

The Use of Death Certificate Data to Characterize Mortality Associated With Respiratory Syncytial Virus, Unspecified Bronchiolitis, and Influenza in the United States, 1999–2018

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Background. Death certificate data can improve our understanding of the mortality burden associated with respiratory syncytial virus (RSV) and influenza.

Methods. We used *International Classification of Diseases, Tenth Revision* codes listed on death certificates to characterize deaths from 1999 to 2018 as RSV, influenza, and unspecified bronchiolitis. We described the distribution of each cause of death by age, sex, race/ethnicity, place of death, and contributing causes of death.

Results. Over the 20-year study period, RSV, bronchiolitis, and influenza were listed as the underlying causes of death on 932, 1046, and 52 293 death certificates, respectively. Children <1 year of age accounted for 39% of RSV and bronchiolitis deaths, while 72% of influenza deaths were in adults ≥65 years. Children <1 year were more likely to die outside of the hospital from RSV, bronchiolitis, or influenza compared to all causes ($P < .01$), and black infants had the highest mortality rate for all 3 causes. Most infants dying from RSV did not have a high-risk condition listed on the death certificate. Death certificates captured 20%–60% of estimated excess RSV-attributable mortality in infants and <1% in seniors.

Conclusions. Thorough reporting on death certificates is an important public health goal, especially as new therapeutics become available. Infants had higher odds of dying out of hospital from respiratory pathogens compared to other causes, and race/ethnicity alone did not explain this disparity.

Keywords. RSV; influenza; bronchiolitis; death certificates; excess mortality; infant mortality.

Understanding the mortality burden associated with respiratory syncytial virus (RSV) and influenza has important public health implications when considering allocation of resources to health programs, policy implications of new treatments, and targeting of prevention strategies. Despite decades of research, the burden of respiratory viruses remains debated, particularly in population subgroups for whom testing is not routinely conducted. As a case in point, estimates of RSV hospitalizations and deaths among the elderly are conflicting [1–4]. Previous work has noted the limitations of relying on mortality codes listed on death certificate data in determining

pathogen-specific mortality burdens [5–10]. Alternative statistical approaches, such as excess mortality models, have been used to estimate disease burden from RSV and influenza and have been considered a superior method for tracking deaths during the coronavirus disease 2019 (COVID-19) pandemic [11, 12]. Despite limitations, death certificates are unique sources for demographic information that can provide insights on health inequalities (eg, sex, race) and access to care (eg, place of death) that cannot be easily assessed when using other analytical approaches or data sources [7, 13]. Furthermore, as excess mortality estimates have recently been updated for influenza and RSV [4], and testing and reporting practices have changed substantially in the last 2 decades [14–16], it is important to evaluate trends in death certificate assessment.

Here we have analyzed deaths in the United States (US) from 1999 to 2018 with a mention of RSV, bronchiolitis, or influenza in the death certificate, with our primary analysis focusing on these conditions listed as the underlying cause of death. Bronchiolitis was included as it is a common presentation of RSV in young children and has been used to estimate RSV burden [17]. We describe the distribution of each cause of death by

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The Journal of Infectious Diseases® 2022;226(S2):S255–66

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age, sex, race/ethnicity, and place of death, examine the contributing causes of death most frequently associated with underlying RSV, bronchiolitis, and influenza deaths, and compare with excess mortality estimates.

METHODS

We requested death certificates from the US National Center for Health Statistics from 1999 to 2018. Death certificates indicate 1 underlying cause of death, defined as “the disease or injury which initiated the train of events leading directly to death” [18], and can include up to 20 contributing causes. US territories and foreign residents (<0.01%) and death certificates with missing ages (<0.001%) were excluded from analysis. The study was based on publicly available datasets and did not involve live human subjects; therefore, it was exempt from Institutional Review Board review and approval.

We classified deaths based on the *International Classification of Diseases, 10th Revision (ICD-10)* [19] as underlying RSV, bronchiolitis, or influenza. Underlying RSV deaths included codes J12.1 (RSV-pneumonia), J20.5 (RSV-bronchitis), and J21.0 (RSV-bronchiolitis). We included only unspecified bronchiolitis deaths (J21.9) in our underlying bronchiolitis category as J21.0 deaths were already captured in the RSV category and J21.1 and J21.8 include bronchiolitis deaths due to other, non-RSV-specific causes. Underlying influenza deaths included codes J09 (identified influenza viruses), J10.0 (identified influenza-pneumonia), J10.1 (identified influenza-other respiratory manifestations), J10.8 (identified influenza-other manifestations), J11.0 (unidentified influenza-pneumonia), J11.1 (unidentified influenza-other respiratory manifestations), and J11.8 (unidentified influenza-other manifestations). Codes J10.2 and J11.2 (influenza with gastrointestinal manifestations) were not listed as the underlying cause on any death certificates.

We grouped underlying and contributing causes of death based on broad condition categories (first letter of *ICD-10* codes A–Z) separately by age group and considered specific codes present on $\geq 5\%$ of death certificates for at least 1 age group and cause of death. For children <1 year of age, we examined the contribution of high-risk conditions including prematurity (P05–P07), chronic lung disease (P19–P29), and congenital heart disease (Q20–Q28), listed anywhere in the death certificate [17]. We also examined the frequency of other underlying causes of death when RSV, bronchiolitis, or influenza were included as contributing causes of death, using the same definitions as above. We used all-cause mortality (excluding underlying RSV, bronchiolitis, and influenza) as a benchmark when comparing distribution patterns related to age, race/ethnicity, and place of death.

Each underlying cause of death was stratified by age group (<1, 1–4, 5–49, 50–64, ≥ 65 years), sex, race/ethnicity, and

place of death. We considered 3 categories for place of death: deaths occurring in the hospital, deaths occurring out of hospital, and other. We defined out-of-hospital deaths as death certificates listing place of death as outpatient/emergency room, death on arrival, or decedent’s home; these patients would have had little opportunity for interventions. Deaths occurring in nursing homes or hospices are included in the “other” category.

