Deaths Associated with Respiratory Syncytial and Influenza Viruses among Persons ≥5 Years of Age in HIV-Prevalent Area, South Africa, 1998–2009[1]

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Learning Objectives

Upon completion of this activity, participants will be able to:

- Distinguish general trends in rates of respiratory death in South Africa
- Discuss trends in influenza-related mortality in South Africa
- Analyze trends in mortality related to respiratory syncytial virus in South Africa

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We estimated deaths attributable to influenza and respiratory syncytial virus (RSV) among persons ≥5 years of age in South Africa during 1998–2009 by applying regression models to monthly deaths and laboratory surveillance data. Rates were expressed per 100,000 person-years. The mean annual number of seasonal influenza–associated deaths was 9,093 (rate 21.6). Persons ≥65 years of age and HIV-positive persons accounted for 50% (n = 4,552) and 28% (n = 2,564) of overall seasonal influenza-associated deaths, respectively. In 2009, we estimated 4,113 (rate 9.2) influenza A(H1N1) pdm09–associated deaths. The mean of annual RSV-associated deaths during the study period was 511 (rate 1.2); no RSV-associated deaths were estimated in persons ≥45 years of age. Our findings support the recommendation for influenza vaccination of older persons and HIV-positive persons. Surveillance for RSV should be strengthened to clarify the public health implications and severity of illness associated with RSV infection in South Africa.

Influenza virus and respiratory syncytial virus (RSV) infections cause substantial numbers of illness and deaths globally each year; the highest rates are in young children and persons ≥65 years of age (*1*–*4*). However, national estimates of deaths caused by these infections remain scarce in Africa.

Available data suggest that the severity of influenza and RSV illness is higher among HIV-positive persons (*5*–*11*). During 2009 in South Africa, ≈5.1 million HIV-positive persons ≥5 years of age were reported (*12*). The highest prevalence was in the 20–44-year age group, among whom HIV prevalence increased from 10% in 1998 to 24% in 2009. Coverage with highly active antiretroviral therapy (HAART) among HIV-positive persons slowly increased from 2004 to reach a plateau of ≈14% in 2009 (*12*). The lowest reported occurrence of HIV infection in the country was in persons ≥75 years of age; data showed a 0.6% prevalence and 26% HAART coverage for this group in 2009 (*12*). Pneumonia ranked within the top 5 leading causes of death among persons ≥15 years of age in South Africa in 2009 (*13*).

Clarification of the annual number of deaths associated with influenza and RSV in South Africa could assist with the prioritization of interventions. Because influenza virus and RSV infections are rarely confirmed by laboratory diagnosis and related deaths may be attributed to co-morbid conditions or secondary infections, we applied modeling approaches (*14*) to estimate seasonal and pandemic influenza- and RSV-associated deaths among persons ≥5 years of age during 1998–2009.

Methods

Mortality Data and Population Denominators

We obtained data on underlying causes of death for persons ≥5 years of age during 1998–2009 from Statistics South Africa (*15*). We used codes from the International Classification of Diseases, 10th Revision (ICD-10), to compile an age-specific (5–19, 20–44, 45–64, 65–74, and ≥75 years) monthly mortality data time series for all-cause (ICD-10: any); all respiratory (ICD-10: J00–J99); all circulatory (ICD-10: I00–I99); and pneumonia and influenza (P&I) (ICD-10: J10–J18), a subset of all respiratory deaths. During the study period, underreporting of deaths was estimated to be <5% (*13*). Population denominators were obtained from Statistics South Africa (*16*); we obtained year- and age-specific estimates of HIV prevalence in the population and HAART coverage among HIV-positive older children and adults from the Actuarial Society of South Africa AIDS and Demographic Model (*12*).

Influenza and RSV Surveillance Data

For the study period before 2002, we obtained influenza virus data, including types and subtypes, from influenza-like illness surveillance implemented by the National Institute for Communicable Diseases, a division of the National Health Laboratory Service, South Africa (*17*), and RSV data from a cohort study (*10*). For the years after 2002, we acquired virologic data on influenza and RSV from the National Health Laboratory Service corporate data warehouse, a national database that includes all patients tested for respiratory viruses in the public sector in South Africa. We considered an influenza type or subtype to be dominant during the influenza season if it represented >50% of the circulating viruses.

Estimation of Influenza- and RSV-Associated Deaths

We conducted a 2-stage analysis. In the first stage, we estimated the annual number of deaths associated with influenza and RSV in South Africa; in the second stage, we estimated the proportion of these deaths that were experienced by HIV-positive and HIV-negative persons. During the first stage, to estimate the number of deaths associated with seasonal and pandemic influenza and RSV, we fitted age-specific generalized regression models with a Poisson distribution and an identity link to the number of monthly deaths as previously described (*14*). The full model (model 1) included co-variates for time trends, seasonal variation, and proxies for viral circulation. Model specification, selection procedures and sensitivity analysis are provided in the online Technical Appendix (http://wwwnc.cdc.gov/EID/article/21/4/14-1033-Techapp1.pdf). Separate models were fitted for each age group and cause of death.

