Respiratory Syncytial Virus–Associated Mortality in Hospitalized Infants and Young Children

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abstract

BACKGROUND AND OBJECTIVE: Respiratory syncytial virus (RSV) is a common cause of pediatric hospitalization, but the mortality rate and estimated annual deaths are based on decades-old data. Our objective was to describe contemporary RSV-associated mortality in hospitalized infants and children aged <2 years.

METHODS: We queried the Healthcare Cost and Utilization Project Kids' Inpatient Database (KID) for 2000, 2003, 2006, and 2009 and the Pediatric Health Information System (PHIS) administrative data from 2000 to 2011 for hospitalizations with *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis codes for RSV infection and mortality.

RESULTS: The KID data sets identified 607 937 RSV-associated admissions and 550 deaths (9.0 deaths/10 000 admissions). The PHIS data set identified 264 721 RSV-associated admissions and 671 deaths (25.4 deaths/10 000 admissions) ($P < .001$ compared with the KID data set). The 2009 KID data set estimated 42.0 annual deaths (3.0 deaths/10 000 admissions) for those with a primary diagnosis of RSV. The PHIS data set identified 259 deaths with a primary diagnosis of RSV, with mortality rates peaking at 14.0/10 000 admissions in 2002 and 2003 and decreasing to 4.0/10 000 patients by 2011 (odds ratio: 0.27 [95% confidence interval: 0.14–0.52]). The majority of deaths in both the KID and PHIS data sets occurred in infants with complex chronic conditions and in those with other acute conditions such as sepsis that could have contributed to their deaths.

CONCLUSIONS: Deaths associated with RSV are uncommon in the 21st century. Children with complex chronic conditions account for the majority of deaths, and the relative contribution of RSV infection to their deaths is unclear.

WHAT'S KNOWN ON THIS SUBJECT: Respiratory syncytial virus (RSV) infection is a common cause of pediatric hospitalizations. Mortality rates associated with RSV hospitalizations are based on estimates from studies conducted decades ago. Accurate understanding of mortality is required for identifying high-risk infants and children.

WHAT THIS STUDY ADDS: Mortality associated with RSV is uncommon in the 21st century, with annual deaths far lower than previous estimates. The majority of deaths occurred in infants with complex chronic conditions or in those with life-threatening conditions in addition to RSV infection.

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Respiratory syncytial virus (RSV) is one of the most common infections of childhood. Almost all children experience RSV infection by age 2 years.[1] In young children, RSV infection often manifests as bronchiolitis or pneumonia and is a common cause of both outpatient visits and hospital admission.[2] RSV may result in mortality.[3,4] However, because public health agencies do not require deaths due to RSV to be reported (unlike influenza deaths in children), the relative contribution of RSV infection to childhood mortality is unclear.

Using data from a single tertiary center from 1976 to 1980, the Institute of Medicine estimated that there were 4500 RSV-associated deaths annually in children aged <5 years, with 60% of deaths (~2700) occurring in infants.[5] The estimate was based on an assumption that 5% of infants and children hospitalized with RSV infection in the United States would die. Over the decades, there have been significant improvements in medical technology, and a mortality rate of 5% for US infants and children hospitalized with RSV infection is unlikely to reflect contemporary experience. More recent analyses found significantly lower estimates for bronchiolitis and RSV-associated mortality, with estimates of ≤510 deaths annually in children aged <5 years, with 80% (≤408) occurring in infants.[4] Another study estimated 214 deaths in infants aged <1 year due to RSV and an additional 132 deaths in children aged 1 to 4 years.[3] These studies monitored trends only through the 1990s. Data from the first decade of the 21st century demonstrate a significant decline in bronchiolitis hospitalizations in the United States.[6] It is possible that trends in RSV-associated mortality have also changed.

