Pediatric Pulmonology 52:556–569 (2017)

Respiratory Syncytial Virus Hospitalization and Mortality: Systematic Review and Meta-Analysis

Renato T. Stein, MD,[1] Louis J. Bont, MD,[2] Heather Zar, MD,[3] Fernando P. Polack, MD,[4,5] Caroline Park, PharmD,[6] Ami Claxton, PhD,[7] Gerald Borok, PhD,[7] Yekaterina Butylkova, PharmD,[7] and Colleen Wegzyn, PharmD[6]*

Summary. Background: Respiratory syncytial virus (RSV) is a major public health burden worldwide. We aimed to review the current literature on the incidence and mortality of severe RSV in children globally. Methods: Systematic literature review and meta-analysis of published data from 2000 onwards, reporting on burden of acute respiratory infection (ARI) due to RSV in children. Main outcomes were hospitalization for severe RSV-ARI and death. Results: Five thousand two hundred and seventy-four references were identified. Fifty-five studies were included from 32 countries. The global RSV-ARI hospitalization estimates, reported per 1,000 children per year (95% Credible Interval (CrI), were 4.37 (2.98, 6.42) among children <5 years, 19.19 (15.04, 24.48) among children <1 year, 20.01 (9.65, 41.31) among children <6 months and 63.85 (37.52, 109.70) among premature children <1 year. The RSV-ARI global case-fatality estimates, reported per 1,000 children, (95% CrI) were 6.21 (2.64, 13.73) among children <5 years, 6.60 (1.85, 16.93) for children <1 year, and 1.04 (0.17, 12.06) among preterm children <1 year. Conclusions: A substantial proportion of RSV-associated morbidity occurs in the first year of life, especially in children born prematurely. These data affirm the importance of RSV disease in the causation of hospitalization and as a significant contributor to pediatric mortality and further demonstrate gestational age as a critical determinant of disease severity. An important limitation of case-fatality ratios is the absence of individual patient characteristics of non-surviving patients. Moreover, case-fatality ratios cannot be translated to population-based mortality. **Pediatr Pulmonol. 2017;52:556–569.**

[1]Department of Pediatrics, Hospital da PUCRS & Biomedical Research Institute, Porto Alegre, Brazil.

[2]Department of Pediatrics, University Medical Center Utrecht, Utrecht, The Netherlands.

[3]Department of Paediatrics and Child Health, Red Cross Childrens Hospital and MRC Unit on Child and Adolescent Health, University of Cape Town, Cape Town, South Africa.

[4]Fundacion INFANT, Buenos Aires, Argentina.

[5]Department of Pediatrics, Vanderbilt University Medical Center, Nashville, Tennessee.

[6]AbbVie Inc., North Chicago, Illinois.

[7]Doctor Evidence, LLC, Santa Monica, California.

Conflict of interest: RTS has been compensated as an advisor and has received a speaker's honorarium from AbbVie. HZ has received a speaker's honorarium from AbbVie. FPP has been compensated as an advisor and has received a speaker's honorarium from AbbVie. LJB has received compensation through the University Medical Center Utrecht from Ablynx, MedImmune, Janssen, and Regeneron, and has received research funding related to observational and interventional studies from AbbVie, MedImmune, and MeMed. CW and CP are employees of AbbVie and may hold AbbVie stock or stock options. YB, GB, and AC are employees of Doctor Evidence and received compensation from AbbVie for their participation in the database analysis. RTS, as primary author, CW, as corresponding author, and AbbVie, as sponsor, hereby provide assurances regarding the absence of bias in reporting these results.

*Correspondence to: Colleen M. Wegzyn, PharmD, AbbVie Inc., 1 North Waukegan Road, North Chicago, IL 60064-6075. E-mail: colleen.wegzyn@abbvie.com

Received 9 February 2016; Revised 24 June 2016; Accepted 18 July 2016.

DOI 10.1002/ppul.23570
Published online 14 October 2016 in Wiley Online Library (wileyonlinelibrary.com).

Key words: epidemiology; preterm; infant; morbidity; burden.

Funding source: AbbVie Inc.

INTRODUCTION

Respiratory syncytial virus (RSV) is a seasonal disease and causes an enormous burden on health systems across the world. RSV disease manifestations in children range from mild upper respiratory tract infection to severe respiratory infection including pneumonia or bronchio-litis which can lead to hospitalization and serious complications such as respiratory failure.[1–3] Certain high-risk groups, including premature infants; infants with underlying medical conditions such as chronic lung disease of prematurity (CLDP) or bronchopulmonary dysplasia (BPD); hemodynamically significant congenital heart disease (hsCHD); immunocompromised conditions; or severe neuromuscular disease, are prone to serious disease due to RSV with higher morbidity and mortality rates than those without these conditions.[4,5]

In addition to severe acute disease, evidence also suggests that children who had severe RSV infection early in life are more likely to develop subsequent wheezing during early childhood[6] and hyperreactive airways and asthma later in life.[7]

The reported incidence and mortality of RSV acute respiratory infection (ARI) is highly variable by geographic location, case ascertainment, populations under surveillance, and the diagnostic method used to identify RSV. In 2005, Nair et al.[3] estimated that there were 33.8 million new episodes of RSV-associated acute lower respiratory infections (ALRIs) worldwide in children <5 years of age, including 3.4 million episodes of severe RSV-ALRI requiring hospitalization with 66,000–190,000 deaths from RSV-associated ALRI in 2005.

The aim of this study was to review the global burden of RSV disease in children and update current published data. In addition we focused on prematurity as a risk factor for RSV disease as premature infants have been reported to be disproportionately affected by RSV, and at higher risk for worse outcomes due to interrupted lung development[8] and reduced maternally transmitted antibodies.[9]

METHODS

Search Strategy and Screening Criteria

This study was a systematic literature review and meta-analysis of published scientific evidence on the burden of severe ARI due to RSV (RSV-ARI). A technology-assisted search and screening was conducted at the direction of the authors by Doctor Evidence (Santa Monica, CA). Professional medical librarians, in collaboration with the authors, developed search strategies for Medline search (via PubMed) and Embase search (via Ovid; e-Appendix). The search was performed in February 2015, and was limited to published primary literature in the English language, human subjects, and children (birth to 5 years). The search terms used are detailed in the e-Appendix. The authors (CW, CP) reviewed all potentially relevant references independently and selected relevant publications for data analysis.

The study inclusion criteria for the systematic review were studies: (1) reporting the incidence of first episode of community acquired, medically attended, severe RSV-ARI in children ≤ 5 years of age not receiving RSV immunoprophylaxis with palivizumab. Cases of severe ARI included hospitalized ARI or hospitalized lower or acute lower respiratory infection, pneumonia, and bronchiolitis. Medically attended was defined as either hospitalized (on the basis of the assessment of the admitting physician) for RSV infection or outpatient visit (emergency department, urgent care, or pediatric clinic) with RSV-ARI; (2) reporting data on laboratory confirmed diagnosis of RSV through enzyme-linked immunosorbent assay, polymerase chain reaction (PCR; Multiplex), immunofluorescence (IF), culture, direct fluorescent antibody test (DFA), or by relevant International Classification of Diseases-9 (ICD-9) diagnosis codes; (3) research conducted from the year 2000 to the present date. Studies from pre- and post-2000 periods were included only if data were reported separately for the post-2000 period. As the molecular assays such as multiplex PCR, RT-PCR for respiratory virus detection did not become available for research/commercial use until the early 2000 s the date limit of 15 years (2000–2015) was used to capture studies that used molecular essays rather than older diagnostic methods with lower sensitivity and specificity.

Exclusion criteria for the systematic review were studies: (1) reporting data for children prophylaxed with palivizumab or other prevention strategies for RSV infection; (2) reporting data on treatment of RSV infection; (3) reporting data in special populations including children with cystic fibrosis or immunocompromised conditions; (4) reporting data for nosocomial acquired RSV-ARI; (5) reporting preliminary results such as an abstract or poster displayed at

a professional meeting, single case reports, letters/editorials, and commentaries.

