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## Mortality Associated With Seasonal and Pandemic Influenza and Respiratory Syncytial Virus Among Children <5 Years of Age in a High HIV Prevalence Setting—South Africa, 1998–2009

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### Abstract

**Background.**—There are few published data describing the mortality burden associated with influenza and respiratory syncytial virus (RSV) infection in children in low- and middle-income countries and particularly from Africa and settings with high prevalence of human immunodeficiency virus (HIV).

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#### Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.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.

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**Methods.**—We modeled the excess mortality attributable to influenza (seasonal and pandemic) and RSV infection by applying Poisson regression models to monthly all-respiratory and pneumonia and influenza deaths, using national influenza and RSV laboratory surveillance data as covariates. In addition, we estimated the seasonal influenza- and RSV-associated deaths among HIV-infected and -uninfected children using Poisson regression models that incorporated HIV prevalence and highly active antiretroviral therapy coverage as covariates.

**Results.**—In children <5 years of age, the mean annual numbers of seasonal influenza- and RSV-associated all-respiratory deaths were 452 (8 per 100 000 person-years [PY]) and 546 (10 per 100 000 PY), respectively. Infants <1 year of age experienced higher mortality rates compared with children 1–4 years of age for both influenza (22 vs 5 per 100 000 PY) and RSV (35 vs 4 per 100 000 PY). HIV-infected compared with HIV-uninfected children <5 years of age were at increased risk of death associated with influenza (age-adjusted relative risk [aRR], 11.5; 95% confidence interval [CI], 9.6–12.6) and RSV (aRR, 8.1; 95% CI, 6.9–9.3) infection. In 2009, we estimated 549 (11 per 100 000 PY) all-respiratory influenza A(H1N1)pdm09-associated deaths among children aged <5 years.

**Conclusions.**—Our findings support increased research efforts to guide and prioritize interventions such as influenza vaccination and HIV prevention in low- and middle-income countries with high HIV prevalence such as South Africa.

### Keywords

influenza; respiratory syncytial virus; HIV; mortality; South Africa

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Globally, pneumonia is the leading cause of mortality in children [1], with the highest burden experienced in sub-Saharan Africa and Asia [2]. Influenza and respiratory syncytial virus (RSV) infections are common causes of pneumonia and are responsible for substantial global morbidity and mortality, in particular among individuals <5 and 65 years of age [3–5].

Recent studies estimated that worldwide there were between 13 and 32 million cases of influenza-associated pneumonia and as many as 110 000 deaths in children <5 years of age [6], whereas in the same age group RSV accounted for 33.8 million hospitalizations and between 66 000 and 199 000 deaths [7], 99% occurring in developing nations for both pathogens. These studies suggest a greater burden in developing countries, but available data are insufficient to prioritize strategies for influenza prevention and control, especially in sub-Saharan Africa [8], highlighting the importance of generating disease burden estimates from developing nations.

The influenza season in South Africa is well defined and occurs during the southern hemisphere's winter months (May to August) [9], whereas peak activity of RSV is observed from February to May [10, 11]. In 2009, following the introduction of pandemic influenza A(H1N1)pdm09 in the country, South Africa experienced 2 distinct waves of influenza virus circulation. The first wave was dominated by influenza A(H3N2) followed by influenza A(H1N1) pdm09 [10].

Available data suggest that the burden of influenza and RSV infection may be higher among individuals infected with human immunodeficiency virus (HIV) [11–21], with nearly two-thirds of the 34 million people (3.5 million children) with HIV infection worldwide living in sub-Saharan Africa in 2010 [22]. In South Africa in 2009, there were approximately 210 000 HIV-infected children <5 years of age [23], and the HIV prevalence among the same age group increased from 1.4% in 1998 to 4.5% in 2006, slowly declining thereafter to 4% in 2009 [24]. The highly active antiretroviral treatment (HAART) uptake in the same age group slowly increased over time and reached a plateau of approximately 20% in 2009 [24].

