MAJOR ARTICLE

Pediatric Investigators Collaborative Network on Infections in Canada Study of Respiratory Syncytial Virus–associated Deaths in Pediatric Patients in Canada, 2003–2013

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Background. Respiratory syncytial virus (RSV) is a major cause of pneumonia and bronchiolitis in children. Mortality rates in previously healthy children hospitalized with RSV are <0.5%, but up to 37% in patients with underlying medical conditions. The objective of this study was to characterize factors associated with deaths among children hospitalized with RSV infection in Canadian pediatric centers.

Methods. A retrospective case series of children aged ≤18 years with RSV-associated deaths at centers affiliated with the Pediatric Investigators Collaborative Network on Infections in Canada from 2003–2013, inclusive, was performed. Cases were identified using RSV-specific *International Classification of Diseases* codes to capture deaths where a diagnosis of RSV infection was present.

Results. Eleven centers reported 79 RSV-associated deaths. RSV was regarded as primarily responsible for death in 32 cases (40.5%). Median age at death was 11 months (range, <1 month to 16 years). Thirty-nine patients (49.4%) were male. Fourteen patients (17.7%) had no known risk factors for severe RSV infection. Healthcare-associated RSV infections (HAIs) accounted for 29 deaths (36.7%), with RSV judged to be the primary cause of death in 9 of these cases.

Conclusions. RSV-associated deaths were predominantly associated with chronic medical conditions and immunocompromised states among infants; however, 1 in 5 deaths occurred among patients with no known risk factors for severe RSV. Mortality associated with HAI accounted for over a third of cases. These findings highlight patient groups that should be targeted for RSV prevention strategies such as infection control practices, immunoprophylaxis, and future vaccination programs.

Keywords. respiratory syncytial virus; mortality; Canada; pediatrics; child.

Respiratory syncytial virus (RSV) is a major cause of pneumonia and bronchiolitis in childhood, with an estimated incidence of >33 million annual cases worldwide in children <5 years of age; 3.2 million children <5 years of age have severe disease necessitating hospital admission [1].

Mortality from RSV is uncommon, but such cases do occur. Among deaths caused by lower respiratory tract infections globally in 2010, RSV was estimated to account for 2.3% of these deaths in neonates, 6.7% in infants (excluding neonates), and 1.6% in children aged 1–4 years [2]. In infants, RSV-associated mortality exceeds influenza-associated mortality by 2–3 times [2]. The vast majority of deaths occur in developing countries [1]. In developed countries, the case-fatality rate of hospitalized children with RSV is estimated to be <0.5%, with higher rates (up to 37% in some studies) in children at risk for more severe disease, such as those who are immunocompromised, have chronic lung disease, or have congenital heart disease [3–6]. Interestingly, mortality rates have remained generally stable over time despite advances in medical care [3].

Data are lacking on risk factors associated with mortality from RSV infection among children. These factors may provide insight into host susceptibility profiles and, subsequently, which patients should be targeted for preventive strategies such as maternal immunization during pregnancy, infant immunization, and passive immunoprophylaxis. The objective of this study was to characterize the factors associated with deaths among children hospitalized with RSV infection in Canadian pediatric centers.

METHODS

A retrospective review of health records was performed of all RSV-associated deaths from Canadian pediatric centers affiliated with the Pediatric Investigators Collaborative Network on Infections in Canada over the period 2003–2013, inclusive. Patients included were aged ≤18 years. Cases were identified using *International Classification of Diseases*, *Tenth Revision* (*ICD-10*) codes to capture all deaths where a diagnosis of RSV infection was present. These *ICD-10* codes were J121 (RSV pneumonia), B974 (RSV), J205 (bronchitis due to RSV), and J210 (bronchiolitis due to RSV).

Health records of identified patients with relevant *ICD* codes were retrieved for review in this case series. Data were collected using a standardized data collection sheet. Information obtained was basic demographics (age at admission, age at death, month of death, sex, ethnicity), risk factors for severe RSV disease (see below), mode of RSV acquisition (community- vs healthcare-associated RSV infection [HAI], with HAI defined as symptoms beginning >72 hours after admission or <72 hours after hospital discharge from previous admission [7]), level of care required (intensive care unit [ICU] length of stay, ventilation requirements, extracorporeal membrane oxygenation [ECMO] requirements), pharmacologic treatments (palivizumab, RSV immunoglobulin, intravenous immunoglobulin [IVIG], ribavirin), prophylaxis given (palivizumab, RSV immunoglobulin, IVIG), and laboratory-confirmed coinfections (bacterial or viral).