Statistical Analysis

The two main outcomes were (1) hospitalization for severe RSV-ARI, measured as hospitalization rates per 1,000 children per year as defined above; and (2) death among the children with severe RSV-ARI, measured as case fatalities. The data for these primary outcomes were synthesized separately by chronological and gestational age categories (<6 months, <1 year, <2 years, 2–5 years, and <5 years, <1 year and preterm [≤36 weeks gestational age]). When sufficient data were available (i.e., a minimum of four studies), we also conducted analyses by geographic region. The delineation of regions was based on an attempt to define areas by the likeness of their inherent characteristics (i.e., population, economy, and physical environment). Subsequently, five regions were defined, which included Africa, Asia, Australia/Europe/United States, Gulf/Middle East, and Latin America.

The study data were synthesized by means of a random effect meta-analysis using a Bayesian framework. Models with a normal likelihood for the (log-transformed) hospitalization rate data and with a binomial likelihood for case fatality data were used. Prior distributions were chosen to be vague; a normal distribution with mean 0 and variance 10^3 for the (log) summary estimate (hospitalization rate or odds of fatality) and a uniform distribution of range 0–2 for the heterogeneity parameter were employed. Summary statistics (median and 95% credible interval [CrI]) are provided for each analysis, with a minimum of four studies. With a Bayesian approach, the results produce a point estimate and CrI, which arise from the posterior probability distribution. Analyses were performed using R (version 3.0.2) and Bayesian software WinBUGS (version 1.4.3; MRC Biostatistics Unit, Cambridge, UK).

RESULTS

In the first pass of the review strategy, 5,274 potentially relevant references were retrieved (3,628 from Medline and 1,646 from Embase). Of those references, 4,685 were rejected in the first pass (using title/abstract screening), the majority for wrong/divergent outcomes (N = 1,683) or not being a clinical study (n = 1,782). The remaining 589 potentially acceptable references were reviewed using a full-text screening and 293 references were further rejected for out-of-target variables: populations (n = 106), outcomes (n = 169), study design (n = 15), and other reasons (n = 3). From the 296 remaining studies, the majority of further rejections were due to insufficient incidence/mortality data (n = 126) and reporting of pre-2000 data (n = 67). In total, 55 studies were included in the report: 34 reported on the incidence of hospitalization for severe RSV-ARI and 37 reported on death among the children with severe RSV-ARI (Fig. 1).

Incidence of RSV-Associated Severe ARI Hospitalization

Thirty-four studies[10–41] from 26 countries that were published between 2002 and 2014, with RSV-associated ARI hospitalization rates for community-acquired, medically attended, laboratory-confirmed severe RSV-ARI in children <5 years of age, were included in the incidence analysis. The incidence estimates of RSV-associated ARI hospitalization (per 1,000 children per year) were stratified according to age and region (Table 1). The regional estimates for each age group were constructed from separate estimates at the study level, when four or more study-level estimates were available. Global estimates for each age group were constructed from all of the estimates at the study level. The studies estimated incidence for RSV-associated ARI hospitalization by utilizing a passive case ascertainment (patients presented to the health facility with ARI), active case ascertainment (by proactive means of disease monitoring via surveys and home visits), or a combination of both. Most studies (n = 44) used passive hospital or clinic-based case ascertainment, five studies used active community-based case ascertainment, and six studies used a combination approach. In the majority of included studies, RSV was confirmed using standard RSV detection methods (rapid antigen, DFA test, multiplex reverse transcription PCR, reverse transcriptase PCR, immunofluorescence, or other assays). In six studies, RSV-specific ICD-9 codes were used as a basis for case identification. Table 2 provides a summary of characteristics for studies included in the analysis.

Six studies reported incidence rates of RSV-associated ARI hospitalization among children <6 months of age. The global incidence estimate, inclusive of all studies (n = 6), was 20.01 (95 % CrI, 9.65–41.31). The study-level incidence estimates ranged from 9.50 (95% CrI, 8.61–10.48) for Guatemala to as high as 41.90 (95%CrI, 32.69–53.71) for the United States.

Eighteen studies provided incidence rates of RSV-associated ARI hospitalization among children <1 year of age. The global incidence estimate was 19.19 (95% CrI, 15.04–24.48). The study-level incidence estimates ranged from 7.85 (95% CrI, 5.55–11.10) for India to 50.69 (95% CrI, 28.07–91.54) for Denmark. In this age group, there was sufficient data to perform regional estimates of incidence for Asia and Australia/Europe/United States (i.e., greater than four study-level estimates within each region). Interestingly, the incidence was approximately 1.4 times greater in

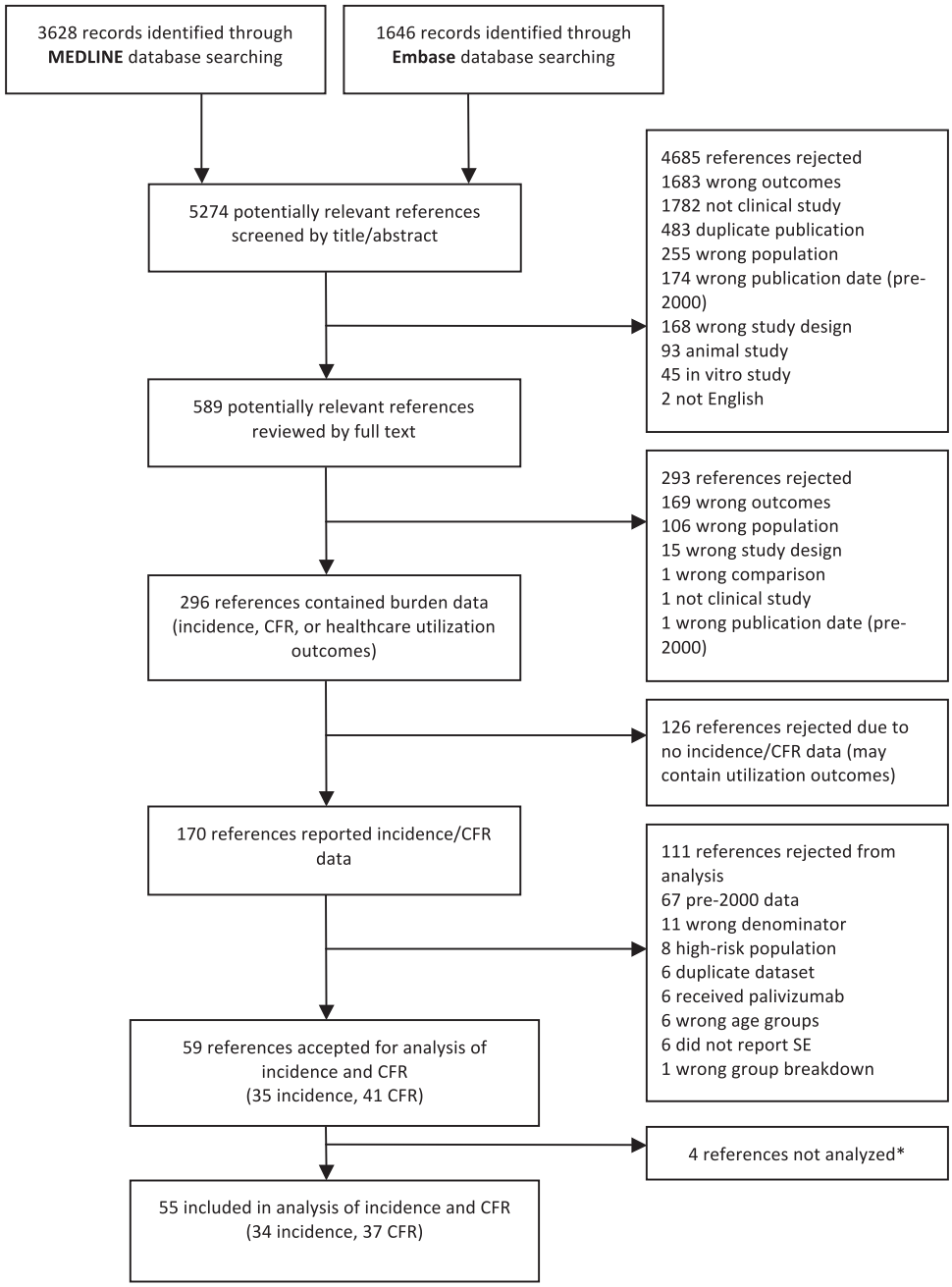

Fig. 1. PRISMA flow diagram: RSV incidence and case fatality analysis. CFR, case fatality ratio; RSV, respiratory syncytial virus; SE, standard error. *Insufficient number of studies for age group analysis.