For each of the 3 underlying causes of death, we used 1-way and 2-way analysis of variance to compare mean age of death in months among infants between race/ethnicities and places of death and to compare the mean number of contributing causes of death included on death certificates between age groups and places of death. We used univariate logistic regression to examine the odds of out-of-hospital death compared to in-hospital death. Deaths in the “other” category were excluded from this part of the analysis. We used χ^2 statistics to test differences in proportions.

For most analyses, deaths were aggregated over the full 20-year period. To obtain death rates, we used the Centers for Disease Control and Prevention’s bridged-race population estimates [20]. Age- and race-specific mortality rates for each cause of death were calculated as the 20-year cumulative number of deaths based on death certificate data divided by the 20-year cumulative age- and race-specific populations, multiplied by 100 000.

Finally, we compared the number of deaths directly coded as influenza, RSV, or bronchiolitis with estimates from an alternative approach commonly used to assess the burden of respiratory viruses, namely excess mortality. Excess mortality is a statistical time series approach applied to broad mortality outcomes, such as total respiratory or cardiorespiratory deaths, which attributes weekly or monthly mortality rises above a seasonal baseline to RSV and influenza virus circulation (often derived from surveillance systems). Excess mortality estimates used for this comparison were taken from an article reporting on a similar data source and period [4]. For comparison with seasonal excess mortality estimates in [4], we aggregated death certificate tallies by respiratory season, which we defined as beginning the 27th week of the year through the 26th week of the following year (July–June). We hypothesized that many of the deaths coded as bronchiolitis were in fact deaths due to RSV. We compared RSV excess mortality estimates in [4] to the number of RSV-only and RSV or bronchiolitis-coded deaths.

RESULTS

Underlying RSV, Bronchiolitis, and Influenza Deaths

There were 50.3 million death certificates included in our 20-year analysis. Children <1 year of age accounted for 1% of these deaths while adults ≥ 65 years of age accounted for 73%. An RSV code was included on 1895 death certificates

and was the underlying cause in 932 (49.2%) (Table 1). When RSV was listed on the death certificate, it was more often an underlying cause in children <1 year than in older age groups (61.2% vs 43.6%; $P < .001$). RSV-pneumonia was the most common RSV code, accounting for 68.7% of all underlying RSV deaths. Unspecified bronchiolitis was included on 2732 death certificates and was the underlying cause on 1046 (38.3%) of these. Influenza was included on 66 322 death certificates and was the underlying cause on 52 293 (78.8%) of these. Identified and unidentified influenza with pneumonia (J10.0 and J11.0) were the most common (58.3%) causes of underlying influenza deaths. The highest proportions of underlying RSV and bronchiolitis deaths occurred in children <1 year of age (39.2% and 39.5%, respectively), while 72.4% of underlying influenza deaths were in adults ≥ 65 years of age.

Demographics and Place of Death

More than half (56.6%) of the underlying bronchiolitis deaths occurred outside of the hospital, vs 36% for underlying

Table 1. Demographic Characteristics and Place of Death for Death Certificates Listing Respiratory Syncytial Virus, Bronchiolitis, or Influenza as the Underlying Cause of Death, United States, 1999–2018

Characteristic	Cause of Death		
	RSV	Bronchiolitis	Influenza
Included anywhere on death certificate (underlying and contributing)	n = 1895	n = 2732	n = 66 322
Underlying cause of death	n = 932 (49.2)	N = 1046 (38.3)	N = 52 293 (78.8)
	No. (%)	No. (%)	No. (%)
Underlying cause of death	932 (100)	1046 (100)	52 293 (100)
Age group, y			
<1	365 (39.2)	413 (39.5)	358 (0.7)
1–4	126 (13.5)	125 (12.0)	517 (1.0)
5–49	69 (7.4)	121 (11.6)	5930 (11.3)
50–64	51 (5.5)	107 (10.2)	7606 (14.5)
≥ 65	321 (34.4)	280 (26.8)	37 882 (72.4)
Sex			
Female	464 (49.8)	508 (48.6)	29 269 (56.0)
Male	468 (50.2)	538 (51.4)	23 024 (44.0)
Race/ethnicity			
White	565 (60.6)	639 (61.1)	42 995 (82.2)
Black	159 (17.1)	218 (20.8)	3752 (7.2)
Hispanic	157 (16.8)	135 (12.9)	3788 (7.2)
Other	51 (5.5)	54 (5.2)	1758 (3.4)
Place of death			
In hospital	732 (78.5)	357 (34.1)	33 494 (64.1)
Outpatient/emergency room	92 (9.9)	290 (27.7)	2260 (4.3)
Home/dead on arrival	47 (5.0)	292 (27.9)	4252 (8.1)
Other	61 (6.5)	107 (10.2)	12 287 (23.5)

Abbreviation: RSV, respiratory syncytial virus.

influenza deaths and 21% for underlying RSV deaths (Table 1). Compared to all causes, the odds of out-of-hospital mortality in children <1 year was significantly higher when the underlying cause of death was RSV, bronchiolitis, or influenza (odds ratio [OR], 1.3 [$P < .05$] for RSV; OR, 10.7 [$P < .001$] for bronchiolitis; and OR, 2.0 [$P < .001$] for influenza) (Figure 1A). For those ≥ 1 year, odds of out-of-hospital mortality due to RSV and influenza were lower than all causes ($P < .001$ for both), while underlying bronchiolitis mortality was comparable to all causes. More than 60% of underlying RSV and bronchiolitis deaths and >80% of underlying influenza deaths occurred in non-Hispanic white individuals (Table 1). However, this differed substantially by age group, with >50% of deaths occurring in nonwhite children <1 year for all 3 underlying causes of death (Figure 1B). For all 3 underlying causes of death and all-cause mortality, the highest mortality rate per 100 000 population among children aged <1 year was in black infants (Supplementary Figure 1). Black adults ≥ 65 years of age had the lowest mortality rate for RSV, bronchiolitis, and influenza, but not for all-cause mortality. There were significantly more underlying influenza deaths in women than men ($P < .001$), but no significant differences in sex for underlying RSV and bronchiolitis deaths (Table 1).