Influenza vaccine is available in South Africa, although uptake is low, and RSV has been considered as an important future target for vaccination [25]. Understanding the mortality burden of influenza and RSV in South Africa could assist to prioritize interventions; however, such information remains scanty, especially among South African children. In South Africa and elsewhere, influenza and RSV infections are rarely confirmed by laboratory diagnosis and related deaths may be attributed to other comorbid conditions or secondary infections, making it difficult to assess the mortality burden associated with these pathogens. In recent years, excess mortality models have become a popular statistical time series approach to estimate the mortality burden of respiratory pathogens [4, 26–30]. We used excess mortality models to estimate national influenza- (seasonal and pandemic) and RSV-associated mortality among children <5 years of age from 1998 through 2009.

## METHODS

### Mortality Data and Population Denominators

We obtained data on underlying causes of death for children <5 years of age from Statistics South Africa [31] for the period 1998–2009. We used *International Classification of Diseases, Tenth Revision* codes to compile age-specific (<1 year and 1–4 years) monthly mortality time series for all-respiratory (J00–J99) and pneumonia and influenza (P&I) (J10–J18, a subset of all-respiratory) deaths. To account for a systematic misclassification of cause of death due to coding practices that occurred between 1998 and 2005 in children 1–11 months of age, we reallocated postneonatal causes of death (ie, P23–congenital pneumonia) to more appropriate causes of infant death (ie, J18–pneumonia, organism unspecified) as recommended by Statistics South Africa [32]. In addition, we adjusted for underreporting of deaths from 1998 to 2006 using the year-specific estimates of proportion of underreported deaths provided by Darikwa and Dorrington [33]. According to these estimates, data completeness increased from 55% in 1998 to 89% in 2006. From 2007, underreporting was estimated to be <5% [34]. Population denominators were obtained from Statistics South Africa [35], whereas age- and year-specific estimates of HIV prevalence in the population and HAART coverage among HIV-infected children were obtained from the Actuarial Society of South Africa AIDS and Demographic Model [24].

### Influenza and RSV Surveillance Data

Prior to 2002, we obtained monthly influenza virus data by type and subtype from influenza-like illness surveillance implemented by the National Institute for Communicable Diseases, a division of the National Health Laboratory Services (NHLS), South Africa [9] and from

a cohort study for RSV [19]. From 2002, we acquired influenza and RSV virological data from a national database (the NHLS corporate data warehouse) that includes all patients tested by the NHLS laboratory network. We considered an influenza type or subtype to be dominant during the influenza season when it accounted for >50% of the circulating viruses.

### Estimation of Influenza- and RSV-Associated Mortality

To estimate the influenza- (seasonal and pandemic) and RSV-associated mortality, we fitted age-specific Poisson regression models to monthly deaths. The full model (model 1) included covariates for time trends and seasonal variation as well as viral circulation. The full model is provided in the Supplementary Data.

To reduce possible bias associated with differences in specimen sampling and laboratory methods over time, we standardized the monthly numbers of specimens testing positive for influenza or RSV by the annual total of all specimens tested for the specific pathogen [5]. We estimated excess mortality associated with influenza and RSV by subtracting an expected baseline from the model 1 monthly mortality estimates. The baseline was obtained by setting the viral covariates to 0 and the annual excess mortality was obtained as the sum of the monthly excess mortality estimates for each year. We obtained the 95% confidence interval (CI) for the estimated excess mortality using bootstrap resampling on blocks of calendar years (12-month block resampling with replacement) over 1000 replications [36]. In brief, for each resampled dataset we refitted the Poisson regression model, and the 95% CIs were obtained from the 2.5th and 97.5th percentiles of the estimated influenza- and RSV-associated mortality from the 1000 resampled datasets.

In South Africa, the diagnosis of AIDS is rarely coded on the death certificate [32]. To assess changes in annual seasonal influenza and RSV excess mortality rates (as obtained from model 1) in relation to the HIV prevalence in the population and the HAART coverage over the years, we fitted separate multivariable Poisson regression models (model 2) for annual all-respiratory and P&I seasonal influenza- and RSV-associated mortality rates by age group. The full model is provided in the Supplementary Data. We estimated the excess mortality associated with HIV infection among influenza- and RSV-associated deaths by subtracting an expected baseline from the model 2 annual estimates. The baseline was obtained by setting the HIV and HAART covariates to 0. Mortality rates by HIV status were obtained by dividing the estimated excess deaths by the population at risk within each category. Age-specific and age-adjusted relative risk for influenza- and RSV-associated mortality related to HIV infection were estimated using log-binomial regression. The statistical analysis was implemented using Stata software version 12 (StataCorp, College Station, Texas).