RSV-attributable mortality was determined from the medical records, with the initial determination done according to the *ICD* coding definitions. This coding assigned the most responsible diagnosis (primary cause) and different categories of comorbidities or secondary diagnoses (secondary causes). In Canada, *ICD* coding is done by trained coders and therefore not expected to result in much misclassification. The investigators reviewed each medical record to ensure that the *ICD* coding was consistent with their assessment of attribution in the unlikely event that there were errors in *ICD* coding. The role that RSV played in death was then classified as one of the following: primary cause of death, contributed to death but was not the primary cause, role undetermined (RSV might have contributed to death), or unrelated to death (would have died during this hospitalization even if they did not have RSV). Patients whose RSV infection was deemed to be unrelated to death (eg, if the RSV infection occurred many months prior to death) were excluded. If there was uncertainty whether RSV played a role in death, the case was included as "role undetermined."

Non-immunodeficiency-related risk factors for severe RSV disease were prematurity (defined as ≤37 weeks, 0 days of gestational age [GA]), chronic lung disease of prematurity, other symptomatic chronic lung disease (eg, cystic fibrosis, ciliary defects), airway anomalies, asthma or reactive airway disease, neuromuscular disease, congenital heart defects, or trisomy 21.

Chronic lung disease was defined as oxygen requirement at 36 weeks of GA or at discharge (whichever comes first) in infants <32 weeks of GA, or oxygen requirement at age >28 days or at discharge (whichever comes first) in infants ≥32 weeks of GA. Immunodeficiency risk factors were hematopoietic stem cell transplant, solid organ transplant, long-term immunosuppression with medication, chemotherapy within the past 6 months, or congenital immunodeficiency.

Descriptive statistics were used to summarize patient demographics, risk factors, modes of RSV acquisition, level of care, treatment received, prophylaxis given, presence of coinfections, and role of RSV in death. Patient characteristics were compared between those with known risk factors for severe disease vs those without known risk factors, those <2 years old vs those ≥2 years old, and those who died during the typical RSV season vs those who died outside the typical RSV season. The Mann-Whitney *U* test was used for nonparametric comparisons of continuous variables, and the Fisher exact test was used for categorical variable comparisons. Statistical significance was defined as *P* < .05 on a 2-tailed test of hypothesis. No adjustment was made for multiple comparisons.

Research ethics board approval was obtained from each participating institution.

RESULTS

Ninety cases were identified across 11 pediatric centers (Table 1). This represents 69% (11/16) of the pediatric institutions in Canada and 100% and 75% of the centers from the largest Canadian provinces (Ontario and Quebec, respectively). Eleven deaths judged to be unrelated to RSV infection were excluded, leaving 79 cases for further analysis. RSV was judged to be the primary cause of death in 40.5% of children, a contributor to death in 39.2%, and played an undetermined role in 20.3% of deaths. All cases had laboratory confirmation of RSV by viral culture, direct fluorescent antibody, enzyme immunoassay, or polymerase chain reaction testing.

Patient characteristics are illustrated in Table 2. The median age at death was 11 months (range, <1 month to 16 years; interquartile range [IQR], 5–37 months) (Figure 1). Two age groups commonly examined in previous literature on RSV-associated mortality are children <2 years old and children <5 years old; the median ages at death when considering these age groups in our case series were 7 months and 9 months, respectively. Twenty-seven cases (34.2%) occurred in those >2 years or age, with 14 cases occurring where RSV was judged to be the primary cause of death. Those who were ≥2 years old had shorter durations of admission (median, 13 vs 39 days; *P* = .048) and fewer days in the ICU (median, 6 vs 14 days; *P* = .014) prior to death, but were not more likely to have risk factors for severe RSV disease compared to those <2 years old (85.2% vs 80.8%, respectively; *P* = .761). There were no trends in the number of cases that occurred per year over the time period examined.

