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Respiratory syncytial virus hospitalization and mortality: Systematic review and meta-analysis

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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.**

Keywords: epidemiology, preterm, infant, morbidity, burden

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 bronchiolitis which can lead to hospitalization and serious complications such as respiratory failure.[1], [2], [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).

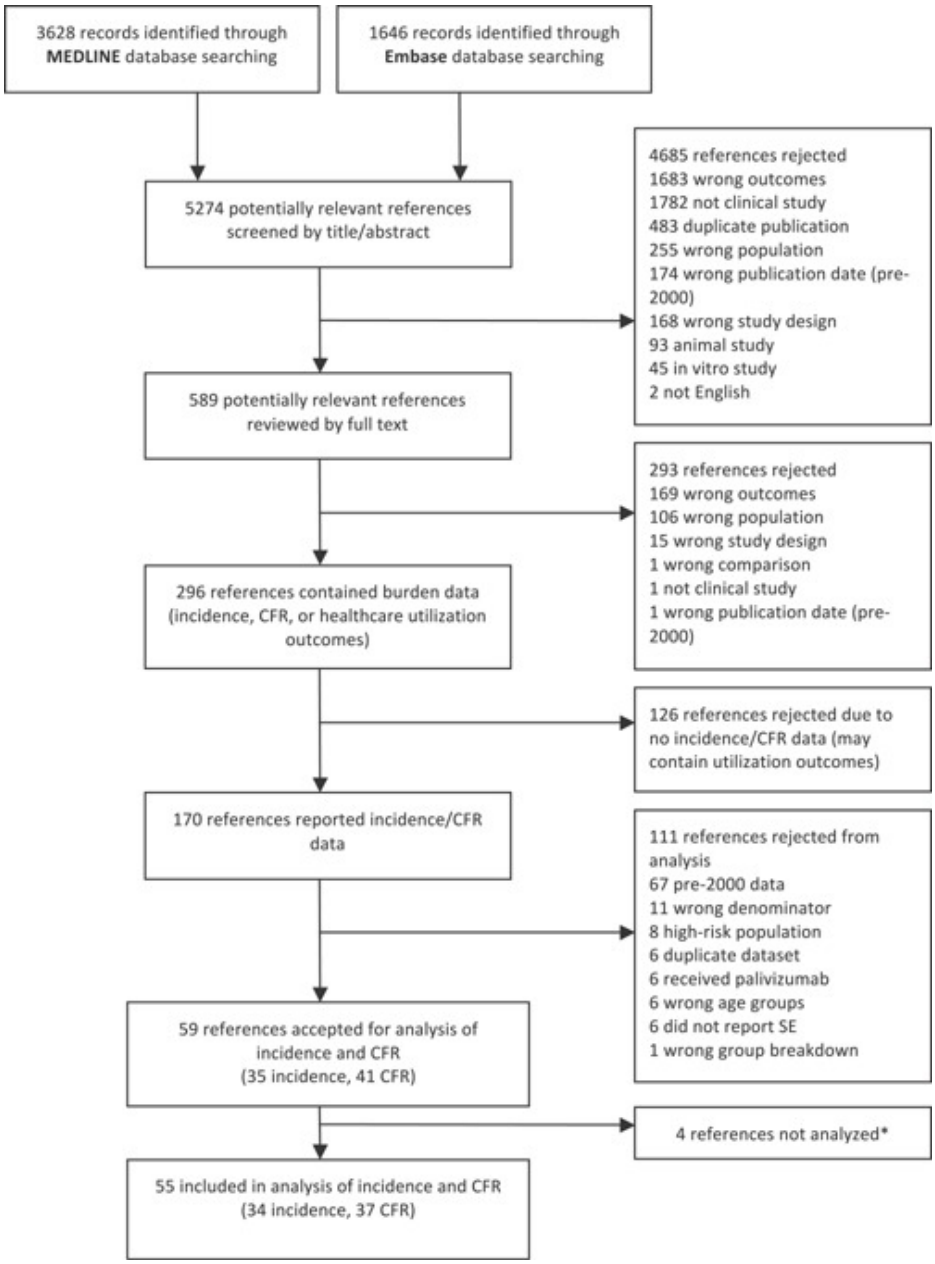

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Figure 1

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.

Incidence of RSV-Associated Severe ARI Hospitalization

Thirty-four studies10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 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.

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)	

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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.

Table 2

Study Characteristics

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
Cho et al., 2013[45]	South Korea	January 2009–May 2010	Neonates <1 month old admitted to the NICU because of ARI	108	Passive	Multiple
Chen et al., 2005[44]	Taiwan	January 2001–December 2003	Children <5 years old admitted with ARI	650	Passive	Rapid E
Chi et al., 2011[14]	Taiwan	2004–2007	Children with RSV-associated hospitalization	11,081	Passive	ICD-
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
Nao	Thailand	January	Children	13,982	Passive	RT

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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.

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 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.

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

Thirty-seven studies[10, 14, 17, 19, 20, 22, 24, 25, 26, 27, 28, 29, 30, 31, 32, 34, 37, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 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.

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)	

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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.
‡Gestational age: <37 weeks.

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 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 report3 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 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.

Supporting information

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

Supporting Information.

Click here for additional data file.(16K, docx)

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Notes

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.

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