### Ethics

Because this analysis used only publicly available mortality data and de-identified and aggregated laboratory data, the analysis was considered to be exempt from human subjects ethics review.

## RESULTS

### Mortality Data

South Africa had a population of approximately 5.1 million children <5 years of age in 2009: 1.1 million (21%) aged <1 year and 4.0 million (79%) aged 1–4 years. A mean of 20 441 (range, 14 560–23 320) all-respiratory deaths occurred annually among South African children <5 years of age over the study period (Table 1). Of these deaths, 76% occurred among children <1 year of age. The mean mortality rate for all-respiratory deaths was 12-fold higher in children <1 year compared with children 1–4 years of age (1442 vs 112 per 100 000 person-years [PY]). In children <5 years of age, the annual mortality rate per 100 000 PY for all-respiratory deaths increased from 273 in 1998 to 373 in 2004, subsequently declining to 202 in 2009 (monthly trends reported in Figure 1A). A similar trend was observed for P&I and across age groups (results not shown).

### Influenza and RSV Laboratory Surveillance

A mean of 3403 (range, 227–15 321) and 1810 (range, 578–5247) samples was tested annually for influenza and RSV, respectively. The mean annual number of specimens testing positive was 937 (27%) for influenza virus and 356 (20%) for RSV. Over the study period, the influenza detection rates peaked between May and August with 10 of the 12 years experiencing peak activity in June–July (Figure 1B). In 2009, a first wave of influenza A(H3N2) peaked in June followed by a second wave of influenza A(H1N1)pdm09 that peaked in August. Conversely, RSV peak activity was observed between March and April in 8 of the 12 years with early or late peaks observed in February or May in the remaining years.

### Influenza and RSV-Associated Mortality

Using model 1, we estimated that over the study period the annual number of all-respiratory seasonal influenza-associated deaths in children <5 years of age ranged between 284 and 667 (rate, 6–13 per 100 000 PY; Table 2). In the same age group, the annual RSV-associated mortality for all-respiratory deaths ranged between 404 and 609 (rate, 7–12 per 100 000 PY; Table 3).

Using model 2, we estimated that among children <5 years of age the mortality rate for all-respiratory cause of death was greater in HIV-infected compared with HIV-uninfected individuals for both seasonal influenza (age-adjusted relative risk [aRR], 11.5; 95% CI, 9.6–12.6) and RSV (aRR, 8.1; 95% CI, 6.9–9.3) (Table 4). A similar trend was observed for P&I seasonal influenza- and RSV-associated deaths and across age groups.

Overall among HIV-uninfected children, RSV was associated with 1.2 times as many all-respiratory deaths as seasonal influenza: 1.6 and 0.8 among children <1 year and 1–4 years of age, respectively. Similar trends were observed among P&I deaths related to RSV and seasonal influenza virus infections.

In 2009, we estimated 549 (rate, 10.9 per 100 000 PY) all-respiratory influenza A(H1N1)pdm09-associated deaths among children aged <5 years: 311 (rate, 27.0 per 100

000 PY) and 238 (rate, 5.9 per 100 000 PY) among children <1 year and 1–4 years of age, respectively. Among P&I deaths in children aged <5 years, 470 (rate, 9.2 per 100 000 PY) were associated with influenza A(H1N1)pdm09: 279 (rate, 25.3 per 100 000 PY) and 191 (rate, 4.8 per 100 000 PY) among children <1 year and 1–4 years of age, respectively. In children <5 years of age, all-respiratory influenza A(H1N1)pdm09-associated mortality rates (10.9 per 100 000 PY) were 1.3-fold (95% CI, 1.2- to 1.5-fold) higher than the mean annual seasonal influenza-associated mortality rates (8.1 per 100 000 PY) over the study period and 1.8-fold (95% CI, 1.6- to 2.1-fold) higher than seasonal influenza-associated mortality (5.9 per 100 000 PY) in 2009.