In South Africa, a diagnosis of AIDS is rarely coded on the death certificate (*13*), which hinders direct estimation of respiratory virus–associated deaths by HIV status. To assess the proportionate number of deaths associated

with influenza and RSV among HIV-positive and HIV-negative persons, we used a previously developed methodology (*14*) that leverages the increasing trend in HIV prevalence in South Africa. The rationale is that if HIV is a risk factor for influenza- or RSV– associated death, influenza- or RSV– related mortality rates should increase over time proportionately to the observed increase in HIV prevalence. Our approach also controls for increasing HAART coverage, which may decrease the severity of influenza or RSV in HIV-positive patients (*18*). In this second-stage analysis, we fitted regression models (model 2) to annual estimates of influenza- and RSV-associated excess mortality rates by age group, including data for HIV prevalence and HAART coverage, time trends, and dominant influenza subtypes (for the influenza model) (*14*). Model specifications are provided in the online Technical Appendix.

Subsequently, we obtained mortality rates associated with HIV status by dividing the estimated influenza-associated deaths by HIV status from model 2 by the mid-year population estimates within each category (i.e., HIV-positive and HIV-negative persons). Mortality rates were expressed per 100,000 person-years. We used log-binomial regression (*14*) to estimate age-specific and age-adjusted relative risk for influenza- and RSV-associated death related to HIV infection by comparing influenza- or RSV-associated mortality rates among HIV-positive and HIV-negative persons. We used STATA version 12 (StataCorp, College Station, Texas, USA) to implement the statistical analysis.

Sensitivity Analysis of Influenza- and RSV-Associated Deaths among Persons ≥45 Years of Age

In contrast to previous studies (*3*,*4*), our models estimated that influenza, but not RSV, was associated with excess deaths in South Africa among persons aged ≥45 years. We hypothesized that differences in the timing of the RSV and influenza seasons may explain these discrepancies because RSV and influenza rarely co-circulate in South Africa, but they do in other temperate settings (*3*,*4*). This difference could potentially confound burden of illness estimates for these pathogens. We implemented a sensitivity analysis to explore this hypothesis by artificially shifting the RSV surveillance time series so that it overlapped with the influenza season and repeating model 1 calculations (online Technical Appendix).

Ethics

This analysis used only publicly available mortality data and deidentified and aggregated laboratory data. Therefore, the study was considered to be exempt from human subjects ethics review.

Results

Deaths and Mortality Rates

South Africa had a population of ≈44.8 million persons ≥5 years of age in 2009; persons 5–64 years of age accounted for 85% of this population. During the study period, a mean of 463,594 deaths occurred annually among persons from South Africa ≥5 years of age, of which 101,450 (22%) were attributable to respiratory and 112,716 (24%) to circulatory causes of death (online Technical Appendix Table 1). The mean annual mortality rate for all-cause death increased from 112 for persons 5–19 years of age to 9,732 for persons ≥75 years of age. Similar patterns were observed regarding the other underlying causes of death evaluated in this study. Among persons 20–44 years of age, for which the HIV burden is greatest (24% HIV prevalence in 2009 [*12*]), the annual mortality rate for all respiratory deaths increased from 78 in 1998 to 310 in 2004, subsequently declining to 233 in 2009 (monthly trends provided in the Figure, panel A). In contrast, no evident secular trend for all respiratory mortality rates was observed among persons ≥75 years of age, for whom HIV incidence is lowest (<0.01% HIV prevalence in 2009 [*12*]) (Figure, panel B).

Influenza and RSV Laboratory Surveillance

A mean of 3,403 (range 227–15,321) and 1,810 (range 578–5,247) respiratory specimens were tested annually for influenza virus and RSV, respectively. The mean annual number of specimens that tested positive was 937 (27%) for influenza virus and 356 (20%) for RSV. During the study period, the influenza season peaked between May and August (winter in South Africa); 10 of the 12 years showed peak activity during June–July (Figure, panel C). In 2009, an epidemic of influenza A(H3N2) peaked in June, and influenza A(H1N1) pdm09 activity peaked in August. RSV peak activity was observed during March and April (autumn in South Africa) in 8 of the 12 years. Early or late peaks were observed in February or May in the remaining years.

Influenza- and RSV-Associated Deaths

During 1998–2009, the estimated annual number of all-cause seasonal influenza-associated deaths in persons ≥5 years of age (model 1) ranged from 6,450 to 11,012 (rate 16.7–24.5) (online Technical Appendix Table 2). In the same population, estimated annual all-cause RSV-associated deaths ranged from 292 to 626 (rate 0.7–1.4) (online Technical Appendix Table 2).

The estimated mean seasonal influenza–associated mortality rate for all-cause deaths increased progressively from 0.8 for the 5–19-year age group to 379.2 for the ≥75-year age group. Similar trends were observed for the other causes of death evaluated in this study (Table 1). Overall, the estimated mean seasonal influenza–associated mortality

rate for all-cause deaths was higher for HIV-positive persons than for those who were HIV-negative (age-adjusted relative risk [aRR] 7.9, 95% CI 7.1–8.9). Overall, 28% (2,564/9,093) of estimated all-cause seasonal influenza–associated deaths occurred among HIV-positive persons.