Table 1. Number of Deaths With Detection of Respiratory Syncytial Virus During Final Hospitalization in Canadian Tertiary Care Pediatric Hospitals

Pediatric Center	City	Deaths With RSV Identified	Cases Where RSV Contributed to Death
Hospital for Sick Children	Toronto	28	27
CHU Sainte-Justine	Montreal	10	10
Stollery Children's Hospital	Edmonton	12	8
Children's Hospital of Eastern Ontario	Ottawa	9	8
Montreal Children's Hospital	Montreal	9	8
University of Western Ontario	London	8	6
University of Manitoba	Winnipeg	5	4
McMaster University	Hamilton	5	4
IWK Health Centre	Halifax	3	3
Kingston General Hospital	Kingston	1	1
CIUSSS de l'Estrie-CHUS Fleurimont	Sherbrooke	0	0
Total		90	79

Abbreviations: CHU, Centre Hospitalier Universitaire; CHUS, Centre Hospitalier Universitaire de Sherbrooke; CIUSSS, Centre Intégré Universitaire de Santé et de Services Sociaux; RSV, respiratory syncytial virus.

Most deaths (86%) occurred during the winter respiratory season in Canada (Table 2 and Figure 2). Those who died outside the typical RSV season had similar characteristics to those that occurred during the typical RSV season. Most children (86.7%) did not have viral coinfection (Table 2). Seven cases (10.9%) had received palivizumab within the 4 weeks prior to symptom onset.

Fourteen patients (17.7%) had no recognized risk factors for severe RSV. Five patients (6.3%) had both immunodeficiency and non-immunodeficiency-related underlying risk factors, 49 (62.0%) had non-immunodeficiency-related risk factors

Table 2. Characteristics of Children Where Respiratory Syncytial Virus Was Associated With Death

Patient Characteristic (n = 79)	No. (%)
Age at death, mo, median (range)	11 (0–197)
Male sex	39 (49.4)
Death occurred during RSV season[a]	68 (86.1)
Healthcare-associated RSV infection	29 (36.7)
Viral coinfection detected	10 (13.3)[b]
Patients with respiratory viral pathogens	6 (8.0)[b]
Patients with opportunistic viral pathogens	4 (5.3)[b]
Received palivizumab within 4 wk prior to symptom onset	7 (10.9)[c]

Data are presented as No. (%) unless otherwise indicated.

Abbreviation: RSV, respiratory syncytial virus.

[a]RSV season was defined as November through April.

[b]Denominator of 75 (4 values not recorded). Respiratory viral pathogens: adenovirus, coronavirus, enterovirus, parainfluenza (n = 3). Opportunistic viral pathogens: herpes simplex virus type 1 (HSV-1), Epstein-Barr virus (EBV) (n = 2), cytomegalovirus (CMV) (n = 2), human herpesvirus type 6 (HHV-6), human herpes virus type 7 (HHV-7); 1 patient had 2 viral coinfections isolated (HSV-1 and HHV-6) and another patient had 3 viral coinfections isolated (EBV, CMV, and HHV-7). The presence of opportunistic viral pathogens was based on isolation of the virus from blood or respiratory fluid.

[c]Denominator of 64 (15 values not recorded).

only, and 11 (13.9%) had immunodeficiency-related risk factors only. The most common non-immunodeficiency-related risk factor identified was premature birth (n = 23/68 [33.8%]) with 7 patients (10.3%) born at <29 weeks of GA, 4 patients (5.9%) born at 29 to <33 weeks of GA, and 12 patients (17.6%) born at 33 to <37 weeks of GA. Other non-immunodeficiency-related risk factors, in decreasing order of frequency, were congenital heart defect (n = 22/78 [28.2%]), neuromuscular disease (n = 15/78 [19.2%]), chronic lung disease (n = 14/76 [18.4%]), other symptomatic chronic lung disease (n = 10/78 [12.8%]), airway anomaly (n = 9/79 [11.4%]), asthma/reactive airway disease (n = 6/77 [7.8%]), and trisomy 21 (n = 2/77 [2.6%]). The most common immunodeficiency risk factor was hematopoietic stem cell transplant (n = 7/79 [8.9%]), followed by chemotherapy within the last 6 months (n = 5/78 [6.4%]), congenital immunodeficiency (n = 5/78 [6.4%]), long-term immunosuppression (n = 3/79 [3.8%]), and solid organ transplant (n = 1/79 [1.3%]). The solid organ transplant case was a lung transplant. Thirty-five patients (44.3%) had >1 risk factor.