Accurate estimates of RSV-associated mortality may help to guide prevention and treatment strategies. Mortality is also an important variable in cost-effectiveness studies. Recent studies of cost-effectiveness for palivizumab have produced estimates that differ markedly.[7] Differences in mortality estimates included in the models strongly influence the cost-effectiveness ratios, which in turn may influence prophylaxis guidelines such as those published by the American Academy of Pediatrics.[8]

Large administrative databases offer an opportunity to use data coded from inpatient encounters to monitor trends in health care utilization and outcomes, including mortality. The objectives of the present study were to describe contemporary RSV mortality rates and to identify conditions associated with RSV mortality in hospitalized infants and children aged <2 years. We used the Agency for Healthcare Research and Quality (AHRQ) and Healthcare Cost Utilization Project (HCUP) Kids' Inpatient Database (KID) and the Pediatric Health Information System (PHIS) database.

METHODS

Human Subjects

An AHRQ and HCUP data use agreement and training was completed for the KID data set. The Children's Hospital Association approved use of the PHIS data set. The research was reviewed by the institutional review board of the University of Utah and was deemed exempt and classified as non–human subjects research.

Database Description and Queries

Two national pediatric databases were used to describe the annual number of inpatient admissions and deaths associated with *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) codes for RSV infection. We queried the HCUP KID database for 2000, 2003, 2006, and 2009[9–12] and the PHIS administrative database from 2000 to 2011.[13] We identified hospitalizations with ICD-9-CM diagnosis codes 480.1 (RSV pneumonia), 466.11 (RSV bronchiolitis), and 466.19 (bronchiolitis, other) in infants and children aged <2 years. The codes were chosen to try and maximize the number of admissions and deaths potentially related to RSV. Bronchiolitis may be caused by many viral pathogens,[14] but RSV is the most common, and diagnostic testing may not always be performed. Although including ICD-9-CM code 466.19 for case detection may falsely elevate the RSV mortality rate due to the potential inclusion of deaths from viruses other than RSV, this code is commonly used when diagnostic testing is not performed and during months when RSV is known to be the most common pathogen. We chose to focus on the age range younger than 2 years because the majority of hospitalizations[15] and deaths occur in infants,[3,4] and the American Academy of Pediatrics recommendations for the use of palivizumab prophylaxis currently do not extend to children aged >2 years.[8]

HCUP KID

The KID is compiled by the AHRQ and is the only all-payer inpatient data set for children in the United States. The unweighted data include discharge information for ~3 million pediatric hospitalizations each year, and weighted estimates for ~7 million discharges can be determined. The large size and weighting allow calculation of national estimates for both rare and common conditions.[16]

We analyzed cross-sectional data for hospitalizations for the years 2000, 2003, 2006, and 2009.[9–12] States that participate in HCUP provide discharge-level data for all inpatient discharges for children from short-term, nonfederal general and specialty hospitals. Data are available every 3 years. State participation in KID increased from 22 in 1997 to 44 in 2009. In 2009, the KID database

contained information on 7.4 million weighted discharges from 4121 community and children's hospitals in 44 states.

All admissions meeting the aforementioned criteria for RSV-associated hospitalization were extracted from the KID database, including: sampling weight, admission year, admission month, discharge quarter, admission age, length of stay in days, discharge disposition, flag for death, and ICD-9-CM coding. The denominator used to calculate an RSV mortality rate was total RSV-associated admissions. To classify whether an RSV-associated admission or death occurred within the RSV season (November–March),[17] we used discharge quarter, length of stay, and admit month.

PHIS Database

Operated by the Children's Hospital Association, the PHIS is an administrative database that captures inpatient data from 44 specialty children's hospitals in the United States.[13] The PHIS data represent a sample of children's hospitals, and participating hospitals may choose to contribute specific data elements. The PHIS data set has not been designed to be a representative sample of all children's hospitals and, unlike the KID data set, cannot be used to generate national estimates.[18] The same criteria used to identify RSV-associated admissions within the KID data set were applied to the PHIS database. RSV admissions, mortality rate, total RSV deaths, and RSV deaths during RSV season were calculated for each year from 2000 through 2011.