Australia/Europe/United States (23.69; 95% CrI, 15.08–39.98) compared with Asia (16.40; 95% CrI, 7.79–34.08).

Fifteen studies provided incidence rates of RSV-associated ARI hospitalization among children <5 years of age. The global incidence estimate was 4.37 (95% CrI, 2.98–6.42), with study-level incidence estimates ranging from 1.40 (95% CrI, 0.97–2.03) for Mozambique to 11.20 (95% CrI, 10.61–11.82) for South Africa. The regional incidence estimates were similar for Africa (4.57; 95% CrI, 1.25–16.19) and Asia (4.95; 95% CrI, 2.69–8.95).

Six studies focused specifically on the incidence of RSV-associated ARI hospitalization among preterm children <1 year of age and resulted in a global estimate of 63.85 (95% CrI, 37.52–109.7). The incidence estimates at the study level ranged from 39.42 (95% CrI, 28.69–54.17) for the Netherlands to 116.20 (95% Crl 83.81, 161.10) for Peru.

TABLE 1— Estimates of Incidence of RSV-ARI Hospitalization for Children <6 Months to 5 Years of Age (Per 1,000 Children Per Year)

Age	Study	Incidence rate (95% CI)	Meta-analysis of incidence rates (95% CI)
Africa			
<6 months			
<1 year	Kenya[28]	11.07 (10.12–12.11)	n/a
	South Africa[25]	32.00 (29.55–34.65)	
	South Africa[33]	15.00 (9.59–23.45)	
<2 years			
2–5 years	South Africa[25]	4.00 (3.10–5.16)	n/a
<5 years	Kenya[28]	2.93 (2.50–3.43)	4.57 (1.25–16.19)
	Mozambique[29]	1.40 (0.97–2.03)	
	South Africa[25]	11.20 (10.61–11.82)	
	South Africa[33]	9.00 (7.53–10.76)	
<1year preterm			
Asia			
<6 months	Hong Kong[15]	31.12 (27.80–34.83)	n/a
	India[12]	13.68 (9.06–20.65)	
	Thailand[26]	11.95 (9.78–14.60)	
<1 year	Hong Kong[15]	23.34 (20.49–26.59)	16.40 (7.79–34.08)
	India[13]	14.00 (4.22–46.23)	
	India[12]	7.85 (5.55–11.10)	
	Thailand[20]	10.87 (9.82–12.03)	
	Thailand[26]	15.43 (13.73–17.34)	
	Vietnam[41]	40.90 (33.34–50.18)	
<2 years	Indonesia[17]	10.00 (9.25–10.82)	n/a
	Vietnam[40]	23.43 (21.11–26.00)	
2–5 years	Hong Kong[15]	3.39 (2.39–4.81)	n/a
	Thailand[26]	6.38 (5.77–7.06)	
<5 years	Bangladesh[27]	4.11 (2.64–6.40)	4.95 (2.69–8.95)
	India[12]	2.63 (2.01–3.44)	
	Taiwan[14]	2.32 (2.24–2.41)	
	Thailand[20]	5.07 (4.61–5.58)	
	Thailand[26]	9.81 (9.21–10.45)	
	Thailand[37]	5.80 (4.33–7.77)	
	Vietnam[40]	9.59 (8.71–10.56)	
<1 year preterm	Korea[32*]	45.29 (32.81–62.50)	n/a
Australia, Europe, United States			
<6 months	United States[22]	41.90 (32.69–53.71)	n/a
<1 year	Denmark[38]	50.69 (28.07–91.54)	23.69 (15.08–39.98)
	Germany[39]	27.21 (21.76–34.02)	
	United States[22]	27.40 (21.51–34.90)	
	United States[31]	17.38 (17.09–17.68)	
	United States[36]	26.00 (20.59–32.84)	
	United States[35]	14.40 (14.10–14.70)	
<2 years	Australia[16]	20.40 (17.51–23.76)	n/a
	Germany[39]	15.90 (12.93–19.55)	
	United States[23]	23.00 (22.70–23.30)	
2–5 years	Germany[39]	1.81 (1.07–3.06)	n/a
	United States[39]	0.80 (0.62–1.03)	
<5 years	United States[31]	4.53 (4.46–4.60)	n/a
	United States[39]	6.70 (5.42–8.28)	
<1 year preterm	France[68†]	64.26 (39.37–104.89)	n/a
	Netherlands[69‡]	39.42 (28.69–54.17)	
	United Kingdom[18§]	51.80 (35.99–74.53)	
Latin America			
<6 months	Argentina[19]	31.00 (28.60–33.60)	n/a
	Guatemala[24]	9.50 (8.61–10.48)	
<1 year	Argentina[19]	23.70 (22.31–25.18)	n/a
<2 years	Argentina[19]	14.10 (13.13–15.14)	
	Chile[11]	5.54 (4.70–6.52)	
2–5 years	Guatemala[24]	0.20 (0.14–0.26)	n/a

TABLE 1— (*Continued*)

Age	Study	Incidence rate (95% CI)	Meta-analysis of incidence rates (95% CI)
<5 years	Guatemala[24]	1.80 (1.68–1.93)	n/a
<1 year preterm	Brazil[10§]	99.01 (69.22–141.61)	n/a
	Peru[30‖]	116.20 (83.81–161.10)	
Gulf/Middle East			
<6 months			
<1 year	Egypt[34]	17.45 (16.24–18.75)	n/a
	Turkey[21]	13.40 (11.74–15.29)	
<2 years	Turkey[21]	7.70 (6.81–8.71)	n/a
2–5 years			
<5 years	Egypt[34]	2.42 (2.27–2.59)	n/a
<1 year preterm			
Global			
<6 months			20.01 (9.65–41.31)
<1 year			19.19 (15.04–24.48)
<2 years			13.42 (8.20–21.89)
2–5 years			1.71 (0.53–5.46)
<5 years			4.37 (2.98–6.42)
<1 year preterm			63.85 (37.52–109.7)

ARI, acute respiratory infection; CI, confidence interval; n/a, not analyzed; RSV, respiratory syncytial virus.
*Gestational age: <35 weeks.
†Gestational age: <33 weeks.
‡Gestational age: 32–36 weeks.
§Gestational age: <36 weeks.
‖Gestational age: <37 weeks.

Death Among the Children With Severe RSV-ARI, Measured as Case Fatality

Thirty-seven studies[10,14,17,19,20,22,24–32,34,37,42–62] from 24 countries published between 2002 and 2014, with suitable case fatality data among children <5 years of age with community-acquired, medically attended, confirmed RSV-ARI were included in the mortality analysis. The case fatality estimates (reported per 1,000 children) were stratified according to age and region (Table 3). The case fatality estimates for each age group at the regional level were constructed from separate estimates at the study level, when four or more study estimates were available. Global case fatality estimates for each age group were constructed from all of the estimates at the study level.

Twelve studies provided case fatality data among children <1 year of age with severe RSV-ARI. The estimated global case fatality, inclusive of all studies (n = 12), was 6.60 (95% CrI, 1.85–16.93). The study-level incidence estimates ranged from 0 in Taiwan, Thailand, Switzerland, Brazil, and Mexico, to 53.9 (11/204) in Egypt. In this age group, there were sufficient data to perform regional estimates of case fatality for Asia, which was 8.43 (95% CrI, 1.79–23.88).

Four studies from Brazil, Korea, and Peru focused specifically on case fatality among preterm children <1 year of age with severe RSV-ARI. The estimated global case fatality, inclusive of all studies (n = 4), was 1.04 (95% CrI, 0.17–12.06). Two studies were conducted in Brazil and resulted in different case fatality estimates, 0 and 33.3. The case fatality estimates for Korea and Peru were 0 and 27.8, respectively.