Management of patients is summarized in Table 3. More than 93% of RSV-infected children were admitted to an ICU during this terminal illness, with mechanical ventilator support used in 83.3%. Seven patients (8.9%) received ECMO. Treatments for established RSV infection included ribavirin (12.7%), palivizumab (8.9%), IVIG (5.1%), and/or RSV immunoglobulin (1.3%).

Patient characteristics and management of 65 patients with known risk factors for severe RSV were compared with 14 patients with no known risk factors for severe RSV (Table 4). None of the characteristics were statistically significantly different, although those with no known risk factors had a length of stay that was almost significantly shorter than those with known risk factors (median, 13 days vs 27 days; P = .054). In both groups, cases occurred throughout the entire study period without any clear patterns or trends.

DISCUSSION

This study identified 79 cases of RSV-associated deaths at 11 Canadian pediatric tertiary centers over a 10-year period from 2003 to 2013. To put this into context, there were 33 200 childhood deaths in Canada over the same time period, confirming that RSV-associated deaths are relatively uncommon [8]. This is the first study examining RSV-associated mortality in Canada. Consistent with previous studies of children in higher-income countries [3, 4, 9–11], most deaths occurred in infants and patients with known risk factors for severe RSV.

Two recent studies examined RSV-associated deaths in children <2 years old in the United States [9, 10]. Prill et al performed a retrospective review from 2004 to 2007 using *ICD-10* codes in the United States with further characterization of mortality cases from 4 states (California, Georgia, Michigan, and Texas); of 275 RSV-associated deaths, RSV was the primary underlying
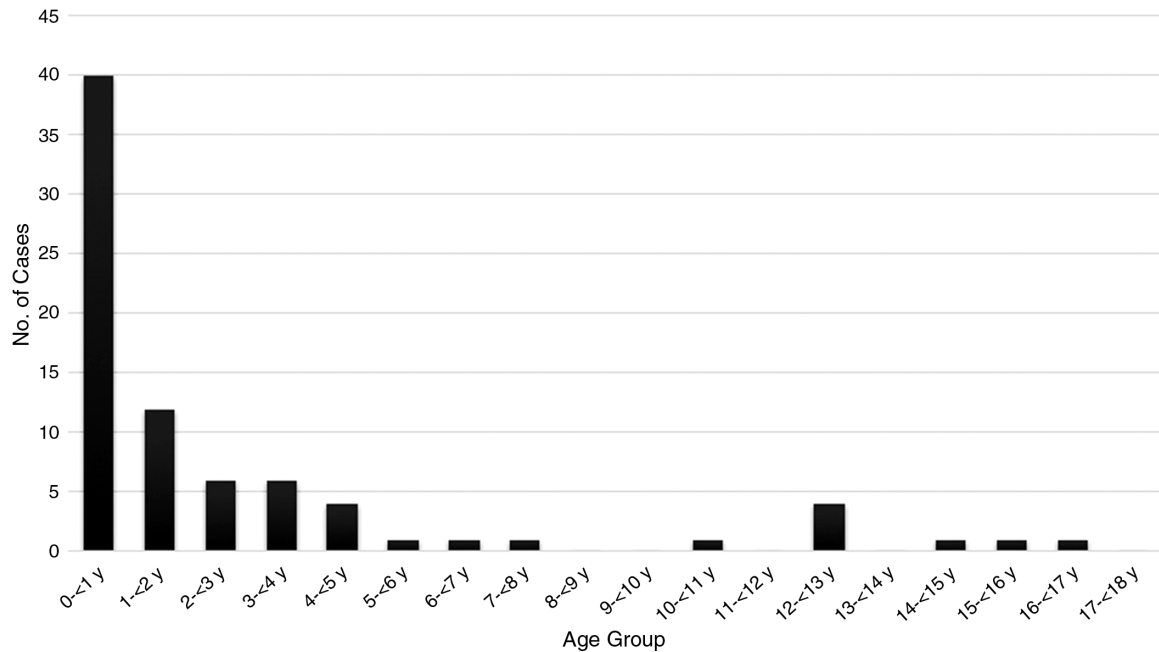
Figure 1. Age distribution of children in whom respiratory syncytial virus was associated with death in Canadian tertiary care pediatric hospitals, 2003–2013.