Additional Data Obtained From KID and PHIS Data Sets

Additional information was gathered from both data sets for infants and children with RSV-associated deaths, including: whether the death had a primary ICD-9-CM code for RSV; complex chronic conditions (CCC)[19]; surgical complications (using >300 ICD-9-CM codes); cardiac arrest, 427.5 (cardiac arrest), 779.85 (newborn cardiac arrest), V1253 (history of cardiac arrest), 99.60 (cardiopulmonary resuscitation), 99.63 (closed chest cardiac massage); and sepsis, 995.91 (sepsis), 995.92 (severe sepsis), 785.52 (septic shock), 771.81 (newborn septicemia), 790.7 (bacteremia), 04.184 (anaerobe infection [necrotizing enterocolitis (NEC)]), 04.185 (Gram-negative bacterial infection NEC), 04.189 (bacterial infection NEC), 038.0 (streptococcal septicemia), 038.10 (staphylococcal septicemia not otherwise specified), 038.11 (methicillin-susceptible *Staphylococcus aureus* septicemia), 038.12 (methicillin-resistant *S aureus* septicemia), 038.19 (staphylococcal septicemia NEC),038.2 (pneumococcal septicemia), 038.3 (anaerobic septicemia), 038.40 (Gram-negative septicemia NEC), 038.41 (*Haemophilus influenzae* septicemia), 038.42 (*Escherichia coli* septicemia), 038.43 (*Pseudomonas* septicemia), 038.44 (*Serratia* septicemia), 038.49 (Gram-negative septicemia NEC), 038.8 (septicemia NEC), 038.9 (septicemia not otherwise specified), and 040.0 (gas gangrene). Interfacility transfers were also evaluated because these transfers could result in an underestimation of mortality.

Statistical Analysis

We performed analyses taking into account the complex sampling and weighting scheme of KID by using sampling survey procedures in SAS version 9.3 (SAS Institute, Inc, Cary, NC). Numbers of RSV admissions, RSV deaths, RSV mortality rates, and number of RSV deaths occurring during RSV season were generated in each of the study years. For mortality rates, 95% confidence intervals (CIs) were calculated based on binomial distribution. To calculate KID yearly admission and death estimates, we weighted our estimates by using the sampling weights from each of the sample years. This method allowed us describe the RSV admissions and deaths across the study period, while taking into account the differences in the KID sampling frame across time and the different numbers of hospitals that contributed data to the PHIS database each year. To calculate PHIS yearly admission and death estimates, we weighted our estimates by using the total number of PHIS RSV admissions for each study year.

To determine whether differences between groups were significant, 2-sample unpooled t tests with unequal variances were used and 2-proportion unpooled z tests were used to compare rates. A significance level of $\alpha = 0.05$ was used to determine statistical significance. Odds ratios (ORs) and 95% CIs were calculated when a comparison was made between different years of study.

RESULTS

RSV-Associated Hospitalizations and Mortality Rates in KID and PHIS Data Sets

The KID data sets identified a total of 607 937 RSV-associated admissions and 550 deaths in the 2000, 2003, 2006, and 2009 data sets (9.0 deaths/10 000 admissions). The PHIS data set identified a total of 264 721 RSV-associated admissions and 671 deaths from 2000 to 2011 (25.4 deaths/10 000 admissions) ($P < .001$ compared with the KID data set). Interfacility transfers in the KID data set occurred in 2.2% of encounters overall, with 0.4% of encounters in a children's hospital resulting in a transfer. The PHIS data set identified that 1.3% of its overall emergency department volume consisted of interfacility transfers.[20]

All annual RSV-associated admissions, deaths, and mortality rates for the KID and PHIS data sets are shown in Table 1. The annual mortality rates were higher in the PHIS data set for the years 2000, 2003, 2006, and 2009 compared with

TABLE 1 RSV-Associated Annual Admissions and Deaths in the HCUP KID and PHIS Data Sets