Eighteen studies provided case fatality data among children <5 years of age with severe RSV-ARI. The estimated global case fatality, inclusive of all studies (n = 18), was 6.21 (95% CrI, 2.64–13.73), with the highest rates reported from studies in Africa, including Kenya, Morocco, Mozambique, and South Africa.

DISCUSSION

Our analysis of 34 studies from 26 countries, representing data on the incidence of hospitalization for community-acquired, medically attended, severe RSV-ARI, demonstrates that a substantial proportion of RSV-associated morbidity occurs in the first year of life, especially in children with a history of prematurity. The global incidence of RSV-associated ARI hospitalization among preterm infants (63.85; 95% CrI, 37.52–109.7) was 3 times greater than was reported for term children <1 year of age (19.19; 95% CrI, 15.04–24.48). This is consistent with published data reporting earlier gestational age and younger chronological age to be associated with severe RSV disease and risk of RSV hospitalization.

The global incidence estimate of RSV-associated ARI hospitalization among children <6 months (20.01; 95 % CrI, 9.65–41.31) was similar compared with children <1

TABLE 2—Study Characteristics

Author, year	Country	Study period analyzed	Study population (description)	Study population (enrolled)	Surveillance method	RSV diagnosis method
Africa						
Robertson et al., 2004[33]	South Africa	April 2000–March 2001	Children <5 years old with ARI	NR	Passive	ELISA
Nokes et al., 2009[28]	Kenya	January 2002–December 2007	Children <5 years old with severe or very severe pneumonia	6,026	Passive	DFA
Jroundi et al., 2014[49]	Morocco	November 2010–December 2011	Children 2–59 months old admitted with respiratory symptomatology and WHO definition of clinical severe pneumonia	700	Passive	Multiplex RT-PCR
O'Callaghan-Gordo et al., 2011[29]	Mozambique	September 2006–September 2007	Children <5 years old admitted with clinical severe pneumonia	807	Passive	Multiplex RT-PCR
Cohen et al., 2015[46]	South Africa	February 2009–December 2012	Children <5 years old admitted with physician-diagnosed ARI	8,723	Passive	Multiplex RT-PCR
Madhi et al., 2003[52]	South Africa	April 2000–September 2001	Children <24 months old diagnosed with ARI	220	Passive	ELISA
Moyes et al., 2013[25]	South Africa	January 2010–December 2011	Children <5 years old admitted with physician-diagnosed neonatal sepsis or ARI	4,489	Passive	Multiplex RT-PCR
Venter et al., 2011[60]	South Africa	2006–2007	Children <5 years old	1,637	Passive	DFA, ELISA, Multiplex RT-PCR
Asia						
Nasreen et al., 2014[27]	Bangladesh	June 2010–October 2010	Children <5 years old with severe ARI	12,850	Active and passive	Multiplex RT-PCR
Leung et al., 2014[51]	China	January 2009–June 2011	Children with severe RSV requiring PICU admission	4,912	Passive	DFA and/or viral culture
Zhang et al., 2014[61]	China	January 2005–December 2009	Children admitted with RSV infection	959	Passive	DFA
Zhang et al., 2014[62]	China	March 2011–February 2012	Infants <1 year old with RSV-associated ARI	913	Passive	DFA
Chiu et al., 2010[15]	Hong Kong	October 2003–September 2006	Children <18 years old admitted with febrile ARI	1,031	Passive	DFA
Broor et al., 2007[13]	India	October 2001–December 2004	Newborns followed until 3 years	281	Active	DFA
Broor et al., 2014[12]	India	August 2009–July 2011	Children <5 years old admitted with an acute medical illness	245	Passive	RT-PCR
Hemalatha et al., 2010[48]	India	2007–2008	Children with respiratory infection (pneumonia, bronchiolitis, or upper respiratory infection)	126	Passive	ELISA
Djelantik et al., 2003[17]	Indonesia	2000–2001	Children <2 years old admitted with severe ARI	3,777	Passive	Rapid EIA
Park et al., 2012[32]	Korea	April 2007–September 2009	Newborn infants born <35 weeks gestational age and discharged from NICU	1,111	Active	Antigen test, culture
Cho et al., 2013[45]	South Korea	January 2009–May 2010	Neonates <1 month old admitted to the NICU because of ARI	108	Passive	Multiplex RT-PCR
Chen et al., 2005[44]	Taiwan	January 2001–December 2003	Children <5 years old admitted with ARI	650	Passive	Rapid EIA, culture
Chi et al., 2011[14]	Taiwan	2004–2007	Children with RSV-associated hospitalization	11,081	Passive	ICD-9 codes
Fry et al., 2010[20]	Thailand	September 2003–December 2007	Hospitalized patients with RSV infections (including pneumonia) from all age groups in a population-based surveillance	11,097	Passive	RT-PCR
Naorat et al., 2013[26]	Thailand	January 2008–December 2011	Children admitted with ARI	13,982	Passive	RT-PCR
Suntarattiwong et al., 2011[59]	Thailand	December 2007–August 2009	Children 1–12 months old admitted with ARI	349	Passive	RT-PCR
Suwanjutha et al., 2002[37]	Thailand	November 1998–February 2001	Children <5 years old in the community	7,890	Passive	IF
Yoshida et al., 2010[41]	Vietnam	February 2007–March 2008	Hospitalized children with ARI	958	Passive	Multiplex RT-PCR
Yoshida et al.,	Vietnam	April 2007–	Children 1–60 months old with ARI	1,786	Passive	Multiplex RT-PCR

TABLE 2— (*Continued*)

Author, year	Country	Study period analyzed	Study population (description)	Study population (enrolled)	Surveillance method	RSV diagnosis method
2013[40]		March 2010	in the community			
Australia, Europe, United States						
Dede et al., 2010[16]	Australia	January 2000–December 2004	Children <2 years old admitted with RSV	173	Passive	DFA
von Linstow et al., 2008[38]	Denmark	May 2004–May 2005	Healthy infants in the community	242	Active	ELISA, RT-PCR
Gouyon et al., 2013[68]	France	September 2008–April 2009	Infants admitted for bronchiolitis	554	Active and passive	IF
Weigl et al., 2002[39]	Germany	July 1994–June 2001	Newborn to 16-year-old children admitted with ARI	2,367	Passive	Multiplex RT-PCR
Gijtenbeek et al., 2014[69]	Netherlands	2002–2003	Children born moderately preterm, full-term, or early preterm	2,099	Passive	Antigen detection, cell culture
Stollar et al., 2014[58]	Switzerland	2010–2012	Children <1 year old admitted to the ED with acute bronchiolitis	202	Passive	ELISA, RT-PCR
Drysdale et al., 2013[18]	United Kingdom	2008–2009	Infants born at <36 weeks gestational age	177	Active	RT-PCR
Byington et al., 2015[43]	United States	2000–2011	Children <2 years old hospitalized with ICD-9-CM diagnosis codes for RSV pneumonia, RSV bronchiolitis, and bronchiolitis, other	NR	Passive	ICD-9 codes
Holman et al., 2004[22]	United States	2000–2001	Infants hospitalized with RSV	7,796	Passive	ICD-9 codes
Light et al., 2008[23]	United States	2001–2004	Children <24 months old hospitalized because of RSV-ARI	>23,000	Passive	ICD-9 codes, antigen detection or culture
Paramore et al., 2004[31]	United States	2000	Children with RSV-related discharge diagnosis	NR	Passive	ICD-9 codes
Sangaré et al., 2006[35]	United States	2000–2003	Infants with RSV-coded hospitalizations	45,330	Passive	ICD-9 codes
Stockman et al., 2012[36]	United States	1997–2006	Children <5 years old with ARI and RSV-related discharge diagnoses	NR	Passive	ICD-9 codes, RT-PCR, or viral culture
Gulf/Middle East						
Rowlinson et al., 2013[34]	Egypt	April 1, 2009–March 31, 2012 (hospital); May 1, 2011–April 30, 2012 (outpatient)	Hospitalized or outpatient children with respiratory illness	5,852	Passive	RT-PCR
El Kholy et al., 2013[47]	Egypt	February 2010–May 2011	Hospitalized children with severe ARI	240	Passive	RT-PCR
Khuri-Bulos et al., 2010[50]	Jordan	January 2007–March 2007	Children <5 years old admitted with ARI and/or fever	743	Active and passive	RT-PCR
Al-Muhsen et al., 2010[42]	Saudi Arabia	January 2003–January 2009	Children <6 months old with RSV-associated bronchiolitis admitted to the PICU	70	Passive	DFA
Hacimustafaoglu et al., 2013[21]	Turkey	March 2010–February 2011 (hospitalized)	Children ≤2 years old admitted for ARI	671	Passive	Immunochromatographic assay
Latin America						
Ferolla et al., 2013[19]	Argentina	2011	Children <2 years old with severe ARI and oxygen saturation <93%	2,587	Passive	RT-PCR
Arruda et al., 2014[10]	Brazil	January 2008–December 2010	Infants ≤35 weeks gestational age, followed for 1 year	310	Active and passive	RT-PCR
Oliveira et al., 2008[54]	Brazil	2000–2007	Children <5 years old with acute respiratory distress	475	Active and passive	DFA, RT-PCR
Pecchini et al., 2008[55]	Brazil	February 2005–September 2006	Children <5 years old admitted with ARI	455	Passive	IFA
Riccetto et al., 2006[57]	Brazil	April 2004–September 2004	Infants 0–12 months old admitted with ARI	152	Passive	DFA
Avendano et al., 2003[11]	Chile	January 1989–December 2000	Children <2 years old admitted with ARI	4,618	Passive	IFA