cause in 52.7%. From the 4 states more closely examined, the median age at death was 3.5 months (IQR, 1–10 months) with 2–7 times more deaths among children between 1 and 2 months of age [9]. Byington et al performed a database review using *ICD, Ninth Revision* codes in the United States from 2000 to 2011 to characterize RSV-associated mortality and associated conditions in hospitalized children <2 years old. Similar to the

study by Prill et al, most deaths occurred in those <12 months old (77%–88% depending on the database used) and most had a complex chronic condition, mostly cardiovascular [10].

A global retrospective case series of community-acquired RSV-associated mortality from 1995 to 2015 in hospitalized patients aged <5 years was performed by Scheltema et al [11]. This study, involving 23 countries across 6 continents,
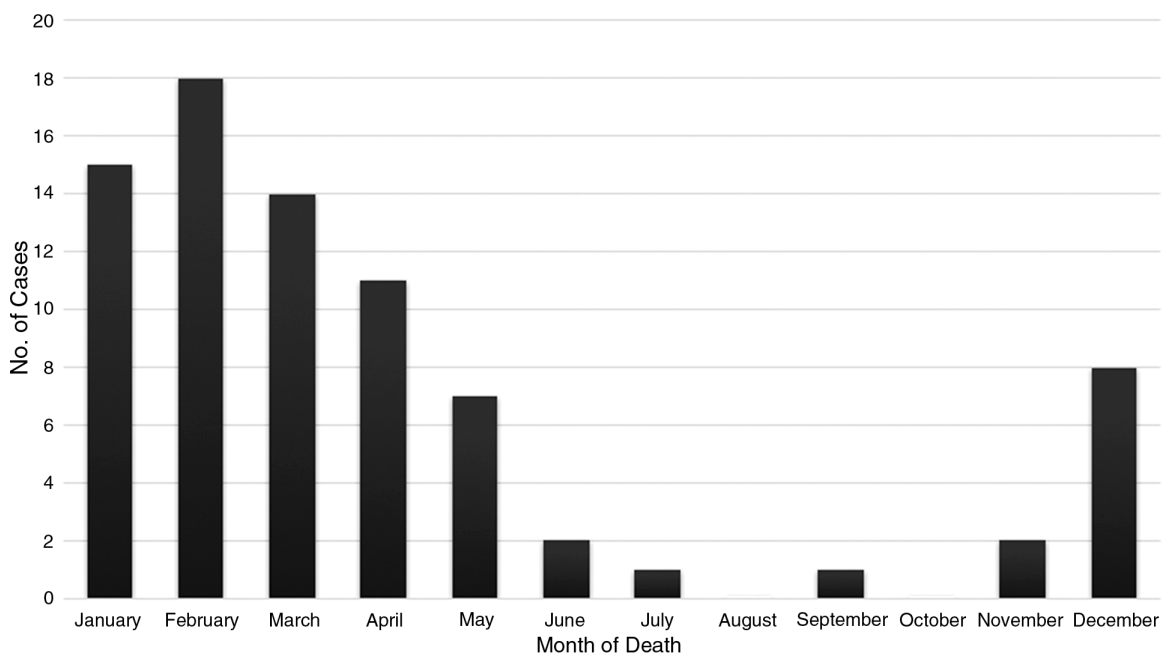

Figure 2. Month of death of children in whom respiratory syncytial virus was associated with death in Canadian tertiary care pediatric hospitals, 2003–2013.

Table 3. Management of Children Prior to Respiratory Syncytial Virus-Associated Death

Patient Outcome/Intervention (n = 79)	No. (%)
Length of hospital admission, d, median (range)	25 (1–780)
ICU admission	74 (93.7)
Days in ICU, d, median (range)	10 (1–191)
In ICU for reason other than RSV	19 (24.1)
Received mechanical ventilation	65 (83.3)[a]
Received ECMO	7 (8.9)
Treated with palivizumab	7 (8.9)
Treated with RSV IVIG	1 (1.3)
Treated with IVIG	4 (5.1)
Treated with ribavirin	10 (12.7)

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IVIG, intravenous immunoglobulin; RSV, respiratory syncytial virus.