Discharge Year	RSV-Associated Annual Admissions	RSV-Associated Annual Deaths	RSV-Associated Annual Deaths per 10 000 Admissions	Odds Ratio (95% CI) and *P* Value (Mortality Rate)
	N	*N*	*N* (95% CI)	
HCUP KID (no. of states/no. of hospitals)				
2000 (27/2784)	15 4046	161	10.4 (7.3–13.6)	Ref
2003 (36/3438)	15 6279	141	9.0 (6.8–11.1)	0.86 (0.69–1.08)
2006 (38/3739)	15 6367	127	8.1 (6.9–10.3)	0.78 (0.62–0.98)
2009 (44/4121)	14 1245	121	8.5 (6.7–10.4)	0.82 (0.65–1.04)
PHIS (no. of hospitals)[a]				
2000 (33)	15 675	53	33.8 (26.2–44.0)	
2001 (35)	19 166	49	25.6 (18.8–32.9)	
2002 (35)	19 319	62	32.1 (24.9–40.9)	
2003 (37)	18 630	64	34.4 (26.8–44.0)	
2004 (39)	19 505	48	24.6 (19.0–32.8)	
2005 (41)	20 310	57	28.1 (22.2–35.9)	
2006 (41)	23 330	57	24.4 (18.9–32.1)	
2007 (43)	24 321	54	22.2 (16.9–29.2)	
2008 (43)	24 014	56	23.3 (17.9–30.0)	
2009 (43)	25 314	56	22.1 (17.0–28.8)	
2010 (44)	27 381	68	24.8 (19.7–31.0)	
2011 (44)	27 756	47	16.9 (13.0–22.0)	

[a] OR: 0.75 (95% CI: 0.64–0.87), $P < .001$; 2006–2011 compared with 2000–2005.

the mortality rates in the KID data sets ($P < .01$ for all years). In the KID data set, the RSV mortality rate ranged from a high of 10.4/10 000 in 2000 to a low of 8.1/10 000 in 2006 (OR: 0.78 [95% CI: 0.62–0.98]). The mortality rates in the PHIS data set ranged from a high of 34.4/10 000 in 2003 to a low of 16.9/10 000 in 2011; PHIS mortality rates were lower in the later years of the study period (2006–2011) compared with the earlier years (2000–2005) (OR: 0.75 [95% CI: 0.64–0.87]).

The diagnostic codes associated with admissions and mortality varied. The ICD-9-CM diagnosis code of 466.19, which identifies bronchiolitis due to other infectious organisms, accounted for 41% and 43% of admissions and 24% and 27% of the deaths in the KID and PHIS data sets, respectively. The use of this code increased significantly over the study period in patients who had died (18% to 35% in KID and 17% to 46% in PHIS; $P < .001$ for both) but did not change for admissions overall.

RSV-Associated Mortality According to Season and Primary Diagnosis

The majority of RSV-associated mortality occurred between the months November and March (ie, the typical RSV season in the United States) in both data sets, with 70% to 77% of deaths in the KID data sets and 61% to 71% in the PHIS data sets occurring during these months.

The KID data sets identified 262 deaths with a primary diagnosis code for RSV. The RSV-associated mortality rate in these patients peaked at 6.5/10 000 admissions in 2000 and decreased to 3.0/10 000 admissions by 2009 (OR: 0.45 [95% CI: 0.32–0.66]). The PHIS data set identified 259 deaths with a primary diagnosis code for RSV. The RSV-associated mortality for these patients peaked at 14.0/10 000 admissions in 2002 and 2003 and decreased to 4.0/10 000 patients in 2011 (OR: 0.27 [95% CI: 0.14–0.52]).

Characteristics of Infants and Children With RSV-Associated Mortality

Characteristics of infants and young children with RSV-associated mortality are shown in Table 2. The proportions were similar for the majority of variables in the KID 2000, 2003, and 2006 data sets compared with 2009 (data not shown); for ease of comparison, only 2009 data are reported in Table 2. The exceptions included the primary diagnosis of RSV, which decreased significantly from the 2000 through the 2009 data sets (61% in 2000 vs 34% in 2009; $P < .001$) and the presence of CCC (60% in 2000 vs 76% in 2009; $P = .007$) and other conditions associated with death (63% in 2000 vs 82% in 2009; $P = .001$), which all increased significantly in the 2009 data set.