Deaths in children <1 year were concentrated in the first 6 months of life for all underlying causes of death (Figure 2). RSV mortality peaked at 1 month of age, while bronchiolitis and influenza mortality peaked at 2 months of age. Pairwise comparisons in mean age of death between RSV, influenza, and bronchiolitis were significantly different ($P < .01$). The mean age of death due to underlying RSV in children <1 year was 4.5 months, compared to 5.3 months for bronchiolitis and 6.0 months for influenza. There were no statistically significant differences in mean age of death for in-hospital vs out-of-hospital mortality for any of the 3 causes of death. The only statistically significant differences in mean age of death between race/ethnicities were that infants of other race/ethnicity were older than black and white infants (6.3 months vs 5.1 months; $P = .03$).

Contributing Causes of Death

Death certificates listing bronchiolitis as the underlying cause of death had significantly fewer contributing causes of death than underlying RSV and underlying influenza deaths (average of 2.0 [Standard Deviation (SD)1.7] vs 2.4 [SD1.8] and 2.5 [SD1.8]; $P < .001$ for both). In Pairwise comparisons, children <1 year of age had significantly fewer causes of death listed than those aged ≥ 5 years ($P < .001$ for all), with an average of 1.9 (SD1.5), 1.4 (SD1.3), and 1.8 (SD1.5) contributing causes of death for underlying RSV, bronchiolitis, and influenza. Deaths occurring outside of the hospital had an average of 0.5 (95% confidence interval, .6–.5) fewer contributing causes of death compared to deaths occurring in the hospital ($P < .001$).

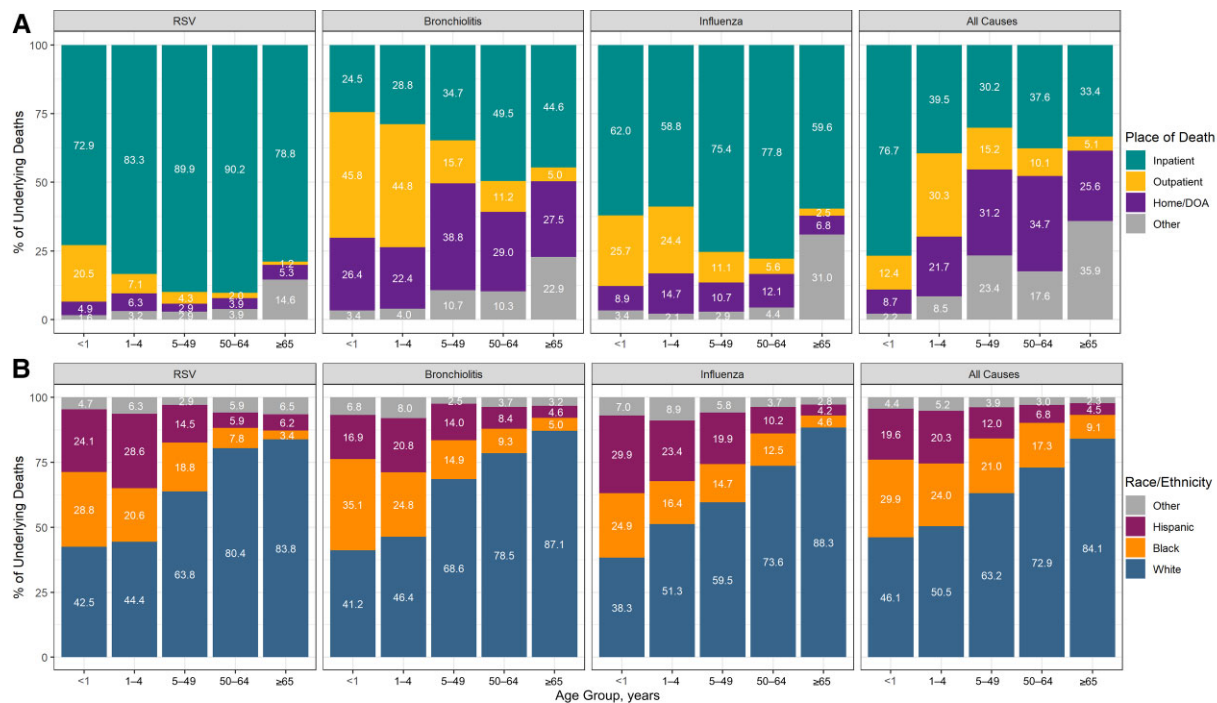


Figure 1. Place of death and race/ethnicity by age group for deaths attributed to underlying respiratory syncytial virus (RSV), bronchiolitis, influenza, and all causes. *A*, Distribution of deaths in each age group (<1, 1–4, 5–49, 50–64, ≥65 years) occurring in each location. Each bar represents 100% of deaths in the specified age group, and colors represent the percentage of deaths in each location, for each cause of death. *B*, Distribution of deaths in each age group in years by race/ethnicity. Each bar represents 100% of deaths in the specified age group. Colors indicate the percentage of deaths represented by each race/ethnicity.