[a]Denominator of 78 (1 value not recorded).

Table 4. Comparison of Patients With Known Risk Factors Versus No Known Risk Factors for Severe Respiratory Syncytial Virus (RSV) Infection Where RSV Was Associated With Death

Characteristic	Risk Factors[a] (n = 65)	No Risk Factors (n = 14)	P Value
Age at death, mo, median (range)	10 (0–197)	21.5 (1–154)	.922
Male sex	33 (50.8)	7 (50.0)	1.000
Death occurred during RSV season[b]	57 (87.7)	11 (78.6)	.401
Healthcare-associated RSV infection	24 (36.9)	5 (35.7%)	1.000
Viral coinfection	6 (9.7)[c]	4 (30.8)[d]	.064
Received palivizumab within 4 wk prior	7 (13.7)[e]	0 (0)[f]	.329
Length of admission, d, median (range)	27 (1–780)	13 (1–202)	.054
ICU admission	61 (93.8)	13 (92.9)	1.000
Days in ICU, median (range)	11 (0–191)	7.5 (0–69)	.514
Received mechanical ventilation	53 (82.8)[g]	12 (85.7)	1.000
Received ECMO	4 (6.2)	3 (21.4)	.102
Treated with palivizumab	7 (10.8)	0 (0)	.342
Treated with RSV IVIG	1 (1.5)	0 (0)	1.000
Treated with IVIG	4 (6.2)	0 (0)	1.000
Treated with ribavirin	9 (13.8)	1 (7.1)	.681

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IVIG, intravenous immunoglobulin; RSV, respiratory syncytial virus.

[a]Risk factors were defined as prematurity, congenital heart defect, chronic lung disease, neuromuscular disease, airway anomaly, asthma/reactive airway disease, trisomy 21, other symptomatic chronic lung disease, hematopoietic stem cell transplant, solid organ transplant, long-term immunosuppression, chemotherapy within the last 6 months, congenital immunodeficiency.

[b]RSV season was defined as November through April.

[c]Denominator of 62 (3 values not recorded).

[d]Denominator of 13 (1 values not recorded).

[e]Denominator of 51 (14 values not recorded).

[f]Denominator of 13 (1 values not recorded).

[g]Denominator of 64 (1 values not recorded).

highlighted that patients who experience RSV-associated mortality in low-income countries are different from those in high-income countries. For example, patients from high-income countries were more likely to have comorbidities (70% vs 28%) and were older at time of death (7 months vs 5 months). Regardless of socioeconomic status, however, infants remained the most affected age group.

The median age of death in our study was 11 months. Unlike the aforementioned studies, we included children up to 18 years old. When only considering children <2 years old, the median age of death was 7 months in children in our case series compared with 3.5 months in Prill et al's study [9]. When only considering children <5 years old, the median age of death was 9 months in our case series compared to 7 months in Scheltema et al's study [11]. Therefore, it appears that the population in our case series was older than previous studies. Of note, more than one-third of our identified cases occurred in those >2 years old. RSV infection in older children may become more relevant with medical and technological advances, enabling patients with underlying complex medical conditions (eg, congenital heart disease and ventilator-dependent lung disease) to live longer while remaining vulnerable to severe RSV disease. Interestingly, however, the patients >2 years of age did not have more known risk factors for severe RSV infection compared to their younger counterparts, suggesting there may be other factors predisposing them to RSV-associated mortality. It is unclear why those older than 2 years had shorter durations of admission to hospital (P = .048) and to the ICU (P = .014) prior to death. Possibilities may include more rapid progression of disease or more delayed presentation to hospital. Nonetheless, nearly half of the deaths in our study occurred in infants, confirming this population as most vulnerable among pediatric patients, although older children may account for an increasing proportion of RSV-associated mortality in the future, which definitely warrants further study.

Most deaths occurred in children with recognized risk factors for severe RSV. Reviews examining case fatality rates (CFR) among RSV hospitalizations have consistently found higher rates in patients with underlying medical conditions such as prematurity (CFR range, 0–6.1%), chronic lung disease (3.5%–23%), and congenital heart defects (2%–37%) [5, 6]. In contrast, the CFR in those with no risk factors in high-income countries has been found to be <1% [10, 11] and is often cited as <0.5% [3] in more recent reviews.