The majority of deaths in both data sets occurred in infants aged ≤12 months (85% of deaths in the KID data set and 77% of deaths in the PHIS data set). The mean age at death was 6.2 months in the 2009 KID data set and 7.5 months in the PHIS data set.

The majority of RSV-associated deaths occurred in infants and children with CCC. CCC increased with age and in both data sets. In the KID and PHIS data sets, respectively, 68% and 76% of infants aged ≤12 months who died had CCC compared with 85% and 84% of those aged 13 to 24 months ($P < .001$ for both). In both data sets, cardiovascular conditions were the most frequent single CCC identified, and nearly 40% of children who died had ≥2 CCC identified.

TABLE 2 Characteristics of Infants and Children With RSV-Associated Hospital Mortality

Variable	No. (%) of RSV-Associated Deaths	
	KID 2009	PHIS 2000–2011
Annual deaths	121 (100)	56[a]
Deaths occurring in a children's hospital	58 (48)	56 (100)
Deaths during RSV season, November–March	84 (70)	39 (70)
Deaths with a primary ICD-9-CM code for RSV	42 (34)	21 (38)
Death associated with CCC, any	92 (76)	44 (79)
Cardiovascular condition	45 (37)	25 (45)
Neuromuscular condition	32 (26)	11 (20)
Respiratory condition	26 (21)	10 (19)
Congenital or genetic condition	15 (13)	11 (19)
Multiple conditions, range: 2–5	47 (39)	21 (37)
Other conditions associated with death[b]	99 (82)	42 (74)
Sepsis	50 (41)	24 (42)
Cardiac arrest	41 (34)	18 (32)
Surgical complication	33 (28)	18 (32)
Hospital length of stay >30 days	45 (38)	21 (37)

[a] Mean number of annual deaths.
[b] Subjects may have had >1 condition.

Those patients who died had prolonged hospital stays, with a mean duration of 40.5 days in the 2009 KID data set and 40.2 days in the PHIS data set. Those who died outside of the typical RSV season (ie, who died in April–October) had longer hospital stays than those who died during the typical season: 74.9 days compared with 25.7 days ($P < .001$) in the 2009 KID data set and 63.5 days compared with 30.6 days ($P < .001$) in the PHIS data set. The majority of those who died had ICD-9-CM codes for potentially life-threatening conditions such as sepsis or surgical complications in addition to RSV infection.

DISCUSSION

We report estimates of RSV mortality in infants and children aged <2 years based on 2 national data sources over the course of the first decade of the 21st century. RSV mortality rates declined significantly in both data sets. They both indicated that mortality during RSV-associated hospitalizations is uncommon, occurring in 3 to 4/10 000 admissions in those with a primary diagnosis of RSV in the KID and PHIS data sets, respectively. The KID data set estimated 121 deaths nationally in infants and children with RSV-associated admissions, 84 deaths during RSV season, and 42 deaths with a primary diagnosis of RSV in 2009. The PHIS data set had a mean of 56 deaths per year, with 39 during RSV season and 21 with a primary diagnosis of RSV. The annual deaths documented in these contemporary data sources are 5 to 100 times lower than 20th century estimates.[3,4] Both data sets increased in size during the study period and identified characteristics of infants and children who died during RSV-associated hospitalizations that were almost identical. The size of the data sets and the concordance of the findings enhance the generalizability of the results. The majority of deaths occurred in children who had CCC and other life-threatening conditions such as sepsis. Overall, RSV mortality was more common in the tertiary children's hospitals of the PHIS data set compared with the KID data, perhaps reflecting the medical complexity of children cared for in these facilities.[21]

RSV is one of the most significant causes of infection and hospitalization in young children in the United States and worldwide.[17] The number of deaths in young infants and children during RSV-associated hospitalizations is an important public health measurement. Our analysis provides mortality rates for infants and children aged <2 years with RSV-associated hospitalizations. Both data sets provided mortality rates for a variety of situations, including death during the traditional RSV season, and for those with a primary diagnosis of RSV. These mortality rates are lower than previous estimates, which reported mortality rates up to 5% of admissions.[5] For those with a primary diagnosis of RSV, mortality rates were similar in both data sets at 3 to 4 deaths per 10 000 admissions. The KID data set, estimates nationally, only 42 deaths annually with a primary diagnosis of RSV. The number of deaths with a primary diagnosis of RSV is comparable to the number of annual deaths for children aged <2 years associated with influenza (9–56 deaths/year reported during 2004–2013 seasons),[22] for which effective vaccines are available.