## DISCUSSION

To the best of our knowledge, this report is the first to provide national estimates of influenza- and RSV-associated mortality in children <5 years of age in a high HIV prevalence setting in Africa. The mortality burden was substantial for both influenza and RSV and the mortality rates were higher among HIV-infected compared with HIV-uninfected children across age groups and underlying cause of death. Whereas the mortality rates were greater among HIV-infected children, the burden remained considerable among HIV-uninfected individuals and was highest in infants compared with older children. These findings support increased efforts for control of seasonal influenza in children in South Africa and other low- and middle-income countries. In addition, in countries with high HIV prevalence such as South Africa, programs to prevent HIV infection and mortality, such as prevention of mother-to-child transmission and early antiretroviral therapy, will remain important interventions to reduce the mortality associated with RSV and influenza virus infection.

The all-respiratory seasonal influenza-associated mortality rate in children <5 years of age in South Africa (8 per 100 000 PY) was elevated compared with estimates obtained from similar studies in the United States and Europe (range, 0.1–2 per 100 000 PY for all-respiratory or respiratory and circulatory influenza-associated deaths in equivalent age groups) [4, 37–39]. South African estimates were closer to those of other middle-income countries such as Mexico, where rates in the range of 3.4–8.5 per 100 000 PY (for all-respiratory deaths among children <5 years of age) have been reported [40]. The rates of seasonal influenza-associated mortality remained elevated even among HIV-uninfected South African children <5 years of age (6 per 100 000 PY) compared with more developed nations. A similar trend was observed for South African elderly individuals (>65 years of age), an age group where the burden of HIV is lowest and where seasonal influenza-associated mortality rates were >4-fold higher than among seniors in the United States [41].

Similar to influenza, all-respiratory RSV-associated mortality rates among HIV-uninfected children in South Africa (28 per 100 000 PY in children <1 year of age and 3 per 100 000 PY in children 1–4 years of age) were elevated compared with those reported in the United States and England (range, 2.9–5.3 per 100 000 PY and 0.2–0.3 per 100 000 PY for all-respiratory or respiratory and circulatory RSV-associated deaths in children aged <1 year and 1–4 years, respectively) [4, 37], indicating a heavy burden of both pathogens even among HIV-uninfected individuals in South Africa.

Recent meta-analyses have reported higher seasonal influenza– [6] and RSV-associated lower respiratory tract infection [7] case fatality rates in children from developing countries (2.9% for influenza and 2.1% for RSV) compared with those in more developed nations (0.2% for influenza and 0.3% for RSV). Whereas the high HIV infection rate in developing countries [22] may partially explain the elevated burden of influenza and RSV infection, other factors such as poor nutritional status and poor access to healthcare, as well as other comorbidities and coinfections, have been suggested as potential additional risk factors for poor outcome in developing nations [42].

We found that HIV-infected children experienced approximately a 10 times greater risk of death associated with seasonal influenza and RSV infection compared with HIV-uninfected individuals. Other studies, using methodology that differed from ours, have reported increased risk of death associated with HIV infection among seasonal influenza– and RSV-infected individuals [11–14, 20, 21].

In South African HIV-uninfected children, RSV was associated with 1.6 and 0.8 times as many deaths as seasonal influenza in children aged <1 year and 1–4 years, respectively. In the same age groups, reports from the United States indicated that RSV accounted for approximately 10 and 0.5 times the seasonal influenza mortality rate [4], whereas ratios of approximately 1.5 and 1 were reported in England [37]. Whereas the South African estimates are closer to those from England, the observed wide range of the relative contribution of these 2 pathogens, especially to infant mortality, highlights the need to implement additional studies in different countries and settings. In particular, ecological studies conducted in settings similar to ours, where influenza and RSV peak activities are not synchronous, may assist in better differentiating the relative burden of these 2 pathogens.

We found that in 2009, the influenza A(H1N1)pdm09-associated mortality among South African children <5 years of age was 1.3-fold higher compared with mean annual estimates for seasonal influenza over the study period. The comparison of the mortality associated with influenza A(H1N1)pdm09 and seasonal influenza during previous seasons remains difficult in South Africa because of the changes in HIV prevalence and HAART coverage in the population that impact the annual seasonal influenza–associated mortality over the study period. However, the mortality associated with influenza A(H1N1) pdm09 was approximately 1.8-fold higher even when compared with those associated with influenza A(H3N2) in 2009. This suggests a moderately higher mortality burden of influenza A (H1N1)pdm09 in 2009 compared with seasonal influenza among South African children <5 years of age. Other studies have reported similar or higher mortality associated with influenza A(H1N1)pdm09 compared with seasonal influenza in children <5 years of age [26, 39, 40, 43–45].