TABLE 2— (*Continued*)

Author, year	Country	Study period analyzed	Study population (description)	Study population (enrolled)	Surveillance method	RSV diagnosis method
Pineros et al., 2013[56]	Colombia	April 2005–April 2006	Infants <1 year old presenting to the ED with respiratory symptoms	717	Passive	Rapid IF
McCracken et al., 2013[24]	Guatemala	November 2007–April 2012	Hospital or clinic patients with ARI	6,626	Active	RT-PCR
Noyola et al., 2006[53]	Mexico	May 2003–April 2005	Hospitalized patients <3 years old with ARI	2,036	Passive	DFA
Ochoa et al., 2014[30]	Peru	March 2009–March 2010	Infants with a birth weight <1500 g and gestational age ≤37 weeks, followed for 1 year	222	Passive and active	IFA

ARI, acute respiratory infection; DFA, direct fluorescent antibody; ED, emergency department; EIA, enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; ICD-9-CM diagnosis codes: 079.6 (RSV infection), 480.1 (RSV pneumonia), 466.11 (RSV bronchiolitis), 466.19 (bronchiolitis, other); IF, immunofluorescence; IFA, indirect immunofluorescent assay; NICU, neonatal intensive care unit; NR, not reported; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; RT-PCR, (real-time) reverse transcriptase polymerase chain reaction; WHO, World Health Organization.

year of age (19.19; 95% CrI, 15.04–24.48). This finding is consistent with the results published by Nair et al.[3] They estimated the incidence of RSV-associated severe ALRI necessitating hospital admission among children <1 year of age in developing countries to be 17.9 (95% CI, 14.5–22.2) and 19 (95% CI, 14.6–24.8) in industrialized countries. Interestingly, we observed the incidence in children <1 year of age was approximately 1.4 times greater in Australia/Europe/United States (23.69; 95% CrI, 15.08–39.98) compared with Asia (16.40; 95% CrI, 7.79–34.08). This perhaps can be explained by differences in case ascertainment, greater access to care, and broader sampling in hospital settings in the former region.[63]

As expected, the global incidence estimate of RSV-associated ARI hospitalization among children <5 years of age (4.37; 95% CrI, 2.98–6.42) was lower compared with children <1 year of age (19.19; 95% CrI, 15.04–24.48). Similar to the results observed from children <1 year of age, our global estimate for children <5 years of age was consistent with the findings by Nair et al,[3] where the reported incidence for RSV-associated severe ALRI for children <5 years of age was 5.6 (95% CI, 4.3–7.4) for developing countries and 5.5 (95% CI, 4.2–7.2) for industrialized countries.

The global incidence estimates of RSV-ARI hospitalization among premature children <1 year of age were nearly 3 times greater than in children <1 year of age and 16 times higher than that of children <5 years of age with no history of prematurity, 63.85 (95% CrI, 37.52–109.7) versus 19.19 (95% CrI, 15.04–24.48) versus 4.37 (95% CrI, 2.98–6.42), respectively. These data clearly demonstrate the important role of RSV in the causation of hospitalization in premature children and gestational age as a critical determinant of disease severity.

Cause-specific mortality is an essential metric of population health intelligence and is vital to inform health care prioritization to target interventions to maximize population health. After malaria, RSV is the dominant pathogen-specific cause of post-neonatal death in the first year of life among infants worldwide.[64] Our analysis from 37 studies from 24 countries, published between 2002 and 2014, affirms the importance of RSV disease as a significant contributor to pediatric mortality.

The estimated global case fatality was lower among preterm children with severe RSV-ARI compared with term children; 1.04 (95% CrI, 0.17–12.06) episodes per 1,000 children at risk versus 6.60 (95% Crl, 1.85–16.93), respectively. However, as only four studies were included in the analysis among preterm children, the paucity of mortality information in this population precludes any conclusions. In addition, 3 of the studies were conducted in developing countries which may introduce bias toward misleadingly low estimates. Further many ALRTI deaths in children in lower middle income countries (LMICs) occur outside a health facility, but published case fatality rates predominantly report in-hospital deaths. Further data regarding childhood mortality in community settings is needed.

The estimated global case fatality for children <5 years of age with severe RSV-ARI was similar to the case fatality estimates in a previous report[3] where Nair et al. estimated the RSV-associated ALRI case fatality ratio (CFR) to be 0.3 and 2.1 per 100 children <5 years of age in industrialized and developing countries, respectively.

Our findings should be interpreted cautiously as there are several limitations to this study. Incidence of RSV-associated ARI hospitalization and case fatality estimates among children with severe RSV-ARI are

TABLE 3— Case Fatality for Children <6 Months to 5 Years of Age (Per 1,000 Children)

Age	Study	Case fatality per 1,000 children (n/N)	Meta-analysis of case fatality (95% CrI)
Africa			
<6 months			
<1 year	Kenya[28]	21.5 (15/697)	n/a
<1 year preterm			
<2 years	South Africa[52]	0 (0/25)	n/a
2–5 years			
<5 years	Kenya[28]	23.8 (21/884)	18.45 (6.13–56.13)
	Morocco[49]	32 (4/125)	
	Mozambique[29]	71.4 (2/28)	
	South Africa[46]	6.4 (14/2204)	
	South Africa[25]	4 (3/751)	
	South Africa[60]	61.5 (8/130)	
Asia			
<6 months	China[61]	0 (0/39)	n/a
	South Korea[45]	0 (0/46)	
<1 year	China[51]	30.8 (2/65)	8.43 (1.79–23.88)
	China[62]	9.9 (9/913)	
	Taiwan[44]	0 (0/83)	
	Thailand[20]	0 (0/148)	
	Thailand[59]	19.2 (2/104)	
<1 year preterm	Korea[32*]	0 (0/37)	n/a
<2 years	China[61]	0 (0/47)	12.12 (1.61–45.17)
	India[48]	53.6 (3/56)	
	Indonesia[17]	19.2 (12/625)	
	Taiwan[44]	0 (0/121)	
2–5 years	Taiwan[44]	0 (0/32)	n/a
<5 years	Bangladesh[27]	0 (0/22)	1.11 (0.25–3.05)
	Taiwan[44]	0 (0/153)	
	Taiwan[14]	1.2 (13/11,081)	
	Thailand[20]	2.4 (1/425)	
	Thailand[26]	1.2 (1/802)	
	Thailand[37]	0 (0/45)	
Australia, Europe, United States			
<6 months	Switzerland[58]	0 (0/130)	n/a
<1 year			
<1 year preterm			
<2 years	United States[43]	0.9 (121/141,245)	n/a
2–5 years			
<5 years	United States[31]	1.3 (23/17,539)	n/a
Latin America			
<6 months	Mexico[53]	0 (0/81)	n/a
<1 year	Brazil[57]	0 (0/26)	n/a
	Mexico[53]	0 (0/121)	
<1 year preterm	Brazil[10†]	33.3 (1/30)	n/a
	Brazil[57*]	0 (0/7)	
	Peru[30‡]	27.8 (1/36)	
<2 years	Argentina[19]	11.3 (9/797)	n/a
	Colombia[56]	9.3 (2/216)	
	Mexico[53]	0 (0/144)	
2–5 years			
<5 years	Brazil[54]	50 (1/20)	n/a
	Brazil[55]	21.7 (2/92)	
	Guatemala[24]	25.1 (34/1353)	
Gulf/Middle East			
<6 months			
<1 year	Egypt[47]	53.9 (11/204)	n/a
	Egypt[34]	0 (0/350)	
	Saudi Arabia[42]	14.3 (1/70)	
<1 year preterm			
<2 years			
2–5 years			
<5 years	Jordan[50]	8.6 (4/467)	n/a