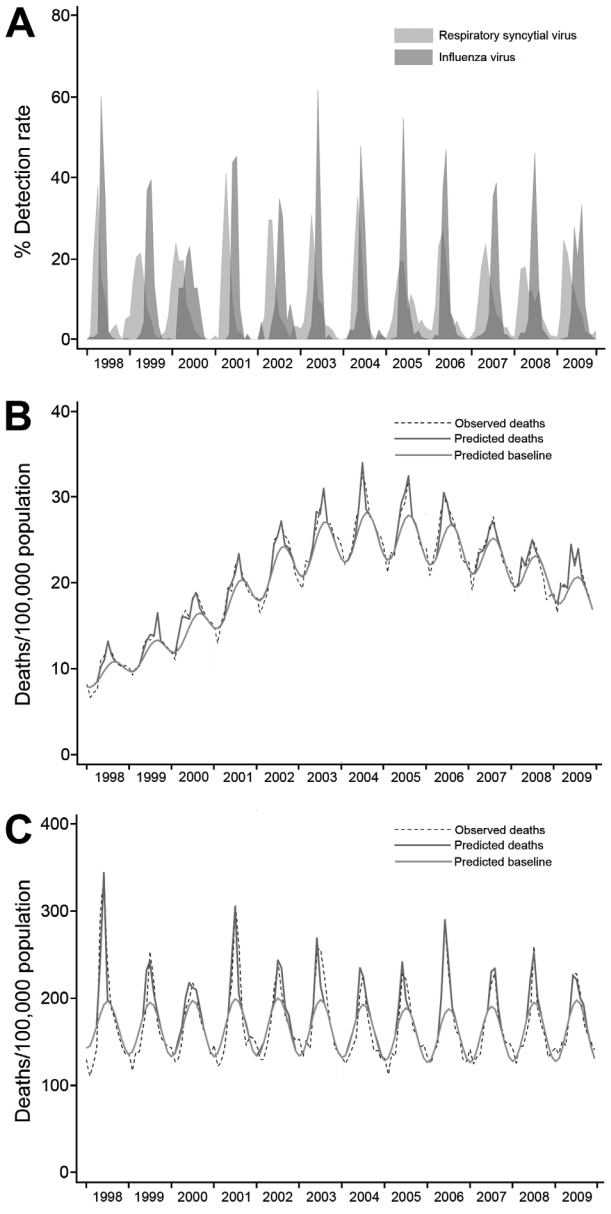

Figure. Monthly mortality and detection rates for influenza and respiratory syncytial virus in South Africa, 1998–2009.
A) Observed respiratory deaths, predicted deaths, and predicted baseline by month (model 1) of persons 20–44 years of age.
B) Observed respiratory deaths, predicted deaths, and predicted baseline by month (model 1) in persons ≥75 years of age.
C) Detection rate (i.e., monthly number of positive specimens divided by annual number of specimens tested) of influenza and respiratory syncytial virus (all ages). A color version of this figure is available online (wwwnc.cdc.gov/eid/article/21/4/14-1033-f.htm)

In 2009, we estimated 4,113 (rate 9.2) all-cause influenza A(H1N1)pdm09–associated deaths among persons ≥5 years of age (Table 2). The mortality rate associated with influenza A(H1N1)pdm09 in 2009 in persons 5–19 years of age was 5.4 times higher than the mean for prepandemic years. In contrast, persons ≥75 years of age experienced ≈100 times lower influenza A(H1N1)pdm09 rates than expected in typical nonpandemic years. A similar trend was observed for other causes of death evaluated in this study.

The estimated RSV-associated mortality rate for all-cause deaths was 0.4 for the 5–19-year age group and 2.4 for the 20–44-year age group (Table 3). However, no RSV-associated deaths were estimated among persons ≥45 years of age. Among persons 5–44 years of age, the RSV-associated mortality rate for all causes of death was considerably higher for HIV-positive than HIV-negative persons (aRR 66.1, 95% CI 26.0–167.8). Similar trends were observed for the RSV-associated mortality rate among all respiratory and P&I deaths. A nonsignificant RSV-associated mortality rate (mean annual deaths: 8) was identified among circulatory deaths only in the 5–19-year age group. Overall, 89% (455/511) of all-cause RSV-associated death occurred among HIV-positive persons.

Sensitivity Analysis of Influenza- and RSV-Associated Deaths among Persons ≥45 Years of Age

On sensitivity analysis, we applied an artificial incremental shift of the RSV laboratory surveillance time series to make the influenza and RSV seasons more synchronous, resulting in a progressive increase in estimated RSV-associated deaths (online Technical Appendix Table 3). We found that annual all-cause RSV-associated deaths peaked at 3,661 among persons ≥45 years of age (compared with 0 in the main analysis) when the RSV and influenza seasons coincided in most years (2 months incremental shift of the RSV season). Thereafter, the estimated mean annual all-cause RSV-associated deaths decreased again to 0 when the peak circulation of the 2 pathogens were farther apart (5-month incremental shift of the RSV season). This trend was observed for all causes of death evaluated in this study. Conversely, the estimated influenza-associated deaths remained stable throughout sensitivity analyses, without regard to the shift in RSV season. Specifically, the estimated all-cause influenza-associated deaths among persons ≥45 years of age remained within 10% of its original value (online Technical Appendix Table 3).