Our study has limitations that warrant discussion. First, the lack of weekly mortality statistics and the paucity of virological data prior to 2002 may have hindered the ability to accurately estimate the relative contribution of RSV and influenza virus on mortality. In addition, the limited information about influenza types and subtypes in the early years of our study hindered the ability to estimate subtype-specific associated mortality. Furthermore, we did not have additional information on individual deaths. Second, because of poor recording

of HIV infection in the death register in the early years of our study, we utilized indirect methods to assess the mortality burden among HIV-infected and -uninfected individuals. Although the HIV epidemic in South Africa is considered to be a major factor responsible for the increased mortality rates observed over the years [32, 34], the lack of time series data for other potential comorbidities/risk factors may have resulted in overestimating the increased risk of death associated with HIV infection. In addition, we could not estimate the influenza A(H1N1)pdm09-associated mortality by HIV status because our method uses HIV prevalence data over several years. Third, we did not include nonrespiratory deaths in our study. Whereas influenza-associated mortality has been reported among individuals with circulatory, diabetes, or other chronic conditions, the prevalence of these conditions is low among the study population included in this study (children <5 years of age). Last, while we utilized methods suggested by Statistics South Africa to account for the systematic misclassification of cause of death in infants from 1998 to 2005 and underreporting of deaths from 1998 to 2006, such adjustments may have introduced potential biases in the early years of our study.

In conclusion, we reported a substantial mortality burden associated with RSV and influenza virus infection in both HIV-infected and -uninfected children in South Africa. The effectiveness of RSV candidate vaccines is being evaluated [46]; vaccination remains the most effective method of preventing influenza virus infection and should be recommended for South African children.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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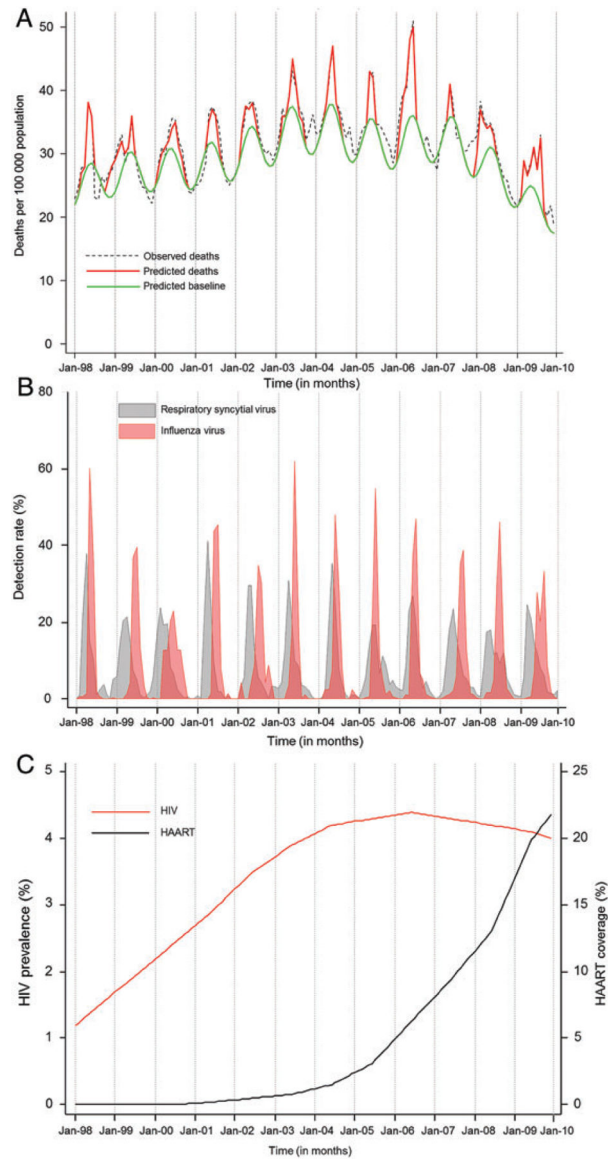
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**Figure 1.** Mortality rate, detection of influenza and respiratory syncytial virus, human immunodeficiency virus (HIV) prevalence, and highly active antiretroviral therapy (HAART) coverage in children <5 years of age in South Africa, 1998–2009. *A*, Observed all-respiratory deaths, predicted deaths, and predicted baseline by month (Poisson model 1). *B*, Monthly detection rate (ie, monthly number of positive specimens divided by total specimens) of influenza and respiratory syncytial virus (all ages). *C*, Annual HIV prevalence and HAART coverage obtained from the Actuarial Society of South Africa AIDS and Demographic Model [24]. Observed deaths [31] are adjusted using estimates of death underreporting from 1998 to 2006 [33].