Respiratory causes (J codes) were the most common contributing causes of death listed on death certificates for all age groups among underlying RSV (54.4%), bronchiolitis (66.6%), and influenza (48.3%) deaths (Table 2). However, specific J codes differed by underlying cause of death, with bronchiolitis more likely to include J18.0 (bronchopneumonia, unspecified organism) and J18.9 (pneumonia, unspecified organism), whereas underlying RSV and influenza deaths were more likely to include J80 (acute respiratory distress syndrome) (Supplementary Table 1). Circulatory causes (I codes) were the next most frequently listed contributing causes among underlying RSV (29.9%), bronchiolitis (18.7%), and influenza (40.3%) deaths. This differed by age group, with I codes appearing more frequently on death certificates in adults ≥65 years. Other infectious diseases (A and B codes) were included on 20.3% of underlying influenza deaths and were mostly accounted for by sepsis from an unspecified organism (A41.9). Endocrine and metabolic diseases (E codes), neurodevelopmental disorders (F codes), and diseases of the nervous system (G codes) were on >10% of underlying influenza deaths, mostly in those ≥50 years of age. Perinatal conditions (P codes) and congenital malformations (Q codes) were common in underlying RSV deaths, mostly in children aged <5 years. In children <1 year, prematurity was a contributing cause listed on 16.4% of underlying RSV deaths, 9.7% of underlying bronchiolitis

deaths, and 8.1% of underlying influenza deaths (Supplementary Table 2). Chronic lung disease (P19–P29) and congenital heart disease (Q20–Q28) were included on <10% of death certificates in children aged <1 year for all 3 causes of death.

When RSV was included on the death certificate as a contributing cause rather than the underlying cause, the most common underlying causes were cancers and blood disorders (C and D codes), included on 26.8% of all death certificates and 62.1% of death certificates in adults 50–64 years (Table 3). This was followed by circulatory causes (16.0%), congenital malformations (13.7%), and respiratory causes (13.4%). Respiratory causes were the most common underlying cause of death when bronchiolitis was a contributing cause (35.1%), whereas circulatory was the most common underlying cause when influenza was a contributing cause (34.3%). Congenital malformations accounted for a third of underlying deaths in children <1 years of age when RSV was a contributing cause of death, and the majority of these were congenital heart disease codes (Q20–Q28) (Supplementary Table 3).

Comparison With Excess Mortality

Excess mortality estimates place the cumulative RSV-associated mortality in children <1 year between 888 and 1820 deaths from July 1999 to June 2018 (Table 4) [4]. During this same period,

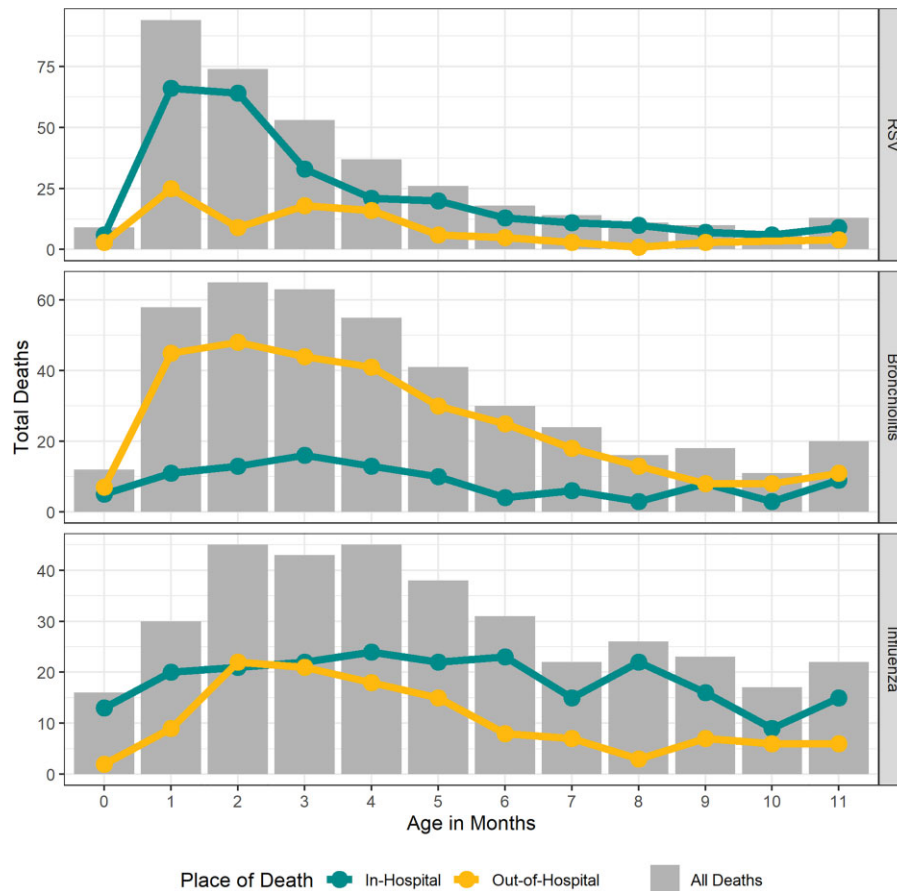


Figure 2. Age (0–11 months) at time of death in infants (<1 year of age) dying from underlying respiratory syncytial virus (RSV), bronchiolitis, or influenza. Bars represent the total number of deaths occurring during that month of age for each cause of death. Colored dots represent the number of deaths based on place of death (in-hospital or out-of-hospital).

there were 549 death certificates in this age group listing RSV, including 337 death certificates listing RSV as the underlying cause, capturing 20%–60% of RSV-associated excess mortality. The difference between death certificates and excess RSV-associated mortality was even larger for the age groups ≥ 5 years, with <1% of excess deaths captured in death certificates in those ≥ 65 years of age. Adding unspecified bronchiolitis deaths to the RSV-coded deaths in children aged <1 year captured 40%–170% of estimated RSV-associated excess deaths (Table 4, Figure 3). For all ages, the difference between death certificate data and excess mortality was considerably less for influenza than RSV, with death certificates capturing nearly all estimated excess influenza-associated deaths in children <5 years.