In our study, almost 1 in 5 patients had no known underlying risk factors for severe RSV disease. Prill et al also revealed a similar finding, with 19% of children with RSV-associated death having no risk factor for severe disease [9]. When we compared the group with known risk factors to those with no known risk factors, the latter had a trend toward shorter duration of admission prior to death (13 days vs 27 days; P = .054). Again, it is unclear whether this is due to more rapid progression of disease or more delayed presentation to hospital. Patients with no known risk factors also tended to have more viral coinfections (30.8% vs

9.7%; $P = .064$), be older (median age of death, 21.5 months vs 10 months; $P = .922$), have infections outside of the typical RSV season (21.4% vs 12.3%; $P = .401$), and receive ECMO (21.4% vs 6.2%; $P = .102$). Other investigators have found that, in children with RSV-associated mortality, previously healthy children were younger than those with comorbidities (3.8–4 months vs 11 months) and occur more commonly within the RSV season (91%–97% vs 39%), in contrast to what we observed in our study [11]. Factors associated with severe disease outcomes such as mortality in previously healthy patients are largely undetermined. While overall small numbers of patients make it difficult to draw any concrete conclusions regarding these comparative findings at this point, it would be worthwhile to explore this further in future studies. Possible factors that have been considered include, but are not limited to: viral load [12, 13], viral coinfections [14], and immune response–related genetic susceptibility markers [15–18].

A prospective surveillance study across 8 Canadian pediatric centers in 2005 found that viral pathogens were the most common cause of healthcare-acquired febrile respiratory infections, with RSV being the most frequently identified agent [19]. One-third of our cases were deemed to have been acquired in hospital (HAIs). Our study may have overestimated the number of HAIs, as the incubation period of RSV is 2–8 days, but we used a cutoff of >72 hours into hospital admission. Nonetheless, minimizing transmission of RSV within healthcare facilities is important, as nosocomially acquired RSV can clearly lead to fatal outcomes.

Limitations of our study include the absence of a control group and the retrospective study design, which meant that only characteristics present in the health record could be identified. Many factors, such as environmental exposures (overcrowding, daycare attendance, smokers in the household, number of siblings, or breastfeeding) or family history could not be captured. Another limitation is that the causative role of RSV in death was based solely on retrospective chart review; the direction of this bias could either be an overestimation or underestimation of RSV-associated deaths. The use of *ICD* codes to identify cases may underestimate the number of RSV-associated deaths. In this study, this would be unlikely, especially if RSV was thought to play a major role in the death. Such cases would have been captured by the *ICD* coding and reviewed by the study team. Also, our study sample was limited to those admitted to 1 of the 11 study sites, so population-based estimates could not be made. However, we expect that it is unlikely that many RSV-associated deaths occur in the community, due to universally accessible healthcare.

This study provides a snapshot of the population with RSV-associated mortality admitted to Canadian children's hospitals. While our findings confirm that mortality from RSV is relatively low, characterization of these deaths may have strategic implications for the use of preventive measures such as future RSV vaccine programs [20] and RSV antivirals [21], as well as existing RSV immunoprophylaxis and infection control programs. For instance, infants and those with premature birth, chronic medical conditions (such as congenital heart defects), and immunodeficiencies (such as following hematopoietic stem cell transplants) would likely benefit most from such preventive programs. The precise impact of these strategies on RSV mortality, however, requires further study. Further studies are also needed to examine individual immunogenetic predispositions to RSV mortality, in view of the documented cases of mortality in children with none of the traditional identifiable risk factors for severe RSV disease.

CONCLUSIONS

RSV-associated deaths were predominantly associated with chronic medical conditions and immunocompromised states among infants. Mortality associated with HAI was observed, highlighting the need for continued improvement on infection control measures. One out of every 5 deaths, however, occurred among patients with no known risk factors for severe RSV. Thus, further research on the underlying reasons for severe disease and mortality in otherwise healthy children with RSV infection (eg, immunogenetic causes) remains pertinent.