**Table 1.**

Mean Annual Respiratory Deaths in Children &lt;5 Years of Age in South Africa, 1998–2009

Cause of Death	Deaths <sup>a</sup>	
	No., Mean (Range)	Rate <sup>b</sup> , Mean (Range)
All respiratory		
<1 y	15 676 (11 135–17 973)	1442 (1070–1696)
1–4 y	4765 (3425–5875)	112 (83–138)
<5 y	20 441 (14 560–23 320)	383 (284–439)
Pneumonia and influenza		
<1 y	13 063 (7889–15 651)	1199 (758–1415)
1–4 y	3701 (2497–4483)	87 (61–105)
<5 y	16 764 (10 387–20 078)	314 (202–373)

Source: Statistics South Africa [31].

<sup>a</sup>Deaths adjusted for underreporting.<sup>b</sup>Death rate per 100 000 person-years.

**Table 2.** Estimated Seasonal Influenza–Associated Deaths in Children <5 Years of Age by HIV Status in South Africa, 1998–2009<sup>a</sup>

Year	Predominant Influenza Type/Subtype	Excess All-Respiratory Deaths						Excess Pneumonia/Influenza Deaths					
		Total		HIV-Positive		HIV-Negative		Total		HIV-Positive		HIV-Negative	
		No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>
1998	A(H3N2)	500	9	101	138	399	8	437	8	105	143	332	6
1999	B	363	6	87	86	276	5	317	6	86	85	231	4
2000	A(H1N1)	456	8	134	102	322	6	438	8	149	114	289	5
2001	A(H3N2)	580	11	190	118	389	7	548	10	206	128	342	6
2002	B	336	6	119	63	217	4	301	5	119	63	183	3
2003	A(H3N2)	533	10	198	95	334	6	479	9	201	96	278	5
2004	A(H3N2)	534	10	201	90	333	6	495	9	209	94	285	5
2005	A(H1N1)	452	8	169	73	282	5	415	8	172	75	242	5
2006	A(H3N2)	667	13	222	96	445	9	504	10	192	83	311	6
2007	A(H3N2)	368	7	121	53	247	4	315	6	113	50	201	4
2008	A(H1N1)	350	7	100	46	250	5	294	6	92	42	202	4
2009	A(H3N2)	284	6	65	31	219	4	238	5	54	26	184	4

Abbreviation: HIV, human immunodeficiency virus.

<sup>a</sup>Estimated from model 1 (overall deaths) and model 2 (deaths by HIV status).

<sup>b</sup>Death rates per 100 000 person-years.

**Table 3.** Estimated Respiratory Syncytial Virus-Associated Deaths in Children <5 Years of Age by HIV Status in South Africa, 1998–2009<sup>a</sup>

Year	Excess All-Respiratory Deaths						Excess Pneumonia/Influenza Deaths												
	Total			HIV-Positive			HIV-Negative			Total			HIV-Positive			HIV-Negative			
	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	No.	Rate <sup>b</sup>	
1998	510	9	85	116	424	8	456	8	91	124	365	7							
1999	553	10	115	113	438	8	502	9	122	121	379	7							
2000	588	11	143	109	444	8	540	10	153	116	387	7							
2001	609	11	165	103	444	8	566	10	176	110	389	7							
2002	599	11	176	93	422	8	559	10	187	99	372	7							
2003	585	12	179	85	405	8	544	10	188	90	355	7							
2004	577	11	177	79	399	8	525	10	181	81	344	7							
2005	575	12	171	74	404	8	505	10	168	73	337	7							
2006	565	11	154	66	410	8	480	9	146	62	333	7							
2007	526	10	131	57	394	8	430	8	121	53	309	6							
2008	467	9	101	46	366	7	371	7	91	41	279	6							
2009	404	7	55	26	348	7	312	6	47	22	265	5							

Abbreviation: HIV, human immunodeficiency virus.