Continued

TABLE 3— (*Continued*)

Age	Study	Case fatality per 1,000 children (n/N)	Meta-analysis of case fatality (95% CrI)
	Egypt[34]	0 (0/467)	
Global			
<6 months			n/a
<1 year			6.60 (1.85–16.93)
<1 years preterm			1.04 (0.17–12.06)
2 years			4.68 (1.23–14.70)
<2–5 years			n/a
<5 year			6.21 (2.64–13.73)

CrI, credible interval; n, number of deaths; N, number of children included in analysis; n/a, not analyzed.
*Gestational age: <35 weeks.
†Gestational age: <36 weeks.

uncertain and can be greatly overestimated or underestimated due to a variety of reasons. Methodological differences such as case ascertainment, and differences among the diagnostic assays used to identify RSV infection may affect estimates. In addition, estimates can be affected by surveillance bias due to disparity in access to hospital care and resources across countries. Finally, in developing countries where the vast majority of deaths due to RSV occur, a high percentage of deaths occur outside of the hospital setting and are not routinely captured or recorded.[19] An important limitation regarding the case-fatality estimates was the absence of individual patient characteristics of non-surviving patients. Consequently, the role of comorbidity, and coinfections in RSV-related deaths could not be evaluated. Moreover, case-fatality ratios cannot be translated to population-based mortality. In addition, our study did not examine the influence of other socio-demographic risk factors for RSV-associated ARI hospitalization or case fatality beyond prematurity. Among them, low birth weight, being male, maternal smoking, siblings, history of atopy, no breastfeeding and crowding (>7 persons in the household), have been observed to be significantly associated with RSV-associated ALRI.[65] Our search excluded non-English language studies. Other limitations include large variability in countries represented in each age group category; therefore any inference from comparing age groups should also be interpreted with caution and some studies had small sample sizes, which led to variability in meta-analytic estimates. Finally, there are minimal published data for several countries with large, high-burden populations, such as specific areas in Latin America and Africa. There are no data for the incidence of RSV-associated ARI hospitalizations or case fatality among Canadian First Nation and Inuit children meeting the inclusion criteria for this systematic review. Notably, Inuit children living in the Baffin (Qikiqtani) Region, Nunavut, have the highest known rates of RSV bronchiolitis requiring hospitalization, with rates up to 484 per 1,000 infants <6 months of age,[66] versus 27 per 1,000 infants in temperate Canada and the United States.[22] Also, Inuit children often experience repeated, severe RSV infections in the same season, which is unusual elsewhere.[67]

A unique aspect and strength of this review include the use of technology-assisted search and screening. Doctor Evidence utilizes a proprietary software platform for literature searching and screening called DOC™ Library, a web-based, centralized literature search and repository tool that retrieves, stores, and categorizes literature. The DOC™ Library software technology supports and enhances the work of experienced librarians to maximize retrieval of relevant studies and to minimize return of irrelevant results through pattern recognition, keyword recognition, correction and/or re-categorization of studies due to inaccuracies found in subject heading descriptor (e.g., MeSH/Emtree) and Pubmed/Embase filters, automated creation of an accurate PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram, and machine learning/natural language processing. This technology helps to provide a more comprehensive and relevant set of results than typical literature searching yields.

CONCLUSIONS

Using a different search methodology, these data are remarkably similar to the findings by Nair et al.[3] and affirm the importance of RSV disease in the causation of hospitalization and as a significant contributor to pediatric mortality. A unique contribution from our study is the systematic review and meta-analysis specific to premature children, which further demonstrate gestational age as a critical determinant of disease severity. A gap in mortality data is the absence of individual patient characteristics and, consequently, the role of comorbidity in RSV-related deaths cannot be excluded. Given the burden of RSV worldwide, and until an effective RSV vaccine is globally available, more research is urgently needed to improve prevention and care across different

populations and resource settings to reduce childhood morbidity and mortality associated with this disease.

ACKNOWLEDGMENTS

We would like to acknowledge Alexandra G. Ellis, MSc, for providing statistical advice and support; Melinda Davies, MLS (Medical Librarian), for help developing and running search strategies; and Ashwani Srivastava, MD, for help with study review and selection. Editorial support in the form of formatting the manuscript for submission was provided by Complete Publication Solutions, LLC (North Wales, PA) and funded by AbbVie.