Discussion

We reported estimates of influenza- and RSV-associated deaths in persons ≥5 years of age in a high HIV prevalence setting in Africa. The number of seasonal influenza–associated deaths was substantial and observed across age groups and underlying causes of death evaluated

Table 1. Seasonal influenza virus mean annual excess deaths and relative risk for death related to HIV infection among persons ≥5 y of age, South Africa, 1998–2009*

Cause of death by age, y	Mean annual excess deaths							Relative risk, HIV+ vs HIV–
	Total			HIV+		HIV–		
	No.	Rate†	% Death over model baseline	No.	Rate†	No.	Rate†	
All causes								
5–19	127	0.8	2.4	52	23.6	75	0.5	46.6
20–44	1,966	10.7	3.0	1,851	56.3	114	0.7	72.8
45–64	2,447	37.3	5.7	661	163.9	1,785	29.3	5.6
65–74	1,664	115.4	8.1	NED	NED	1,664	115.4	NA
≥75	2,888	379.2	10.7	NED	NED	2,888	379.2	NA
≥5	9,093	21.6	5.7	2,564	64.7	7,189	18.9	7.9‡
All respiratory								
5–19	96	0.6	9.8	55	24.6	41	0.3	87.7
20–44	778	4.2	5.0	722	21.5	56	0.4	57.1
45–64	1,106	16.8	11.4	380	93.9	725	11.9	7.9
65–74	626	43.4	14.3	NED	NED	626	43.4	NA
≥75	1,005	132.3	17.3	NED	NED	1,005	132.3	NA
≥5	3,613	8.5	10.0	1,157	28.7	2,455	6.4	11.1‡
All circulatory								
5–19	28	0.2	6.2	NED	NED	28	0.2	NA
20–44	252	1.4	4.0	226	7.2	26	0.2	41.2
45–64	854	13.2	6.9	258	66.3	596	9.9	6.6
65–74	749	52.1	8.3	NED	NED	749	52.1	NA
≥75	1,270	167.4	10.1	NED	NED	1,270	167.4	NA
≥5	3,153	7.5	7.8.	484	12.0	2,669	6.9	6.8‡
Pneumonia and influenza								
5–19	86	0.6	13.7	50	22.4	36	0.2	91.1
20–44	569	3.1	5.4	522	15.5	47	0.3	48.5
45–64	612	9.3	12.5	279	67.1	336	5.5	12.2
65–74	299	20.8	16.1	NED	NED	299	20.8	NA
≥75	620	83.0	21.2	NED	NED	620	83.0	NA
≥5	2,186	5.2	10.8	848	20.9	1,341	3.5	17.3‡

*Estimated from model 1 (excess deaths irrespective of HIV status) and model 2 (excess deaths by HIV status). HIV, human immunodeficiency virus; NED, no estimated deaths; NA, not applicable. An expanded version of this table that includes 95% CIs is available online (http://wwwnc.cdc.gov/EID/article/21/4/14-1033-T1.htm).
†Mortality rates per 100,000 person-years.
‡Age-adjusted relative risk.

in this study, irrespective of the person's HIV status. However, the seasonal influenza-associated mortality rates were highest among persons ≥65 years of age and HIV-positive adults 5–64 years of age. The seasonal influenza–associated deaths in these groups accounted for 50% and 28%, respectively, of the total influenza-associated deaths among persons ≥5 years of age. Conversely, a moderate number of deaths associated with RSV infection was found mainly among HIV-positive persons 5–44 years of age; the model did not estimate RSV-associated deaths for persons ≥45 years of age.

Previous studies have reported elevated influenza-associated mortality rates among the elderly (*3,4,19–21*) and HIV-positive persons (*6,8,9,11,14*). We did not find an excess risk for seasonal influenza–associated death due to HIV infection among persons ≥65 years of age across the underlying causes of deaths evaluated in this study. This finding may reflect the low HIV prevalence among elderly persons that may have hindered our ability to estimate the extent of disease in this group using our described method.

Among persons ≥5 years of age years in South Africa, the number of deaths associated with pandemic influenza A(H1N1)pdm09 during 2009 was approximately half that of an average influenza season in prepandemic years. However, pandemic-related mortality rates were higher in the 5–19-year age group and lower in the ≥45-year age group compared with typical seasons. Other studies have reported overall lower mortality rates associated with the first year of circulation of the 2009 pandemic virus, compared with that of seasonal influenza, but have found a higher disease burden for children and young adults (*4,21–25*). Our estimates are similar to the lower-bound estimates for South Africa from a global influenza A(H1N1)pdm09 mortality model (*26*).