The relatively low RSV-associated mortality identified in our analysis may have several explanations. The first (and most likely) reason for the low findings is the advances in medical care that have occurred in the decades since publication of the last estimates. Advances in the care of preterm infants have resulted in decreased major morbidity in this population, including less chronic lung disease, a major risk factor for severe RSV infection.[23] Second, advances in the care of infants and children outside of the NICUs have also occurred, and much of the care for those with bronchiolitis has been moved from the inpatient to the outpatient setting.[24] It is also possible that the virus itself has changed[25,26] and that changes could have resulted in decreasing morbidity. The use of palivizumab, first licensed in the United States in 1998, is unlikely to account for the significant changes observed in mortality. Palivizumab has not been associated with a reduction in mortality in any

randomized controlled trial.[7,8] Furthermore, the number of infants receiving palivizumab each year is small, and the greatest burden of RSV disease is in previously healthy term infants who are not eligible to receive prophylaxis. In a recent study, <1% of the Medicaid birth cohorts in Florida and Texas received palivizumab.[27] In another multicenter study, only 9% of hospitalized children had ever received palivizumab.[2] Finally, infants who receive palivizumab are generally those with prematurity or CCC, conditions that may also predispose them to death.[28]

Accurate estimates of mortality in the 21st century can inform cost-effectiveness analyses for the use of prophylaxis for the prevention of RSV in high-risk groups and can also be used in the evaluation of experimental preventive and treatment strategies.[29] Mortality is an important variable in economic models. In models that examine the cost-effectiveness of different prophylaxis strategies for the prevention of RSV, mortality rates (when included) drive final cost-effectiveness ratios and should not be based on unsupported assumptions.[7]

The present study identified many important characteristics of infants and children with RSV-associated mortality. Our confidence in the results was strengthened by the consistency seen in the KID and PHIS data sets. First, as demonstrated in previous studies,[3,4] the majority of deaths identified in children occurred in infants. Infants represented 85% of deaths in the KID data set and 77% in the PHIS data set. Infants and children who died also commonly had CCC, with cardiovascular and neuromuscular conditions the most common. Nearly 40% of the deaths in both data sets occurred in medically fragile infants and children with ≥2 CCC. Those infants and children with RSV-associated deaths had long hospital stays, which further illustrates their medical fragility. Although the mean hospital stay for infants and young children with RSV bronchiolitis is ∼2.5 days,[6] infants and children with RSV-associated mortality in our study had hospitals stays that were ∼40 days in both the KID and PHIS data sets. Those whose deaths occurred outside of the traditional RSV season had even longer stays.

The duration of hospitalization before death raises questions regarding the role of RSV in the deaths of these children. The duration of hospitalization may indicate that RSV infection was present during the hospitalization but may have been remote from the actual death. Our finding that the majority of children who died had other potentially life-threatening conditions (including bacterial sepsis and surgical complications during their RSV-associated hospitalizations) supports this possibility. The administrative data sets do not allow us to identify the exact cause of death for each child; however, ∼30% of deaths occurred outside of the typical RSV season and <40% of those who died registered in either of the data sets had a primary diagnosis code for RSV.