REFERENCES

1. Bryce J, Boschi-Pinto C, Shibuya K, Black RE. WHO Child Health Epidemiology Reference Group. WHO estimates of the causes of death in children. Lancet 2005;365:1147–1152.
2. Iwane MK, Farnon EC, Gerber SI. Importance of global surveillance for respiratory syncytial virus. J Infect Dis 2013; 208:S165–S166.
3. Nair H, Nokes DJ, Gessner BD, Dherani M, Madhi SA, Singleton RJ, O'Brien KL, Roca A, Wright PF, Bruce N, et al. Global burden of acute lower respiratory infections due to respiratory syncytial virus in young children: a systematic review and meta-analysis. Lancet 2010;375:1545–1555.
4. Hall CB, Simoes EA, Anderson LJ. Clinical and epidemiologic features of respiratory syncytial virus. Curr Top Microbiol Immunol 2013;372:39–57.
5. Sommer C, Resch B, Simoes EA. Risk factors for severe respiratory syncytial virus lower respiratory tract infection. Open Microbiol J 2011;5:144–154.
6. Blanken MO, Rovers MM, Molenaar JM, Winkler-Seinstra PL, Meijer A, Kimpen JL, Bont L. Dutch RSV Neonatal Network. Respiratory syncytial virus and recurrent wheeze in healthy preterm infants. N Engl J Med 2013;368:1791–1799.
7. Mohapatra SS, Boyapalle S. Epidemiologic, experimental, and clinical links between respiratory syncytial virus infection and asthma. Clin Microbiol Rev 2008;21:495–504.
8. Langston C, Kida K, Reed M, Thurlbeck WM. Human lung growth in late gestation and in the neonate. Am Rev Respir Dis 1984;129:607–613.
9. Yeung CY, Hobbs JR. Serum-gamma-G-globulin levels in normal premature, post-mature, and "small-for-dates" newborn babies. Lancet 1968;1:1167–1170.
10. Arruda E, Jones MH, Escremim de Paula F, Chong D, Bugarin G, Notario G, Matsuno AK, Pitrez PM, Vo P, Suzuki C, et al. The burden of single virus and viral coinfections on severe lower respiratory tract infections among preterm infants: a prospective birth cohort study in Brazil. Pediatr Infect Dis J 2014;33: 997–1003.
11. Avendano LF, Palomino MA, Larranaga C. Surveillance for respiratory syncytial virus in infants hospitalized for acute lower respiratory infection in Chile (1989 to 2000). J Clin Microbiol 2003;41:4879–4882.
12. Broor S, Dawood FS, Pandey BG, Saha S, Gupta V, Krishnan A, Rai S, Singh P, Erdman D, Lal RB. Rates of respiratory virus-associated hospitalization in children aged <5 years in rural northern India. J Infect 2014;68:281–289.
13. Broor S, Parveen S, Bharaj P, Prasad VS, Srinivasulu KN, Sumanth KM, Kapoor SK, Fowler K, Sullender WM. A prospective three-year cohort study of the epidemiology and virology of acute respiratory infections of children in rural India. PLoS ONE 2007;2:e491.
14. Chi H, Chang IS, Tsai FY, Huang LM, Shao PL, Chiu NC, Chang LY, Huang FY. Epidemiological study of hospitalization associated with respiratory syncytial virus infection in Taiwanese children between 2004 and 2007. J Formos Med Assoc 2011; 110:388–396.
15. Chiu SS, Chan KH, Chen H, Young BW, Lim W, Wong WH, Peiris JS. Virologically confirmed population-based burden of hospitalization caused by respiratory syncytial virus, adenovirus, and parainfluenza viruses in children in Hong Kong. Pediatr Infect Dis J 2010;29:1088–1092.
16. Dede A, Isaacs D, Torzillo PJ, Wakerman J, Roseby R, Fahy R, Clothier T, White A, Kitto P. Respiratory syncytial virus infections in Central Australia. J Paediatr Child Health 2010;46: 35–39.
17. Djelantik IG, Gessner BD, Soewignjo S, Steinhoff M, Sutanto A, Widjaya A, Linehan M, Moniaga V, Ingerani. Incidenceand clinical features of hospitalization because of respiratory syncytial virus lower respiratory illness among children less than two years of age in a rural Asian setting. Pediatr Infect Dis J 2003;22: 150–157.
18. Drysdale SB, Alcazar-Paris M, Wilson T, Smith M, Zuckerman M, Broughton S, Rafferty GF, Peacock JL, Johnston SL, Greenough A. Rhinovirus infection and healthcare utilisation in prematurely born infants. Eur Respir J 2013;42:1029–1036.
19. Ferolla FM, Hijano DR, Acosta PL, Rodriguez A, Duenas K, Sancilio A, Barboza E, Caria A, Gago GF, Almeida RE, et al. Macronutrients during pregnancy and life-threatening respiratory syncytial virus infections in children. Am J Respir Crit Care Med 2013;187:983–990.
20. Fry AM, Chittaganpitch M, Baggett HC, Peret TC, Dare RK, Sawatwong P, Thamthitiwat S, Areerat P, Sanasuttipun W, Fischer J, et al. The burden of hospitalized lower respiratory tract infection due to respiratory syncytial virus in rural Thailand. PLoS ONE 2010;5:e15098.
21. Hacimustafaoglu M, Celebi S, Bozdemir SE, Ozgur T, Ozcan I, Guray A, Cakir D. RSV frequency in children below 2 years hospitalized for lower respiratory tract infections. Turk J Pediatr 2013;55:130–139.
22. Holman RC, Curns AT, Cheek JE, Bresee JS, Singleton RJ, Carver K, Anderson LJ. Respiratory syncytial virus hospitalizations among American Indian and Alaska Native infants and the general United States infant population. Pediatrics 2004;114: e437–e444.
23. Light M, Bauman J, Mavunda K, Malinoski F, Eggleston M. Correlation between respiratory syncytial virus (RSV) test data and hospitalization of children for RSV lower respiratory tract illness in Florida. Pediatr Infect Dis J 2008;27:512–518.
24. McCracken JP, Prill MM, Arvelo W, Lindblade KA, Lopez MR, Estevez A, Muller ML, Munoz F, Bernart C, Cortez M, et al. Respiratory syncytial virus infection in Guatemala, 2007-2012. J Infect Dis 2013;208:S197–S206.
25. Moyes J, Cohen C, Pretorius M, Groome M, von Gottberg A, Wolter N, Walaza S, Haffejee S, Chhagan M, Naby F, et al. South, African Severe Acute Respiratory Illness Surveillance G. Epidemiology of respiratory syncytial virus-associated acute lower respiratory tract infection hospitalizations among HIV-infected and HIV-uninfected South African children, 2010-2011. J Infect Dis 2013;208:S217–S226.
26. Naorat S, Chittaganpitch M, Thamthitiwat S, Henchaichon S, Sawatwong P, Srisaengchai P, Lu Y, Chuananon S, Amornintapichet T, Chantra S, et al. Hospitalizations for acute lower