For persons ≥5 years of age in South Africa, ≈90% of RSV-associated deaths were estimated to have occurred among HIV-positive persons 5–44 years of age, although our model did not estimate RSV-associated deaths among persons ≥45 years of age, an age group in which the HIV infection rate is low (1.3% in 2009) (*12*). This finding suggests that HIV infection may be a major risk factor for RSV-associated death for persons ≥5 years of age, consistent with our high estimate of HIV as a risk factor for RSV-associated death (aRR 66.1, 95% CI 26.0–167.8). Other

Table 2. Influenza A(H1N1)pdm09 excess deaths among persons ≥5 y of age, South Africa, July–September 2009*

Cause of death by age, y	Influenza A(H1N1)pdm09 excess deaths in 2009			Mortality rate ratio‡
	No.	Rate†	% Death over model baseline	
All causes				
5–19	682	4.4	12.7	5.4
20–44	1,820	9.3	2.6	0.9
45–64	1,301	17.2	2.5	0.5
65–74	279	17.6	1.2	0.2
≥75	31	3.6	0.1	0.01
≥5	4,113	9.2	2.6	0.4§
All respiratory				
5–19	626	4.1	61.6	6.9
20–44	936	4.8	6.0	1.2
45–64	729	9.6	6.3	0.6
65–74	159	10.1	3.3	0.2
≥75	16	1.8	0.2	0.01
≥5	2,466	5.5	7.1	0.7§
All circulatory				
5–19	7	0.05	1.7	0.2
20–44	252	1.3	4.1	1.0
45–64	404	5.3	3.0	0.4
65–74	75	4.7	0.8	0.1
≥75	13	1.5	0.09	0.01
≥5	751	1.7	1.7	0.2§
Pneumonia and influenza				
5–19	449	2.9	73.1	5.5
20–44	548	2.8	5.7	0.9
45–64	421	5.6	7.3	0.6
65–74	90	5.7	4.3	0.3
≥75	3	0.4	0.08	0.005
≥5	1,511	3.4	3.7	0.7§

*Estimated from model 1 (excess deaths irrespective of HIV status). An expanded version of this table that includes 95% CIs is available online (http://wwwnc.cdc.gov/EID/article/21/4/14-1033-T2.htm).
†Mortality rates per 100,000 person-years.
‡Mortality rate ratio: 2009 influenza A(H1N1)pdm09 vs. 1998–2009 mean annual seasonal influenza.
§Age-adjusted rate ratio.

studies have reported an increased risk for RSV-associated death among HIV-positive persons (*5,7*).

Our findings differ from those of similar studies from the United States and England, where RSV-associated deaths have been reported across age groups (including persons referred to as elderly in the respective studies) and where the influenza and RSV seasons are, in most cases, synchronous (*3,4*). However, there are notable geographic variations in the timing of RSV circulation across the United States (*27*). In southern Florida, where the RSV season precedes the influenza season by several weeks as in South Africa, 1 peak of pneumonia hospitalizations among persons ≥65 years of age could be detected concurrently with the influenza season. In contrast, among children <5 years of age, 2 distinct peaks of pneumonia hospitalizations were observed concomitantly with the RSV and influenza seasons (*27*). Further, a study that used a methodology similar to ours and evaluated data from a large hospital group in South Africa estimated elevated RSV-associated hospitalizations among children <5 years of age but no RSV-associated hospitalizations among adult and elderly persons (*28*). These results are similar to a previous study conducted in South Africa that found influenza- and RSV-associated mortality among children <5 years of age (*14*), but no RSV-associated mortality was estimated among elderly persons in our study.

We performed a sensitivity analysis to test whether the overlap between the RSV and influenza seasons affected mortality estimates. We found that RSV mortality estimates increased substantially among persons ≥45 years of age when the RSV season was artificially shifted to later in the year, so that it coincided with influenza activity. However, influenza estimates remained within 10% of their main analysis values, solidifying our influenza results. This finding suggests that careful interpretation of the results of time series excess mortality models is needed when used to simultaneously estimate the mortality attributable to co-circulating pathogens, particularly for RSV.

Severe illness and death among laboratory-confirmed RSV-infected adults has been reported (*29,30*), even though the clinical association between pathogen detection and disease remains difficult to interpret in the absence of comparison groups (i.e., RSV prevalence among adults without respiratory illness). Studies conducted in Kenya and South Africa that compared the RSV prevalence among patients hospitalized with severe acute respiratory illness (SARI) to control groups found that RSV infection was associated with hospitalization among

Table 3. Respiratory syncytial virus mean annual excess deaths and relative risk of death related to HIV infection among persons ≥5 y of age, South Africa, 1998–2009*