<sup>a</sup>Estimated from model 1 (overall deaths) and model 2 (deaths by HIV status).

<sup>b</sup>Death rates per 100 000 person-years.

Table 4.

Estimated Seasonal Influenza and Respiratory Syncytial Virus Mean Annual Associated Deaths and Relative Risk for Mortality Due to HIV Infection in Children <5 Years of Age in South Africa, 1998–2009<sup>a</sup>

Cause of Death	Mean Annual Excess Deaths										Relative Risk (HIV-Positive vs HIV-Negative) (95% CI)
	Total			HIV-Positive			HIV-Negative				
	No., Mean (95% CI)	Rate <sup>b</sup> , Mean (95% CI)	Percentage Mortality Over Model Baseline, Mean (95% CI)	No., Mean (95% CI)	Rate <sup>b</sup> , Mean (95% CI)	No., Mean (95% CI)	Rate <sup>b</sup> , Mean (95% CI)	No., Mean (95% CI)	Rate <sup>b</sup> , Mean (95% CI)	No., Mean (95% CI)	
Seasonal influenza virus											
All respiratory											
<1 y	240 (117–368)	22 (11–34)	4 (2–7)	72 (33–110)	162 (79–246)	168 (83–257)	16 (8–25)	10.1 (8.7–11.7)			
1–4 y	212 (110–313)	5 (2–7)	9 (7–11)	71 (36–104)	52 (28–78)	141 (73–208)	3 (2–5)	15.4 (11.2–21.1)			
<5 y	452 (227–681)	8 (4–13)	5 (4–8)	143 (69–214)	83 (42–123)	309 (157–466)	6 (3–9)	11.5 (9.6–12.6) <sup>c</sup>			
Pneumonia and influenza											
<1 y	212 (106–330)	19 (10–30)	4 (3–6)	77 (37–119)	174 (87–267)	136 (69–209)	13 (6–20)	13.5 (11.4–15.8)			
1–4 y	186 (97–279)	4 (2–6)	11 (8–13)	65 (33–96)	49 (26–73)	121 (64–180)	3 (2–4)	16.7 (11.8–23.4)			
<5 y	398 (204–606)	7 (4–11)	6 (5–8)	142 (71–216)	83 (43–125)	256 (133–390)	5 (2–7)	14.0 (12.1–16.2) <sup>c</sup>			
Respiratory syncytial virus											
All respiratory											
<1 y	384 (185–589)	35 (17–54)	6 (5–7)	90 (43–138)	204 (98–311)	294 (141–450)	28 (13–43)	7.2 (6.5–8.1)			
1–4 y	162 (63–240)	4 (1–7)	5 (4–6)	47 (18–70)	35 (13–51)	114 (44–169)	3 (1–4)	12.5 (8.8–17.8)			
<5 y	546 (248–829)	10 (5–15)	6 (5–7)	138 (62–208)	81 (36–122)	408 (186–619)	8 (4–12)	8.1 (6.9–9.3) <sup>c</sup>			
Pneumonia and influenza											
<1 y	362 (198–568)	33 (18–52)	6 (5–7)	100 (54–156)	225 (123–351)	263 (144–412)	25 (14–39)	8.9 (7.9–10.1)			
1–4 y	120 (47–191)	3 (1–5)	6 (4–8)	40 (15–63)	29 (11–46)	80 (31–127)	2 (1–3)	14.9 (9.8–22.6)			
<5 y	482 (254–759)	9 (4–14)	6 (5–7)	139 (70–219)	83 (42–130)	343 (175–540)	7 (3–10)	9.4 (8.3–10.5) <sup>c</sup>			

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus.

<sup>a</sup>Estimated from model 1 (overall deaths) and model 2 (deaths by HIV status).

<sup>b</sup>Death rates per 100 000 person-years.

<sup>c</sup>Age-adjusted relative risk.