study design (nationwide claims study vs surveillance), RSV definition (ICD codes vs laboratory testing), time period (2003–2013 vs 2014–2015), and population (infants <1 year vs children <2 years) between these studies limit the ability to directly compare the two. While a study of RSV hospitalizations among California infants reported a hospitalization rate among publicly insured infants more than double that of privately insured infants (24.3 vs 12.0 per 1000 live births, respectively) [59], limited data are available comparing outcomes by payer. Additional research is needed to elucidate the disparity in mortality by insurance payer.

This review highlights several challenges to studying RSV epidemiology. Because American Academy of Pediatrics guidelines do not recommend systematic testing for RSV [4], there may be uncertainties in the estimates of RSV mortality. Furthermore, the definition of RSV was not standard across the included studies. Without systematic testing protocols, these studies may not have identified all RSV cases. Given the variability in the study populations across the included studies, comparison of cohorts should be interpreted with caution. These issues may hinder meta-analyses and quantitative analyses.

Nearly all of the included studies reporting CFR were restricted to RSV or ACB hospitalizations; deaths occurring outside of the inpatient setting would not have been captured. Leader (2003) found that 47.5% of deaths occurred in hospital; 31.5% occurred in the ED or outpatient departments, and 12.6% in a residence [25]. Thus, studies evaluating only in-hospital mortality do not completely reflect the mortality outside the inpatient setting. While the studies using NCHS data capture all deaths due to RSV reported in the United States, the latest available data are nearly 15 years old (2004–2007 [27]) and mortality rates were not calculated. Updated data are needed to interpret recent trends in RSV mortality among US infants and children aged <5 years.

The strengths of this study include the rigorous systematic nature of the review, use of standard bias assessment tools, narrow focus of the study question, and comprehensive evaluation of mortality by demographic and clinical variables. However, the RSV CFRs and mortality rates in the included studies may not be generalizable to older children or other countries as this SLR evaluated infants and children aged <5 years in the United States. The heterogeneity in study design and methodology across the included studies may have contributed to some of the variation in results. The impact of the coronavirus disease 2019 (COVID-19) pandemic on RSV mortality was also not captured in the existing studies as the study time periods ranged from 1979 to 2019.

Gaps remain in determining the infant, parental, and sociodemographic factors that may impact RSV mortality among US infants. Elucidating these factors and quantifying risk is critical to improving patient care and reducing RSV mortality. Even among the nationally representative studies, results varied by chronological age, RSV/bronchiolitis definition, and study time period. The available literature does not provide a comprehensive evaluation of RSV mortality, as limited data were available for otherwise healthy, late-preterm to full-term infants and children aged <5 years in the United States or stratified by factors such as wGA, age, race, ICU admission status, and insurance payer. Ideally, nationally representative studies using systematic RSV diagnostic methods and providing stratification by demographic, clinical, and socioeconomic factors would better describe the burden of RSV and its associated mortality in the United States.

Supplementary Data

Notes

References

1. 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 **2019**; 9: 587–95.

2. Rha B, Curns AT, Lively JY, et al. Respiratory syncytial virus-associated hospitalizations among young children: 2015–2016. Pediatrics **2020**; 146:e20193611.

3. Suh M, Movva N, Jiang X, et al. Respiratory syncytial virus burden and healthcare utilization in United States infants <1 year of age: study of nationally representative databases, 2011–2019. J Infect Dis **2022**; **226**(S2):S184–94.

4. American Academy of Pediatrics. Respiratory syncytial virus. In: Pickerling LK, Baker CJ, Kimberlin DW, Long SS, eds. Red book: 2012 report of the Committee on Infectious Diseases 29th ed. Elk Grove Village, IL: American Academy of Pediatrics, **2012**:609–18.

5. Pickering LK, Baker CJ, Kimberlin DW. Red book: 2012 report of the Committee on Infectious Diseases. Elk Grove Village, IL: American Academy of Pediatrics, **2012**.

6. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. JAMA **2003**; 289:179–86.

7. Hansen CL, Chaves SS, Demont C, Viboud C. Mortality associated with influenza and respiratory syncytial virus in the US, 1999–2018. JAMA Network Open **2022**; 5:e220527.

8. Hansen CL, Viboud C, Chaves SS. The use of death certificate data to characterize mortality associated with respiratory syncytial virus, unspecified bronchiolitis, and influenza in the United States, 1999–2018. J Infect Dis **2022**; 226(S2):S255–66.

9. Centers for Disease Control and Prevention. Principles of epidemiology in public health practice. 3rd ed. An introduction to applied epidemiology and biostatistics. Lesson 3: Measures of risk. Section 3: Mortality frequency measures. https://www.cdc.gov/csels/dsepd/ss1978/lesson3/section3.html. Accessed 14 July 2021.

10. 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.

11. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ **2021**; 372:n71.