Cause of death by age, y	Mean annual excess deaths							Relative risk, HIV+ vs. HIV–
	Total			HIV+		HIV–		
	No.	Rate†	% Death over model baseline	No.	Rate†	No.	Rate†	
All causes								
5–19	61	0.4	0.9	25	11.6	36	0.2	58.4
20–44	449	2.4	0.6	430	13.1	19	0.1	98.3
45–64	NED	NED	NED	NED	NED	NED	NED	NA
65–74	NED	NED	NED	NED	NED	NED	NED	NA
≥75	NED	NED	NED	NED	NED	NED	NED	NA
≥5	511	1.2	0.7	455	12.1	55	0.1	66.1‡
All respiratory								
5–19	39	0.3	3.6	22	10.1	16	0.1	90.2
20–44	389	2.1	2.3	369	11.1	20	0.1	81.7
45–64	NED	NED	NED	NED	NED	NED	NED	NA
65–74	NED	NED	NED	NED	NED	NED	NED	NA
≥75	NED	NED	NED	NED	NED	NED	NED	NA
≥5	429	1.0	1.1	392	9.8	37	0.1	85.4‡
All circulatory								
5–19	8	0.05	1.4	NED	NED	8	0.05	NA
20–44	NED	NED	NED	NED	NED	NED	NED	NA
45–64	NED	NED	NED	NED	NED	NED	NED	NA
65–74	NED	NED	NED	NED	NED	NED	NED	NA
≥75	NED	NED	NED	NED	NED	NED	NED	NA
≥5	8	0.05	1.4	NED	NED	8	0.05	NA
Pneumonia and influenza								
5–19	35	0.2	5.2	20	9.2	15	0.1	92.2
20–44	257	1.4	2.3	243	7.2	14	0.1	73.4
45–64	NED	NED	NED	NED	NED	NED	NED	NA
65–74	NED	NED	NED	NED	NED	NED	NED	NA
≥75	NED	NED	NED	NED	NED	NED	NED	NA
≥5	292	0.7	1.3	263	6.6	29	0.1	82.7‡

*Estimated from model 1 (excess deaths irrespective of HIV status) and model 2 (excess deaths by HIV status). HIV, human immunodeficiency virus; NED, no estimated deaths; NA, not applicable. An expanded version of this table that includes 95% confidence intervals is available online (http://wwwnc.cdc.gov/EID/article/21/4/14-1033-T3.htm).
†Mortality rates per 100,000 person-years.
‡Age-adjusted relative risk.

children <5 years of age, but no association was found among persons ≥5 years of age (*31,32*). This finding may suggest that, although RSV is detected among older children and adults, it may play a less important role as a pathogen in this group. However, both studies were underpowered to look specifically at disease association in persons ≥65 years of age. Studies conducted in Egypt, Guatemala, Kenya, and Thailand, where patients of all ages hospitalized with acute lower respiratory tract infections were systematically enrolled and tested using PCR techniques, reported RSV detection rates of <1%–5% among persons ≥50 or ≥65 years of age, compared with RSV detection rates of >20% in infants and young children (*31,33–35*). Reinfection with RSV during life has been reported (*36*), but titers of serum-neutralizing antibodies ≥6 (log2 scale) have been associated with 3 times lower risk for RSV-associated hospitalizations (*37*). Adults reinfected with RSV may have high levels of serum-neutralizing antibodies that have potential to lower the prevalence and severity of RSV-associated hospitalizations in this age group.

In South Africa during 2009–2010, the RSV detection rate among patients hospitalized with SARI decreased from 26.8% among infants <1 year of age to 0.9% among persons ≥65 years of age. In the same study population, the influenza detection rate across age groups was 8%–12% (*38*). The low RSV detection rate among adults and elderly persons with SARI suggests a lower rate of RSV-associated hospitalization than that for influenza for this group (and as a result, a potentially low number of RSV-associated deaths).

Although RSV-associated deaths among persons ≥45 years of age are expected to occur in South Africa, our modeling approach may fail to statistically estimate a small number of cases. Ecologic studies conducted in settings similar to ours, where influenza and RSV peak activities are not synchronous, may assist in better differentiating the relative impact of these pathogens, especially in adults. In addition, results obtained from ecologic models should be interpreted along with findings from case-based studies and the strengths and weaknesses of both approaches should be evaluated.

Our study has limitations that warrant discussion. First, the lack of weekly mortality statistics and the paucity of virologic data before 2002 may have hindered the ability

to accurately estimate the relative contribution of RSV and influenza virus on number of associated deaths. Second, the lack of influenza incidence data (such as influenza-like illness indicators) hampered our ability to consider more refined indicators of respiratory virus activity in our time series models as reported by Goldstein et al. in 2012 (*39*). Third, because of poor records of HIV infection in the death register documenting the early years of our study, we used indirect methods to estimate the number of deaths associated with respiratory viruses among HIV-positive and HIV-negative persons. Although the HIV epidemic in South Africa is considered to be a major factor responsible for the increased mortality rates observed over the years (*40*), the lack of time series data for other potential co-occurring conditions and risk factors may have resulted in overestimation of the increased risk for death associated with HIV infection. Last, we could not estimate the influenza A(H1N1)pdm09–associated mortality by HIV status because our method requires availability of HIV prevalence data over several years of A(H1N1)pdm09 circulation.

In conclusion, we report a substantial risk for death associated with seasonal influenza virus infection, especially for persons ≥65 years of age and HIV-positive adults 20–64 years of age. The risk for death associated with RSV was mainly found among HIV-positive persons 5–44 years of age; our model did not identify excess RSV-associated deaths in persons ≥45 years of age. We also report low to moderate numbers of RSV-associated deaths among persons ≥5 years of age; however, clinical diagnosis and surveillance for RSV should be continued and strengthened to better describe the consequences and severity associated with RSV infection in this age group.