DISCUSSION

Here we have presented a description of death certificates listing RSV, unspecified bronchiolitis, or influenza as the underlying cause of death from 1999 to 2018. We found substantially more deaths coded as underlying influenza than RSV or bronchiolitis, and when influenza appeared on a death

certificate it was the underlying cause on nearly 80% of death certificates. Underlying RSV and bronchiolitis as cause of death were more common among children <1 year, while most of the underlying influenza deaths were in adults ≥ 65 years of age. Children aged <1 year dying with underlying RSV, bronchiolitis, or influenza were more likely to die outside of the hospital than children dying of other causes. Although race/ethnicity did not seem to explain the disproportionately high out-of-hospital mortality in this age group, black infants had the highest mortality rate for all 3 underlying causes of death. In contrast, black adults aged ≥ 65 years had the lowest mortality rate from these 3 causes. Use of death certificates results in much lower estimates of mortality from RSV and influenza compared to excess mortality modeling, except for influenza in young children. Careful considerations on the underrepresentation of RSV and influenza deaths and specific patterns in contributing causes and place of death should guide estimates of mortality and the impact of public health interventions.

We found that a higher proportion of bronchiolitis deaths occurred outside of the hospital compared to RSV or influenza

Table 2. Contributing Causes of Death Included on the Death Certificate by Age Group and Broad Condition Category When Respiratory Syncytial Virus, Bronchiolitis, or Influenza Is the Underlying Cause of Death

Cause of Death and Age Group, y	Total	Infectious Diseases (A & B Codes)	Cancer and Blood Disorders (C & D Codes)	Endocrine and Metabolic Disorders (E Codes)	Neurodevelopmental Disorders (F Codes)	Diseases of the Nervous System (G Codes)	Diseases of the Circulatory System (I Codes)	Diseases of the Respiratory System (J Codes)	Pregnancy, Puerperium, and Perinatal-Related Disorders (O & P Codes)	Congenital Disorders (Q Codes)	Other Codes (H, K–N, R–Z)	
RSV												
<1	365 (100)	50 (13.7)	NA	NA	NA	20 (5.5)	80 (21.9)	168 (46.0)	100 (27.4)	40 (11.0)	91 (24.9)	
1–4	126 (100)	11 (8.7)	15 (11.9)	12 (9.5)	NA	19 (15.1)	30 (23.8)	77 (61.1)	NA	36 (28.6)	40 (31.7)	
5–49	69 (100)	15 (21.7)	NA	NA	NA	20 (29.0)	15 (21.7)	35 (50.7)	NA	NA	39 (56.5)	
50–64	51 (100)	8 (15.7)	10 (19.6)	NA	NA	NA	12 (23.5)	36 (70.6)	NA	NA	18 (35.3)	
≥65	321 (100)	55 (17.1)	29 (9.0)	45 (14.0)	51 (15.9)	25 (7.8)	142 (44.2)	191 (59.5)	NA	NA	133 (41.4)	
Bronchiolitis												
<1	413 (100)	21 (5.1)	NA	NA	NA	13 (3.1)	37 (9.0)	231 (55.9)	64 (15.5)	29 (7.0)	91 (22.0)	
1–4	125 (100)	11 (8.8)	NA	NA	NA	10 (8.0)	11 (8.8)	77 (61.6)	NA	15 (12.0)	36 (28.8)	
5–49	121 (100)	NA	NA	15 (12.4)	18 (14.9)	13 (10.7)	20 (16.5)	94 (77.7)	NA	NA	36 (29.8)	
50–64	107 (100)	10 (9.3)	NA	15 (14.0)	25 (23.4)	NA	31 (29.0)	82 (76.6)	NA	NA	36 (33.6)	
≥65	280 (100)	18 (6.4)	14 (5.0)	29 (10.4)	40 (14.3)	14 (5.0)	97 (34.6)	213 (76.1)	NA	NA	87 (31.1)	
Influenza												
<1	358 (100)	74 (20.7)	21 (5.9)	16 (4.5)	NA	18 (5.0)	59 (16.5)	138 (38.5)	60 (16.8)	60 (16.8)	87 (24.3)	
1–4	517 (100)	105 (20.3)	34 (6.6)	34 (6.6)	NA	79 (15.3)	120 (23.2)	207 (40.0)	16 (3.1)	58 (11.2)	136 (26.3)	
5–49	5930 (100)	1625 (27.4)	489 (8.2)	958 (16.2)	515 (8.7)	575 (9.7)	1538 (25.9)	3452 (58.2)	15 (0.3)	224 (3.8)	2121 (35.8)	
50–64	7606 (100)	2314 (30.4)	877 (11.5)	1382 (18.2)	1311 (17.2)	582 (7.7)	2724 (35.8)	4627 (60.8)	NA	94 (1.2)	2894 (38.0)	
≥65	37 882 (100)	6287 (16.6)	3160 (8.3)	5494 (14.5)	8094 (21.4)	4099 (10.8)	16 653 (44.0)	16 825 (44.4)	NA	46 (0.1)	12 397 (32.7)	

Data are presented as No. (%). Values <10 not shown (NA).

Abbreviations: NA, not applicable; RSV, respiratory syncytial virus.