The present study had several limitations. First, we used ICD-9-CM diagnosis codes to identify RSV-associated hospitalizations. These codes potentially include all causes of bronchiolitis and may overestimate RSV infections. However, our goal was to identify all deaths potentially associated with RSV hospitalization. The mortality rates were low in both data sets, and the total annual deaths predicted by using the KID data set were orders of magnitude lower than previous estimates. Our mortality rates were similar to recent results from the KID data set for bronchiolitis.[6] This finding is not unexpected because bronchiolitis is the most common presentation of RSV infection in this age group, and RSV is the most common cause of bronchiolitis. Second, we were not able to capture all transfers that occurred between facilities. However, the proportions of children transferred were low in both data sets. In the KID data set, transfers from community hospitals to tertiary children's hospitals accounted for the majority of transfers. By including the PHIS data set, we may have captured a portion of these transfers that resulted in mortality. Third, we were not able to confirm RSV infection in all cases. The ICD-9-CM code 466.19 (bronchiolitis, other) increased significantly over the study period. The increase may reflect the move to molecular diagnostic testing in hospital settings and the identification of viral pathogens other than RSV associated with bronchiolitis admissions.[14] If deaths were due to other viruses, the importance of RSV as a cause of mortality in young children is even less than we report. Fourth, we were not able to capture palivizumab use. However, because palivizumab has never been shown to decrease mortality and is used infrequently, variation in palivizumab administration is unlikely to account for the changes in mortality rates observed. Fifth, we could not identify nosocomial RSV infections. Finally, we could not confirm the exact cause of death in the cases identified. It is likely that, given the medical complexity of the majority of infants and children who died, multiple factors other than RSV infection may have contributed to their deaths. Consideration of making RSV-associated mortality in children a reportable condition, similar to influenza, is indicated.

CONCLUSIONS

Despite these limitations, we are able to draw several conclusions. First, RSV-associated hospitalization and mortality have decreased in the 21st century. Although our data may overestimate the number of

RSV-associated deaths, the number of annual deaths in the United States is low. Infants, especially those with CCC, represent the majority of RSV-associated deaths in the United States. Infants with CCC represent a vulnerable population who, along with the elderly, experience the greatest mortality burden from RSV.[3,30] These populations should be prioritized if a safe and effective RSV vaccine is developed. Our findings may help to inform policy makers as they model the costs associated with RSV prevention and treatment strategies, including palivizumab and investigational therapeutics and vaccines under development.