References

1. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet **2017**; 390:946–58.
2. Lozano R, Naghavi M, Foreman K, 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**; 380:2095–128.
3. Bont L, Checchia PA, Fauroux B, et al. Defining the epidemiology and burden of severe respiratory syncytial virus infection among infants and children in Western countries. Infect Dis Ther **2016**; 5:271–98.
4. Thorburn K. Pre-existing disease is associated with a significantly higher risk of death in severe respiratory syncytial virus infection. Arch Dis Child **2009**; 94:99–103.
5. Szabo SM, Gooch KL, Bibby MM, et al. The risk of mortality among young children hospitalized for severe respiratory syncytial virus infection. Paediatr Respir Rev **2013**; 13:S1–8. doi:10.1016/S1526-0542(12)00095-4.
6. Welliver RC Sr, Checchia PA, Bauman JH, Fernandes AW, Mahadevia PJ, Hall CB. Fatality rates in published reports of RSV hospitalizations among high-risk and otherwise healthy children. Curr Med Res Opin **2010**; 26:2175–81.

7. Langley JM, Wang EE, Law BJ, et al. Nosocomial respiratory syncytial virus infection in Canadian pediatric hospitals: a Pediatric Investigators Collaborative Network on Infections in Canada study. J Pediatr **1997**; 131:113–7.

8. Statistics Canada. Table 051-0002—estimates of deaths, by sex and age group, Canada, provinces and territories, annual (persons), **2017**. Available at: http://www5.statcan.gc.ca/cansim/a47. Accessed 6 November 2017.

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

10. Byington CL, Wilkes J, Korgenski K, Sheng X. Respiratory syncytial virus-associated mortality in hospitalized infants and young children. Pediatrics **2014**; 135:e24–31.

11. Scheltema NM, Gentile A, Lucion F, et al; PERCH Study Group. Global respiratory syncytial virus-associated mortality in young children (RSV GOLD): a retrospective case series. Lancet Glob Health **2017**; 5:e984–91.

12. DeVincenzo JP, El Saleeby CM, Bush AJ. Respiratory syncytial virus load predicts disease severity in previously healthy infants. J Infect Dis **2005**; 191:1861–8.

13. Houben ML, Coenjaerts FE, Rossen JW, et al. Disease severity and viral load are correlated in infants with primary respiratory syncytial virus infection in the community. J Med Virol **2010**; 82:1266–71.

14. Asner SA, Science ME, Tran D, Smieja M, Merglen A, Mertz D. Clinical disease severity of respiratory viral co-infection versus single viral infection: a systematic review and meta-analysis. PLoS One **2014**; 9:e99392.

15. Janssen R, Bont L, Siezen CL, et al. Genetic susceptibility to respiratory syncytial virus bronchiolitis is predominantly associated with innate immune genes. J Infect Dis **2007**; 196:826–34.

16. Awomoyi AA, Rallabhandi P, Pollin TI, et al. Association of TLR4 polymorphisms with symptomatic respiratory syncytial virus infection in high-risk infants and young children. J Immunol **2007**; 179:3171–7.

17. Tulic MK, Hurrelbrink RJ, Prêle CM, et al. TLR4 polymorphisms mediate impaired responses to respiratory syncytial virus and lipopolysaccharide. J Immunol **2007**; 179:132–40.

18. Choi EH, Lee HJ, Chanock SJ. Human genetics and respiratory syncytial virus disease: current findings and future approaches. In: Anderson LJ, Graham BS, eds. Current topics in microbiology and immunology: challenges and opportunities for respiratory syncytial virus vaccines. Vol 372. Berlin: Springer, **2013**:121–37.

19. Vayalumkal JV, Gravel D, Moore D, Matlow A; Canadian Nosocomial Infection Surveillance Program. Surveillance for healthcare-acquired febrile respiratory infection in pediatric hospitals participating in the Canadian Nosocomial Infection Surveillance Program. Infect Control Hosp Epidemiol **2009**; 30:652–8.

20. Giersing BK, Karron RA, Vekemans J, Kaslow DC, Moorthy VS. Meeting report: WHO consultation on respiratory syncytial virus (RSV) vaccine development, Geneva, 25–26 April 2016 [manuscript published online ahead of print 14 March 2017]. Vaccine **2017**. doi:10.1016/j.vaccine.2017.02.068.

21. DeVincenzo JP, McClure MW, Symons JA, et al. Activity of oral ALS-008176 in a respiratory syncytial virus challenge study. N Engl J Med **2015**; 373:2048–58.