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Deaths Associated with Respiratory Syncytial and Influenza Viruses among Persons ≥5 Years of Age in HIV-Prevalent Area, South Africa, 1998–2009

Technical Appendix

Methods

Stage 1 Model: National Estimates of Influenza- and RSV-associated Deaths

To estimate the influenza- (seasonal and pandemic) and RSV-associated deaths, we fitted age-specific Generalized Linear Models (GLM) with a Poisson distribution and an identity link to the number of monthly deaths as previously described (*1*). The identity link was selected because it is considered the most biologically plausible link to model the impact of pathogen circulation on mortality (*2–6*).The full model (Model 1) included covariates for time trends and seasonal variation as well as proxies for viral circulation as follows:

$$E(Y_{i,t}) = \beta_{0,i} + \beta_{1,i}[t] + \beta_{2,i}[t^2] + \beta_{3,i}[t^3] + \beta_{4,i}[t^4] + \beta_{5,i}[\sin(2t\pi/12)] + \beta_{6,i}[\cos(2t\pi/12)]$$

$$+ \beta_{7,i}[Seasonal\_Influenza(t)] + \beta_{8,i}[\mathrm{A}(H1N1)\,pdm09] + \beta 9,i\,[RSV(t)] + \varepsilon_{i,t}$$

$E(Y_{i,t})$ represents age-specific number of deaths in age group i and month t; $\beta_{0,i}$ is the age-specific model constant; $\beta_{1,i}$ to $\beta_{4,i}$ are age-specific coefficients associated with time trends (linear to quartic polynomial terms); $\beta_{5,i}$ and $\beta_{6,i}$ are age-specific coefficients associated with harmonic terms accounting for annual background seasonal variations; $\beta_{7,i}$ to $\beta_{9,i}$ are age-specific coefficients representing the contribution of respiratory viruses to mortality (seasonal influenza ($\beta_{7,i}$): including A(H1N1), A(H3N2) and B; pandemic influenza ($\beta_{8,i}$): A(H1N1)pdm09; and RSV ($\beta_{9,i}$)); and $\varepsilon_{i,t}$ is the age-specific error term. *Seasonal_influenza(t)*, *A(H1N1)pdm09(t)* and *RSV(t)* are proxies for monthly viral activity, estimated as the monthly number of specimen testing positive for influenza or RSV over the annual number of specimens tested for the specific

pathogen. We used standardization by the annual total of all specimens tested for the specific pathogen, to reduce possible bias associated with differences in specimen sampling and laboratory methods over time (*7*). Proxies for viral activity were based on all-age laboratory surveillance data and hence remained the same across all age groups. Models were fitted separately for each age group and cause of death.

Through model selection procedures, we assessed the fit of models including higher order polynomials to represent more subtle time trends (1^{st} to 6^{th} degree) and additional harmonic terms representing annual and semi-annual periodicity ($sin(2t_i\pi/12)$ and $cos(2t_i\pi/12)$; $sin(4t_i\pi/12)$ and $cos(4t_i\pi/12)$). The final model (Model 1) was that for which the Akaike value (AIC) was minimized, that is, the model that provided best fit to the data while maintaining parsimony. We also assessed the effect of removing the RSV covariate on the model estimates for influenza virus. In this model the estimates for influenza-associated deaths remained within 10% of their main-analysis values, solidifying our influenza results. Furthermore, we assessed the model fit using two different proxies for monthly viral activities. Proxy 1 was obtained by dividing the monthly number of specimen testing positive for influenza or RSV to the annual number of specimens tested for the specific pathogen (model presented in equation 1). Proxy 2 was not standardized by the annual number of specimens tested. The estimates from models using proxies 1 or 2 were comparable; however the models fitted using proxy 2 yielded consistently higher AIC values compared to the models fitted using proxy 1. In addition, we implemented a sensitivity analysis where we compared the estimates from our count model (equation 1) to those obtained from a rate model. The estimates obtained from the rate models remained within 3% of their main-analysis values (count model) across the analysis implemented over the different causes of death and age groups evaluated in the study (Technical Appendix Table 4). Modeling counts or rates in equation 1 gives similar results given slow trends in population sizes. Given the minimal difference between the estimates from the count and rates models, we chose to model death counts instead of death rates in line with previously developed methodologies (*1, 8,9*). We also considered b-splines (1 knot per month was best) instead of polynomial terms to model background seasonality, but polynomial terms provided the best fit to the South African data, perhaps because of the relatively crude monthly resolution of the data; however this hypothesis could not be tested.