Table 3. Underlying Causes of Death by Age Group and Broad Condition Category When Respiratory Syncytial Virus, Influenza, or Bronchiolitis Is Listed as a Contributing Cause on the Death Certificate

Cause of Death and Age Group, y	Total	Infectious Diseases (A & B Codes)	Cancer and Blood Disorders (C & D Codes)	Endocrine and Metabolic Disorders (E Codes)	Neurodevelopmental Disorders (F Codes)	Diseases of the Nervous System (G Codes)			Diseases of the Circulatory System (I Codes)			Diseases of the Respiratory System (J Codes)			Pregnancy, Puerperium, and Perinatal-Related Disorders (O & P Codes)	Congenital Disorders (Q Codes)	Other Codes (H, K–N, R–Z)
						Diseases of the Nervous System (G Codes)	Diseases of the Circulatory System (I Codes)	Diseases of the Respiratory System (J Codes)	Diseases of the Nervous System (G Codes)	Diseases of the Circulatory System (I Codes)	Diseases of the Respiratory System (J Codes)						
RSV																	
<1	231 (100)	35 (15.2)	15 (6.5)	NA	NA	NA	NA	21 (9.1)	31 (13.4)	32 (13.9)	77 (33.3)	10 (4.3)					
1–4	137 (100)	NA	20 (14.6)	15 (10.9)	NA	NA	11 (8.0)	13 (9.5)	18 (13.1)	NA	40 (29.2)	NA					
5–49	130 (100)	NA	57 (43.8)	10 (7.7)	NA	NA	15 (11.5)	NA	15 (11.5)	NA	12 (9.2)	NA					
50–64	116 (100)	NA	72 (62.1)	NA	NA	NA	NA	10 (8.6)	13 (11.2)	NA	NA	NA					11 (9.5)
≥65	349 (100)	17 (4.9)	94 (26.9)	10 (2.9)	10 (2.9)	23 (6.6)	103 (29.5)	52 (14.9)	NA	NA	38 (10.9)						
Bronchiolitis																	
<1	540 (100)	75 (13.9)	NA	NA	NA	10 (1.9)	21 (3.9)	193 (35.7)	25 (4.6)	60 (11.1)	148 (27.4)						
1–4	223 (100)	27 (12.1)	NA	NA	NA	10 (4.5)	14 (6.3)	110 (49.3)	NA	31 (13.9)	19 (8.5)						
5–49	314 (100)	11 (3.5)	22 (7.0)	13 (4.1)	NA	14 (4.5)	63 (20.1)	94 (29.9)	NA	NA	80 (25.5)						
50–64	185 (100)	10 (5.4)	19 (10.3)	NA	NA	NA	47 (25.4)	66 (35.7)	NA	NA	30 (16.2)						
≥65	424 (100)	16 (3.8)	45 (10.6)	19 (4.5)	14 (3.3)	15 (3.5)	131 (30.9)	129 (30.4)	NA	NA	55 (13.0)						
Influenza																	
<1	141 (100)	32 (22.7)	NA	NA	NA	NA	12 (8.5)	13 (9.2)	NA	22 (15.6)	38 (27.0)						
1–4	102 (100)	16 (15.7)	11 (10.8)	NA	NA	14 (13.7)	15 (14.7)	NA	NA	13 (12.7)	17 (16.7)						
5–49	1363 (100)	213 (15.6)	155 (11.4)	167 (12.3)	22 (1.6)	68 (5.0)	312 (22.9)	164 (12.0)	NA	40 (2.9)	217 (15.9)						
50–64	2245 (100)	224 (10.0)	280 (12.5)	201 (9.0)	21 (0.9)	57 (2.5)	709 (31.6)	497 (22.1)	NA	13 (0.6)	243 (10.8)						
≥65	10 178 (100)	543 (5.3)	744 (7.3)	444 (4.4)	580 (5.7)	732 (7.2)	3766 (37.0)	2525 (24.8)	NA	NA	837 (8.2)						

Data are presented as No. (%). Values <10 not shown (NA).

Abbreviations: NA, not applicable; RSV, respiratory syncytial virus.

Table 4. Comparison of Total Respiratory Syncytial Virus and Influenza Deaths in the United States Based on Death Certificates and Excess Mortality Estimates for Each Age Group, 1999/2000 to 2017/2018 Respiratory Illness Seasons

Age Group, y	Estimates Based on Excess Mortality ^a		Estimates Based on Death Certificates ^b	
	Pneumonia and Influenza (95% CI)	Respiratory (95% CI)	Underlying (% Excess [PI – Resp])	Underlying + Contributing (% Excess [PI – Resp])
	RSV	RSV	RSV	RSV
<1	888 (725–1051)	1820 (1547–2093)	337 (38.0–18.5)	549 (61.8–30.2)
1–4	88 (–27 to 203)	384 (201–567)	120 (136.4–31.3)	251 (285.2–65.4)
5–49	1125 (160–2090)	2359 (1067–3651)	66 (5.9–2.8)	191 (17.0–8.1)
50–64	4757 (3009–6505)	9658 (5840–13 476)	45 (0.9–0.5)	152 (3.2–1.6)
≥65	50 442 (37 962–62 922)	110 205 (83 387–137 023)	306 (0.6–0.3)	634 (1.3–0.6)
			RSV + Bronchiolitis	RSV + Bronchiolitis
<1			778 (87.6–42.7)	1542 (173.6–84.7)
1–4			251 (285.2–65.4)	606 (688.6–157.8)
5–49			190 (16.9–8.1)	632 (56.2–26.8)
50–64			158 (3.3–1.6)	458 (9.6–4.7)
≥65			601 (1.2–0.5)	1370 (2.7–1.2)
	Influenza	Influenza	Influenza	Influenza
<1	349 (150–549)	431 (98–764)	345 (98.9–80.0)	479 (137.2–111.1)
1–4	437 (296–577)	459 (234–684)	500 (114.4–108.9)	601 (137.5–130.9)
5–49	7966 (8129–11 585)	9857 (8129–11 585)	5816 (73.0–59.0)	7125 (89.4–72.3)
50–64	12 060 (9894–14 227)	25 115 (20 383–29 846)	7423 (61.6–29.6)	9583 (79.5–38.2)
≥65	79 188 (62 982–94 395)	157 390 (124 714–190 067)	36 459 (46.0–23.2)	46 235 (58.4–29.4)

^aCumulative number of deaths (95% CI) for 19 respiratory virus seasons, 1999–2018. Estimates from: Hansen et al. Mortality associated with influenza and respiratory syncytial virus in the US, 1999–2018. JAMA Netw Open 2022; 5:e220527 (<https://doi.org/10.1001/jamanetworkopen.2022.0527>).