respiratory tract infection due to respiratory syncytial virus in Thailand, 2008-2011. J Infect Dis 2013;208:S238–S245.
27. Nasreen S, Luby SP, Brooks WA, Homaira N, Al Mamun A, Bhuiyan MU, Rahman M, Ahmed D, Abedin J, Rahman M, et al. Population-based incidence of severe acute respiratory virus infections among children aged <5 years in rural Bangladesh, June-October 2010. PLoS ONE 2014;9:e89978.
28. Nokes DJ, Ngama M, Bett A, Abwao J, Munywoki P, English M, Scott JA, Cane PA, Medley GF. Incidence and severity of respiratory syncytial virus pneumonia in rural Kenyan children identified through hospital surveillance. Clin Infect Dis 2009;49:1341–1349.
29. O'Callaghan-Gordo C, Bassat Q, Morais L, Diez-Padrisa N, Machevo S, Nhampossa T, Nhalungo D, Sanz S, Quinto L, Alonso PL, et al. Etiology and epidemiology of viral pneumonia among hospitalized children in rural Mozambique: a malaria endemic area with high prevalence of human immunodeficiency virus. Pediatr Infect Dis J 2011;30:39–44.
30. Ochoa TJ, Bautista R, Davila C, Salazar JA, Bazan C, Guerra O, Llanos JP, Lopez L, Zea-Vera A, Ecker L. Respiratory syncytial virus-associated hospitalizations in pre-mature infants in Lima, Peru. Am J Trop Med Hyg 2014;91:1029–1034.
31. 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;22:275–284.
32. Park HW, Lee BS, Kim AR, Yoon HS, Kim BI, Song ES, Kim WT, Lim J, Kim S, Jin HS, et al. Epidemiology of respiratory syncytial virus infection in infants born at less than thirty-five weeks of gestational age. Pediatr Infect Dis J 2012;31: e99–e104.
33. Robertson SE, Roca A, Alonso P, Simoes EA, Kartasasmita CB, Olaleye DO, Odaibo GN, Collinson M, Venter M, Zhu Y, et al. Respiratory syncytial virus infection: denominator-based studies in Indonesia, Mozambique, Nigeria and South Africa. Bull World Health Organ 2004;82:914–922.
34. Rowlinson E, Dueger E, Taylor T, Mansour A, Van Beneden C, Abukela M, Zhang X, Refaey S, Bastawy H, Kandeel A. Incidence and clinical features of respiratory syncytial virus infections in a population-based surveillance site in the Nile Delta Region. J Infect Dis 2013;208:S189–S196.
35. Sangaré L, Curtis MP, Ahmad S. Hospitalization for respiratory syncytial virus among California infants: disparities related to race, insurance, and geography. J Pediatr 2006;149:373–377.
36. Stockman LJ, Curns AT, Anderson LJ, Fischer-Langley G. Respiratory syncytial virus-associated hospitalizations among infants and young children in the United States, 1997-2006. Pediatr Infect Dis J 2012;31:5–9.
37. Suwanjutha S, Sunakorn P, Chantarojanasiri T, Siritantikorn S, Nawanoparatkul S, Rattanadilok Na Bhuket T, Teeyapaiboonsilpa P, Preutthipan A, Sareebutr W, Puthavathana P. Respiratory syncytial virus-associated lower respiratory tract infection in under-5-year-old children in a rural community of central Thailand, a population-based study. J Med Assoc Thai 2002;85: S1111–S1119.
38. von Linstow ML, Hogh M, Nordbo SA, Eugen-Olsen J, Koch A, Hogh B. A community study of clinical traits and risk factors for human metapneumovirus and respiratory syncytial virus infection during the first year of life. Eur J Pediatr 2008;167: 1125–1133.
39. Weigl JA, Puppe W, Schmitt HJ. Seasonality of respiratory syncytial virus-positive hospitalizations in children in Kiel, Germany, over a 7-year period. Infection 2002; 30:186–192.
40. Yoshida LM, Suzuki M, Nguyen HA, Le MN, Dinh Vu T, Yoshino H, Schmidt WP, Nguyen TT, Le HT, Morimoto K, et al. Respiratory syncytial virus: co-infection and paediatric lower respiratory tract infections. Eur Respir J 2013;42:461–469.
41. Yoshida LM, Suzuki M, Yamamoto T, Nguyen HA, Nguyen CD, Nguyen AT, Oishi K, Vu TD, Le TH, Le MQ, et al. Viral pathogens associated with acute respiratory infections in Central Vietnamese children. Pediatr Infect Dis J 2010;29:75–77.
42. Al-Muhsen SZ. Clinical profile of respiratory syncytial virus (RSV) bronchiolitis in the intensive care unit at a tertiary care hospital. Curr Pediatr Res 2010;14:75–80.
43. Byington CL, Wilkes J, Korgenski K, Sheng X. Respiratory syncytial virus-associated mortality in hospitalized infants and young children. Pediatrics 2015;135:e24–e31.
44. Chen CJ, Jeng MJ, Yuan HC, Wu KG, Soong WJ, Hwang B. Epidemiology of respiratory syncytial virus in children with lower respiratory tract infection. Acta Paediatr Taiwan 2005;46:72–76.
45. Cho HJ, Shim SY, Son DW, Sun YH, Tchah H, Jeon IS. Respiratory viruses in neonates hospitalized with acute lower respiratory tract infections. Pediatr Int 2013;55:49–53.
46. Cohen C, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, Hellferscee O, Dawood H, Chhagan M, Naby F, et al. Epidemiology of viral-associated acute lower respiratory tract infection among children <5 years of age in a high HIV prevalence setting, South Africa, 2009–2012. Pediatr Infect Dis J 2015;34:66–72.
47. El Kholy AA, Mostafa NA, El-Sherbini SA, Ali AA, Ismail RI, Magdy RI, Hamdy MS, Soliman MS. Morbidity and outcome of severe respiratory syncytial virus infection. Pediatr Int 2013;55: 283–288.
48. Hemalatha R, Swetha GK, Seshacharyulu M, Radhakrishna KV. Respiratory syncytial virus in children with acute respiratory infections. Indian J Pediatr 2010;77:755–758.
49. Jroundi I, Mahraoui C, Benmessaoud R, Moraleda C, Tligui H, Seffar M, Kettani SC, Benjelloun BS, Chaacho S, Maaroufi A, et al. The epidemiology and aetiology of infections in children admitted with clinical severe pneumonia to a university hospital in Rabat, Morocco. J Trop Pediatr 2014;60:270–278.
50. Khuri-Bulos N, Williams JV, Shehabi AA, Faouri S, Al Jundi E, Abushariah O, Chen Q, Ali SA, Vermund S, Halasa NB. Burden of respiratory syncytial virus in hospitalized infants and young children in Amman, Jordan. Scand J Infect Dis 2010;42:368–374.
51. Leung TF, Lam DS, Miu TY, Hon KL, Chau CS, Ku SW, Lee RS, Chow PY, Chiu WK. Ng DK, Hong Kong Society of Paediatric Respirology RSVCG. Epidemiology and risk factors for severe respiratory syncytial virus infections requiring pediatric intensive care admission in Hong Kong children. Infection 2014;42: 343–350.
52. Madhi SA, Venter M, Alexandra R, Lewis H, Kara Y, Karshagen WF, Greef M, Lassen C. Respiratory syncytial virus associated illness in high-risk children and national characterisation of the circulating virus genotype in South Africa. J Clin Virol 2003;27: 180–189.
53. Noyola DE, Zuviri-Gonzalez A, Castro-Garcia JA, Ochoa-Zavala JR. Impact of respiratory syncytial virus on hospital admissions in children younger than 3 years of age. J Infect 2007;54:180–184.
54. Oliveira TF, Freitas GR, Ribeiro LZ, Yokosawa J, Siqueira MM, Portes SA, Silveira HL, Calegari T, Costa LF, Mantese OC, et al. Prevalence and clinical aspects of respiratory syncytial virus A and B groups in children seen at Hospital de Clinicas of Uberlandia, MG, Brazil. Mem Inst Oswaldo Cruz 2008;103:417–422.
55. Pecchini R, Berezin EN, Felicio MC, Passos SD, Souza MC, Lima LR, Ueda M, Matsumoto TK, Durigon EL. Incidence and clinical characteristics of the infection by the respiratory syncytial virus in children admitted in Santa Casa de Sao Paulo Hospital. Braz J Infect Dis 2008;12:476–479.
56. Pineros JG, Baquero H, Bastidas J, Garcia J, Ovalle O, Patino CM, Restrepo JC. Respiratory syncytial virus infection as a cause of

hospitalization in population under 1 year in Colombia. J Pediatr (RioJ) 2013;89:544–548.
57. Riccetto AG, Ribeiro JD, Silva MT, Almeida RS, Arns CW, Baracat EC. Respiratory syncytial virus (RSV) in infants hospitalized for acute lower respiratory tract disease: incidence and associated risks. Braz J Infect Dis 2006;10:357–361.
58. Stollar F, Alcoba G, Gervaix A, Argiroffo CB. Virologic testing in bronchiolitis: does it change management decisions and predict outcomes?. Eur J Pediatr 2014;173:1429–1435.
59. Suntarattiwong P, Sojisirikul K, Sitaposa P, Pornpatanangkoon A, Chittaganpitch M, Srijuntongsiri S, Chotpitayasunondh T. Clinical and epidemiological characteristics of respiratory syncytial virus and influenza virus associated hospitalization in urban Thai infants. J Med Assoc Thai 2011;94:S164—S171.
60. Venter M, Lassauniere R, Kresfelder TL, Westerberg Y, Visser A. Contribution of common and recently described respiratory viruses to annual hospitalizations in children in South Africa. J Med Virol 2011;83:1458–1468.
61. Zhang T, Zhu Q, Zhang X, Ding Y, Steinhoff M, Black S, Zhao G. Clinical characteristics and direct medical cost of respiratory syncytial virus infection in children hospitalized in Suzhou. China. Pediatr Infect Dis J 2014;33:337–341.
62. Zhang XB, Liu LJ, Qian LL, Jiang GL, Wang CK, Jia P, Shi P, Xu J, Wang LB. Clinical characteristics and risk factors of severe respiratory syncytial virus-associated acute lower respiratory tract infections in hospitalized infants. World J Pediatr 2014;10:360–364.
63. Mills A. Health care systems in low- and middle-income countries. N Engl J Med 2014;370:552–557.
64. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V, Abraham J, Adair T, Aggarwal R, Ahn SY, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012;380:2095–2128.
65. Shi T, Balsells E, Wastnedge E, Singleton R, Rasmussen ZA, Zar HJ, Rath BA, Madhi SA, Campbell S, Vaccari LC, et al. Risk factors for respiratory syncytial virus associated with acute lower respiratory infection in children under five years: systematic review and meta-analysis. Journal of global health 2015;5:020416.
66. Banerji A, Bell A, Mills EL, McDonald J, Subbarao K, Stark G, Eynon N, Loo VG. Lower respiratory tract infections in Inuit infants on Baffin Island. CMAJ 2001;164:1847–1850.
67. Karron RA, Singleton RJ, Bulkow L, Parkinson A, Kruse D, DeSmet I, Indorf C, Petersen KM, Leombruno D, Hurlburt D, et al. Severe respiratory syncytial virus disease in Alaska native children. RSV Alaska Study Group. J Infect Dis 1999;180:41–49.
68. Gouyon JB, Roze JC, Guillermet-Fromentin C, Glorieux I, Adamon L, Di Maio M, Miloradovich T, Anghelescu D, Pinquier D, Escande B, et al. Hospitalizations for respiratory syncytial virus bronchiolitis in preterm infants at <33 weeks gestation without bronchopulmonary dysplasia: the CASTOR study. Epidemiol Infect 2013;141:816–826.
69. Gijtenbeek RG, Kerstjens JM, Reijneveld SA, Duiverman EJ, Bos AF, Vrijlandt EJ. RSV infection among children born moderately preterm in a community-based cohort. Eur J Pediatr 2015;174: 435–442.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.