12. Wells GA, Shea B, O'Connell D, et al. Newcastle-Ottawa quality assessment scale. http://www.ohri.ca/programs/clinical_epidemiology/nosgen.pdf. Accessed 12 June 2021.

13. Lalani K, Yildirim I, Phadke VK, Bednarczyk RA, Omer SB. Assessment and validation of syndromic case definitions for respiratory syncytial virus infections in young infants: a latent class analysis. Pediatr Infect Dis J **2019**; 38:1177–82.

14. Zembles TN, Bushee GM, Willoughby RE. Impact of American Academy of Pediatrics palivizumab guidance for children ≥29 and <35 weeks of gestational age. J Pediatr **2019**; 209:125–9.

15. Walpert AS, Thomas ID, Lowe MC Jr, Seckeler MD. RSV prophylaxis guideline changes and outcomes in children with congenital heart disease. Congenit Heart Dis **2018**; 13:428–31.

16. Sifers F, Patel H, Allen H. High-flow nasal cannula use in bronchiolitis at a tertiary childrens hospital. J Invest Med **2018**; 66:546.

17. Friedman D, Wong PC. Risk of respiratory syncytial virus hospitalization in the first and second years of life in pediatric patients with congenital heart disease. Pediatr Cardiol **2017**; 38:1311–2.

18. Rajah B, Sánchez PJ, Garcia-Maurino C, Leber A, Ramilo O, Mejias A. Impact of the updated guidance for palivizumab prophylaxis against respiratory syncytial virus infection: a single center experience. J Pediatr **2017**; 181:183–8.e1.

19. Byington CL, Wilkes J, Korgenski K, Sheng X. Respiratory syncytial virus-associated mortality in hospitalized infants and young children. Pediatrics **2015**; 135:e24–31.

20. Doucette A, Jiang X, Fryzek J, Coalson J, McLaurin K, Ambrose CS. Trends in respiratory syncytial virus and bronchiolitis hospitalization rates in high-risk infants in a United States nationally representative database, 1997–2012. PLoS One **2016**; 11:e0152208.

21. Friedman D, Fryzek J, Jiang X, Bloomfield A, Ambrose CS, Wong PC. Respiratory syncytial virus hospitalization risk in the second year of life by specific congenital heart disease diagnoses. PLoS One **2017**; 12:e0172512.

22. Hoover J, Eades S, Lam WM. Pediatric antiviral stewardship: defining the potential role of ribavirin in respiratory syncytial virus-associated lower respiratory illness. J Pediatr Pharmacol Ther **2018**; 23:372–8.

23. García CG, Bhore R, Soriano-Fallas A, et al. Risk factors in children hospitalized with RSV bronchiolitis versus non-RSV bronchiolitis. Pediatrics **2010**; 126:e1453–60.

24. McLaurin KK, Farr AM, Wade SW, Diakun DR, Stewart DL. Respiratory syncytial virus hospitalization outcomes and costs of full-term and preterm infants. J Perinatol **2016**; 36:990–6.

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. Holman RC, Shay DK, Curns AT, Lingappa JR, Anderson LJ. Risk factors for bronchiolitis-associated deaths among infants in the United States. Pediatr Infect Dis J **2003**; 22:483–90.

27. Prill MM, Iwane MK, Little D, Gerber SI. Investigation of respiratory syncytial virus-associated deaths among US children aged <2 years, 2004–2007. J Pediatric Infect Dis Soc **2016**; 5:333–6.

28. Willson DF, Horn SD, Hendley JO, Smout R, Gassaway J. Effect of practice variation on resource utilization in infants hospitalized for viral lower respiratory illness. Pediatrics **2001**; 108:851–5.

29. Howard TS, Hoffman LH, Stang PE, Simoes EA. Respiratory syncytial virus pneumonia in the hospital setting: length of stay, charges, and mortality. J Pediatr **2000**; 137:227–32.

30. Randolph AG, Reder L, Englund JA. Risk of bacterial infection in previously healthy respiratory syncytial virus-infected young children admitted to the intensive care unit. Pediatric Infect Dis J **2004**; 23:990–4.

31. Buckingham SC, Quasney MW, Bush AJ, DeVincenzo JP. Respiratory syncytial virus infections in the pediatric intensive care unit: clinical characteristics and risk factors for adverse outcomes. Pediatric Critical Care Med **2001**; 2:318–23.

32. 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.

33. 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.

34. Buckley BC, Roylance D, Mitchell MP, Patel SM, Cannon HE, Dunn JD. Description of the outcomes of prior authorization of palivizumab for prevention of respiratory syncytial virus infection in a managed care organization. J Manag Care Pharm **2010**; 16:15–22.

35. Chang RK, Chen AY. Impact of palivizumab on RSV hospitalizations for children with hemodynamically significant congenital heart disease. Pediatr Cardiol **2010**; 31:90–5.

36. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr. Temporal trends in emergency department visits for bronchiolitis in the United States, 2006 to 2010. Pediatr Infect Dis J **2014**; 33:11–8.

37. Shay DK, Holman RC, Roosevelt GE, Clarke MJ, Anderson LJ. Bronchiolitis-associated mortality and estimates of respiratory syncytial virus-associated deaths among US children, 1979–1997. J Infect Dis **2001**; 183:16–22.

38. Atkins JT, Karimi P, Morris BH, McDavid G, Shim S. Prophylaxis for respiratory syncytial virus with respiratory syncytial virus-immunoglobulin intravenous among preterm infants of thirty-two weeks gestation and less: reduction in incidence, severity of illness and cost. Pediatr Infect Dis J **2000**; 19:138–43.

39. Bender JM, Taylor CS, Cumpio J, et al. Infants 1–90 days old hospitalized with human rhinovirus infection. J Clin Lab Anal **2014**; 28:349–52.

40. Akenroye AT, Baskin MN, Samnaliev M, Stack AM. Impact of a bronchiolitis guideline on ED resource use and cost: a segmented time-series analysis. Pediatrics **2014**; 133:e227–34.

41. Smithgall M, Maykowski P, Zachariah P, et al. Epidemiology, clinical features, and resource utilization associated with respiratory syncytial virus in the community and hospital. Influenza Other Respir Viruses **2020**; 14:247–56.

42. Tripathi S, Al-Sayyed B, Gladfelter TR. Comparative epidemiology, hospital course, and outcomes of viral respiratory infections in hospitalized pediatric patients. Indian J Med Microbiol **2021**; 39:24–9.

43. Walsh EE, Wang L, Falsey AR, et al. Virus-specific antibody, viral load, and disease severity in respiratory syncytial virus infection. J Infect Dis **2018**; 218:208–17.

44. Leimanis Laurens ML, Jaji AM, Montgomery J, et al. Preadmission diet and zip code influences the pediatric critical care clinical course for infants with severe respiratory illness (N = 187). J Pediatr Intensive Care **2020**; 9: 277–883.

45. Shutes BL, Patel AB, Moore-Clingenpeel MD, Mejias A, Karsies TJ. Relationship of viral detection with duration of ventilation in critically ill infants with lower respiratory tract infection. Ann Am Thorac Soc **2021**; 18:1677–84.

46. Carroll CL, Faustino EV, Pinto MG, et al. A regional cohort study of the treatment of critically ill children with bronchiolitis. J Asthma **2016**; 53:1006–11.

47. Jorgensen J, Wei JL, Sykes KJ, et al. Incidence of and risk factors for airway complications following endotracheal intubation for bronchiolitis. Otolaryngol Head Neck Surg **2007**; 137:394–9.

48. Altman CA, Englund JA, Demmler G, et al. Respiratory syncytial virus in patients with congenital heart disease: a contemporary look at epidemiology and success of preoperative screening. Pediatr Cardiol **2000**; 21:433–8.

49. Bockova J, O'Brien KL, Oski J, et al. Respiratory syncytial virus infection in Navajo and White Mountain Apache children. Pediatrics **2002**; 110:e20.

50. Singleton RJ, Bulkow LR, Miernyk K, et al. Viral respiratory infections in hospitalized and community control children in Alaska. J Med Virol **2010**; 82:1282–90.

51. Tsou P, Vadivelan A, Kovvuri M, et al. Association between multiple respiratory viral infections and pediatric intensive care unit admission among infants with bronchiolitis. Arch Pediatr **2020**; 27:39–44.

52. Anderson EJ, DeVincenzo JP, Simões EAF, et al. SENTINEL1: two-season study of respiratory syncytial virus hospitalizations among U.S. Infants Born at 29 to 35 Weeks' gestational age not receiving immunoprophylaxis. Am J Perinatol **2020**; 37:421–9.

53. Children Hospital's Association. Pediatric health information system. https://www.childrenshospitals.org/phis. Accessed 20 January 2021.

54. 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.

55. Welliver RC Sr, Checchia PA, Bauman JH, Fernandes AW, Mahadevia PJ, Hall CB. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. Curr Med Res Opin **2010**; 26:2175–81.

56. Cai W, Buda S, Schuler E, Hirve S, Zhang W, Haas W. Risk factors for hospitalized respiratory syncytial virus disease and its severe outcomes. Influenza Other Respir Viruses **2020**; 14:658–70.

57. Prill MM, Langley GE, Winn A, Gerber SI. Respiratory syncytial virus-associated deaths in the United States according to death certificate data, 2005 to 2016. Health Sci Rep **2021**; 4:e428.

58. Sala KA, Moore A, Desai S, Welch K, Bhandari S, Carroll CL. Factors associated with disease severity in children with bronchiolitis. J Asthma **2015**; 52:268–72.

59. 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.