^bNumbers in parentheses represent the proportion of excess deaths associated with influenza or RSV that is captured by death certificates coded as influenza, RSV, or RSV+ unspecified bronchiolitis (no of death certificates with a specific code/no of excess deaths for a specific virus). Proportion below 100% means that reliance on death certificate coding does not capture the full excess mortality burden of viral infections (eg, RSV among adults); conversely, proportions above 100% indicate that excess mortality approaches may not be sensitive enough to detect all deaths from viral infections (eg, influenza in children)

Abbreviations: PI, Pneumonia & Influenza – Resp, Respiratory; RSV, respiratory syncytial virus.

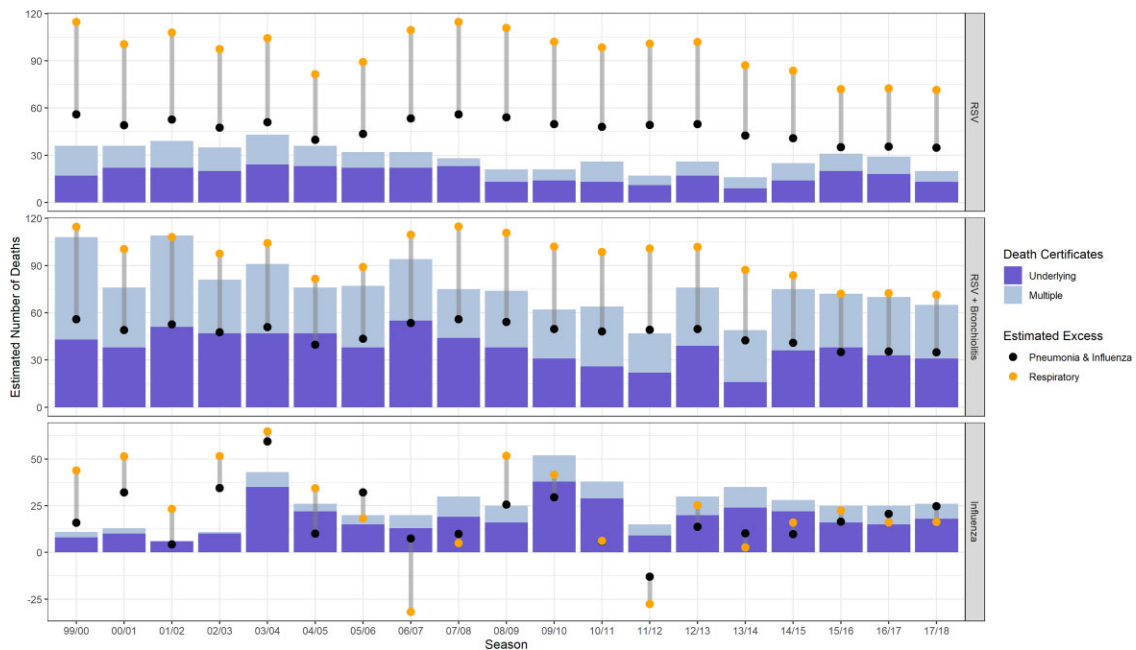


Figure 3. Comparison of number of respiratory syncytial virus (RSV) and influenza deaths based on death certificates and excess mortality estimates for each respiratory illness in children <1 year of age for 19 respiratory illness seasons (1999/2000 [99/00] through 2017/2018 [17/18]). Each bar represents the number of deaths for each season and cause of death (RSV, bronchiolitis, influenza) based on death certificate coding. The dots represent the range of deaths for each cause of death based on excess mortality estimates when using underlying pneumonia & influenza and underlying respiratory mortality as the dependent variables in regression analysis. Excess mortality estimates from: Hansen et al. Mortality associated with influenza and respiratory syncytial virus in the US, 1999–2018. JAMA Netw Open 2022; 5:e220527 (<https://doi.org/10.1001/jamanetworkopen.2022.0527>).

deaths, and that out-of-hospital deaths for all 3 underlying causes had limited information on contributing causes listed. Deaths occurring outside of the inpatient setting may be less likely to have an RSV or influenza code included on the death certificate. Studies have shown that a high proportion of adult deaths due to pneumonia occur after hospital discharge and that linking death certificate data to electronic medical records can improve estimation of respiratory disease burden by better capturing deaths that occur outside of the hospital [21, 22]. No linkage study is available to address this question in young children and hence the only available source of information is from death certificate coding. Additionally, out-of-hospital deaths likely lack detailed clinical documentation surrounding the series of events and comorbidities leading to death. A study of death certificates during the COVID-19 pandemic found an increase in both out-of-hospital deaths and the use of nonspecific cause of death codes [8]. The authors did not have data on out-of-hospital deaths by race/ethnicity, but suggested that racial and ethnic minorities may be more likely to die from COVID-19 outside of the hospital than non-Hispanic white individuals due to structural barriers to accessing medical care [8]. We did not find substantial differences in out-of-hospital mortality compared to in-hospital mortality by race/ethnicity for the endemic respiratory pathogens in our analysis. However, black infants had the highest mortality rate (both in- and out of hospital) for all 3 causes of death and all-cause mortality.

We found that a higher proportion of children <1 year of age died outside of the hospital from underlying RSV, bronchiolitis, or influenza compared to all causes and that a higher proportion of children aged <5 years died outside of the hospital from influenza than RSV. Previous studies have also documented a high proportion (~40%) of children dying from influenza outside of the hospital [23–25]. Following a severe influenza season, pediatric deaths from influenza became a nationally notifiable condition in 2004 [15]. This reporting requirement may have prompted increased influenza testing for children who die outside of the hospital compared to RSV; however, there was no significant trend in our data. A postmortem study in Zambia found that most RSV deaths in infants occur in the community [21]. Patterns will inevitably differ in high-income settings, but without comparable studies in the US, death certificate data is the only source of information. Remarkably, we found that >75% of unspecified bronchiolitis-coded deaths in children <1 year of age occurred outside of the hospital. If a portion of these deaths were in fact RSV-attributable deaths, then the out-of-hospital mortality burden from RSV is at least as great as that of influenza in infants. Accordingly, excess mortality estimates point at a substantially higher burden of RSV than influenza in infants [4]. If pediatric deaths occurring outside of the hospital are unable to benefit from improved medical treatment, vaccination of

pregnant women and young children is the best tool for preventing these deaths.