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REFERENCES

1. Glezen WP, Taber LH, Frank AL, Kasel JA. Risk of primary infection and reinfection with respiratory syncytial virus. *Am J Dis Child*. 1986;140(6):543–546
2. Hall CB, Weinberg GA, Iwane MK, et al. The burden of respiratory syncytial virus infection in young children. *N Engl J Med*. 2009;360(6):588–598
3. Thompson WW, Shay DK, Weintraub E, et al. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA*. 2003;289(2):179–186
4. 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(1):16–22
5. Institute of Medicine. The prospects for immunizing against respiratory syncytial virus. *New Vaccine Development: Establishing Priorities*. Vol. 1. Washington, DC: National Academies Press; 1986;397–409
6. Hasegawa K, Tsugawa Y, Brown DF, Mansbach JM, Camargo CA Jr. Trends in bronchiolitis hospitalizations in the United States, 2000-2009. *Pediatrics*. 2013;132(1):28–36
7. Andabaka T, Nickerson JW, Rojas-Reyes MX, Rueda JD, Bacic Vrca V, Barsic B. Monoclonal antibody for reducing the risk of respiratory syncytial virus infection in children. *Cochrane Database Syst Rev*. 2013;4:CD006602
8. American Academy of Pediatrics Committee on Infectious Diseases; American Academy of Pediatrics Bronchiolitis Guidelines Committee. Updated guidance for palivizumab prophylaxis among infants and young children at increased risk of hospitalization for respiratory syncytial virus infection. *Pediatrics*. 2014;134(2):415–420
9. Healthcare Cost and Utilization Project. Kids' Inpatient Database, 2000. Rockville, MD: Agency for Health Care Research and Quality; 2003
10. Healthcare Cost and Utilization Project. Kids' Inpatient Database 2003. Rockville, MD: Agency for Health Care Research and Quality; 2005
11. Healthcare Cost and Utilization Project. Kids Inpatient Database 2006. Rockville, MD: Agency for Health Care Research and Quality; 2008
12. Healthcare Cost and Utilization Project. Kids' Inpatient Database 2011. Rockville, MD: Agency for Health Care Research and Quality; 2011
13. Kittle K, Currier K, Dyk L, Newman K. Using a pediatric database to drive quality improvement. *Semin Pediatr Surg*. 2002;11(1):60–63
14. Stempel HE, Martin ET, Kuypers J, Englund JA, Zerr DM. Multiple viral respiratory pathogens in children with bronchiolitis. *Acta Paediatr*. 2009;98(1):123–126
15. Zhou H, Thompson WW, Viboud CG, et al. Hospitalizations associated with influenza and respiratory syncytial virus in the United States, 1993-2008. *Clin Infect Dis*. 2012;54(10):1427–1436
16. Healthcare Cost and Utilization Project. Overview of the Kids' Inpatient Database (KID). Available at: www.hcup-us.ahrq.gov/kidoverview.jsp. Accessed September 26, 2014
17. Langley GF, Anderson LJ. Epidemiology and prevention of respiratory syncytial virus infections among infants and young children. *Pediatr Infect Dis J*. 2011;30(6):510–517
18. Children's Hospital Association. PHIS+: augmenting the Pediatric Health Information System with clinical data. Available at: www.childrenshospitals.org/phisplus/index.html. Accessed September 26, 2014
19. Feudtner C, Hays RM, Haynes G, Geyer JR, Neff JM, Koepsell TD. Deaths attributed to pediatric complex chronic conditions: national trends and implications for supportive care services. *Pediatrics*. 2001;107(6). Available at: www.pediatrics.org/cgi/content/full/107/6/e99
20. Li J, Monuteaux MC, Bachur RG. Interfacility transfers of noncritically ill children to academic pediatric emergency departments. *Pediatrics*. 2012;130(1):83–92
21. Berry JG, Hall M, Hall DE, et al. Inpatient growth and resource use in 28 children's hospitals: a longitudinal, multi-institutional study. *JAMA Pediatr*. 2013;167(2):170–177
22. Centers for Disease Control and Prevention. FluView. Influenza-associated pediatric mortality. Available at: http://gis.cdc.gov/GRASP/Fluview/PedFluDeath.html. Accessed September 26, 2014

23. Horbar JD, Carpenter JH, Badger GJ, et al. Mortality and neonatal morbidity among infants 501 to 1500 grams from 2000 to 2009. *Pediatrics*. 2012;129(6):1019–1026

24. Sandweiss DR, Mundorff MB, Hill T, et al. Decreasing hospital length of stay for bronchiolitis by using an observation unit and home oxygen therapy. *JAMA Pediatr*. 2013;167(5):422–428

25. Melero JA, Moore ML. Influence of respiratory syncytial virus strain differences on pathogenesis and immunity. *Curr Top Microbiol Immunol*. 2013;372:59–82

26. Pretorius MA, van Niekerk S, Tempia S, et al; SARI Surveillance Group. Replacement and positive evolution of subtype A and B respiratory syncytial virus G-protein genotypes from 1997-2012 in South Africa. *J Infect Dis*. 2013;208(suppl 3):S227–S237

27. Winterstein AG, Knox CA, Kubilis P, Hampp C. Appropriateness of age thresholds for respiratory syncytial virus immunoprophylaxis in moderate-preterm infants: a cohort study. *JAMA Pediatr*. 2013;167(12):1118–1124

28. Mohan AK, Braun MM, Ellenberg S, Hedje J, Coté TR. Deaths among children less than two years of age receiving palivizumab: an analysis of comorbidities. *Pediatr Infect Dis J*. 2004; 23(4):342–345

29. Turner TL, Kopp BT, Paul G, Landgrave LC, Hayes D Jr, Thompson R. Respiratory syncytial virus: current and emerging treatment options. *Clinicoecon Outcomes Res*. 2014;6: 217–225

30. Hall CB, Simőes EA, Anderson LJ. Clinical and epidemiologic features of respiratory syncytial virus. *Curr Top Microbiol Immunol*. 2013;372:39–57

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