Children had fewer contributing causes of death listed on death certificates than adults, likely indicating fewer comorbidities. Respiratory codes were the most common contributing causes in all age groups for all 3 underlying causes of death. This was followed by circulatory causes, which were particularly frequent in adults ≥ 65 years of age and among influenza deaths. Circulatory causes were also the most frequent underlying cause when influenza was a contributing cause of death. Several studies have found an association between influenza and cardiac events, highlighting a potential benefit of influenza vaccination [26, 27]. While perinatal conditions and congenital malformations were more common in children aged <5 years, most infants dying from underlying RSV, bronchiolitis, or influenza did not have a high-risk condition such as prematurity, chronic lung disease, or congenital heart disease listed as a contributing cause. Current guidelines for administration of palivizumab, a monoclonal antibody that provides immunoprophylaxis against severe RSV infection, only include preterm infants born before 29 weeks' gestation or those with specific high-risk conditions [28]. We found that most infants dying from RSV did not have prematurity included as a contributing cause of death, which could support a broadening of RSV interventions. We acknowledge that prematurity codes may not always be carried forward in death certificates and that the risk of RSV death remains small for healthy infants. Analyses linking birth and death certificates are better placed to provide insight on risk factors of infant deaths [29], while modeling studies can assess the relative merits of expanded RSV interventions [30] including widespread use of new monoclonals and vaccines. In parallel, a study of pediatric influenza deaths found that children without preexisting conditions died more quickly than children with preexisting conditions, and were less likely to be vaccinated for influenza, highlighting the need for prevention of respiratory pathogens even in healthy children [23]. Moreover, there is some evidence that bacterial coinfections, notably with *Staphylococcus aureus*, increase risk of mortality from influenza in children [24, 25, 31]. Other infectious diseases were frequently reported on underlying influenza death certificates; however, these mostly included sepsis from unspecified causes, suggesting a need for increased testing for bacterial coinfections to inform appropriate treatment strategies.

RSV is substantially underestimated in children <1 year when death certificate coding is compared against excess mortality estimates [32]. Including bronchiolitis deaths with RSV deaths reduced the discrepancy between death certificates and excess mortality estimates; however, misclassification is likely still present. In contrast, influenza deaths were well reported on death certificates in children <5 years of age when compared against excess mortality estimates. This seems to be particularly true after 2004 when influenza became a nationally notifiable

condition, though we did not detect a significant trend in the number of influenza deaths reported each year. Concurrent with the increased emphasis on testing and reporting of influenza deaths, infant mortality declined over the study period, and these conflicting factors may affect the number of excess deaths ascribed to respiratory pathogens and partially explain the overlap between excess mortality and death certificates in later years [8]. While no reporting requirements exist for RSV, in 2018 the Council of State and Territorial Epidemiologists approved a standard case definition for potential RSV deaths [33]. Improved surveillance to ascertain etiologic cause of death in children is an important public health goal, especially as complications due to respiratory pathogens can present through unexpected disease processes [31]. Underestimation of RSV mortality in older adults is particularly glaring with <1% of estimated excess deaths captured by death certificates. Though inclusion of RSV on death certificates in those ≥ 50 years has increased since 2012, perhaps a result of increased testing with multipathogen polymerase chain reaction panels [9], it is still substantially underestimated. Several studies have noted an underrecognized RSV burden in this age group [1, 34–37]. Quantifying the true RSV burden in older age groups will be important for evaluating the benefit of vaccines when they become available.

We have a few limitations to consider. We did not link death certificates to birth certificates or electronic medical records. Relying on the contributing causes of death listed on the death certificate may not provide a full picture of comorbidities and preexisting conditions. This is likely more pronounced in out-of-hospital deaths, which we found included significantly fewer contributing causes of death. This is particularly important when considering the lack of prematurity codes included on underlying RSV deaths and implications for use of prophylactic treatment. We did not include other variables (eg, education, Medicaid status) that may provide a better proxy for socioeconomic status than race/ethnicity alone and may help explain disparities in out-of-hospital mortality.

CONCLUSIONS

Ascertaining etiologic cause of death is an important public health goal. RSV and bronchiolitis disproportionately affect children <1 year of age, while most recorded influenza deaths are in adults aged ≥ 65 years. Death certificates alone are likely substantially underestimating the number of deaths from RSV and influenza, particularly when deaths occur outside of the inpatient setting. Infants have higher odds of dying outside of the hospital from respiratory diseases compared to other causes, and race/ethnicity alone does not explain this disparity. Continued improvements in disease reporting on death certificates is important for quantifying the mortality burden of

respiratory pathogens, especially as new vaccines and therapeutics become available.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online (<http://jid.oxfordjournals.org/>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

Author contributions. Statistical analysis was done by C. L. H. All authors contributed to design and conceptualization of the study, interpretation of results, and manuscript preparation.

Disclaimer. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US National Institutes of Health or the US Department of Health and Human Services.

Financial support. This study was funded by Sanofi.

Supplement sponsorship. This article appears as part of the supplement “Respiratory Syncytial Virus Disease Among US Infants,” sponsored by Sanofi and AstraZeneca.

Potential conflicts of interest. C. L. H. received contract-based hourly fees from Sanofi. S. S. C. is an employee of Sanofi and may hold shares and/or stock options in the company. C. V. reports no potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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