We estimated the age-specific excess deaths associated with influenza and RSV each month by subtracting an expected baseline from the monthly deaths predictions of Model 1. The baseline was obtained by setting the relevant viral covariates to 0 (i.e., to obtain a baseline for seasonal influenza, we set the seasonal influenza proxy to 0). Annual excess deaths were estimated as the sum of the monthly excess deaths for each year. We obtained the 95% confidence interval (CI) for the estimated excess deaths using bootstrap resampling on blocks of calendar years (12 months block resampling with replacement) over 1000 replications (*1,10*). For each resampled dataset we refitted the regression model and the 95% CI were obtained from the 2.5^{th} and 97.5^{th} percentiles of the estimated influenza- and RSV-associated deaths from the 1000 resampled datasets.

Stage-2 Model: Estimates of Influenza- and RSV-associated Deaths by HIV Status

In South Africa, a diagnosis of AIDS is rarely coded on the death certificate (*11*) hindering direct estimation of respiratory virus-associated excess deaths by HIV status. Instead, we used a two-stage regression approach that builds on the annual national excess deaths estimates provided by Model 1. The rationale for the annual regression relies on using the increasing trend in HIV prevalence over time to estimate the fraction of national excess deaths attributed to HIV-positive and negative persons (in particular, if HIV was not a risk factor for influenza-related death, then influenza-related mortality rates would not increase over time, and influenza-related deaths would occur among HIV-infected and HIV-uninfected populations proportionally to their group sizes). The annual regression further accounts for increasing HAART coverage (which tends to decrease influenza-related excess deaths among HIV-infected persons over time [*9*]) and circulation of more severe influenza subtypes (A(H3N2) vs A(H1N1) or B). Through model selection procedures, we assessed the fit of models including higher order polynomials (1^{st} to 3^{rd} degree) to represent time trends of health indicators unrelated to influenza, HIV or HAART as well as the removal of the influenza, HIV or HAART covariate from the models. The model with 2^{nd} degree polynomial time trends and influenza, HIV and HAART covariates had the best fit to the data. The model accounts for the combined effect of varying HIV prevalence in the population over the years as well as different HIV interventions, including the prevention of HIV infection and the effect of HAART on HIV infected persons.

We fitted separate multivariate GLM for each age group and cause of death, considering a Poisson distribution and an identity link (Model 2) as previously described (1). The following model was used for influenza:

$$E\left(Y_{i,t}\right) = \alpha_i \begin{pmatrix} \beta_{0,i} + \beta_{1,i}[t] + \beta_{2,i}[t^2] + \beta_{3,i}[Influenza\_Subtype\ (t)] \\ +\beta_{4,i}[HIV_i(t)] + \beta_{5,i}[HAART_i(t)] + \varepsilon_i(t) \end{pmatrix}$$

Where $E(Y_{i,t})$ represents the age-specific number of influenza-associated excess deaths in age group i and year t (as obtained from the stage-1 approach); α_i is an offset representing the population size of age group i; $\beta_{0,i}$ is the age-specific intercept; $\beta_{1,i}$ and $\beta_{2,i}$ are age-specific coefficients associated with time trends (linear and quadratic) included to account for potential variations of health indicators unrelated to influenza, HIV prevalence or HAART coverage in the population; $\beta_{3,i}$ is the age-specific coefficient associated with dominant seasonal influenza type/subtype each year (categorical variable with A(H3N2)-dominant years as reference group versus A(H1N1) or B) (*7,12*); $\beta_{4,i}$ is the coefficient associated with the HIV prevalence in the population in age group i and year t; $\beta_{5,i}$ is the coefficient associated with HAART coverage among HIV-infected persons in the population in age group i and year t; and ε_i is the age-specific error term. The model was not fitted to death estimates for influenza A(H1N1)pdm09 as the approach requires several years of circulation of a specific virus to partition excess deaths by HIV status.

Similar models, with the exclusion of the dominant influenza types/subtypes, were used to estimate RSV-associated mortality rates by HIV status. We estimated the influenza and RSV-related excess deaths among HIV-infected patients by subtracting an expected baseline from the Model 2 annual estimates. The baseline was obtained by setting the HIV and HAART covariates to 0.

Sensitivity Analysis of Influenza- and RSV-associated Deaths among Persons ≥45 Years of Age

In South Africa the RSV season typically precedes the influenza season by several weeks (*13–15*) while in other countries such as the United States of America and England, the influenza and RSV seasons are, in most cases, more synchronous (*12,16*). In these settings, both influenza- and RSV-associated deaths have been reported across age groups including elderly persons (*12,16*), while in our study we estimated only influenza-associated deaths among persons aged ≥45 years. To determine if synchronous RSV and influenza seasons may confound excess

death estimates derived from time series regression models, we implemented a sensitivity analysis whereby we applied a 1 month incremental shift (1 to 5 months) of the RSV laboratory proxy indicator while keeping the influenza proxy as in the main analysis. We then refitted the monthly regression model of stage 1 (equation 1) for each underlying cause of death evaluated in this study among persons ≥45 years of age. Hence, we obtained estimates of influenza- and RSV-associated deaths under each scenario whereby the RSV season progressively approached and then diverged from the influenza season. This allowed us to model artificially synchronous RSV and influenza seasons and compare our estimates with those of the asynchronous seasons observed in South Africa.

Results

Technical Appendix Table 1. Deaths among persons ≥5 y of age, South Africa, 1998–2009

	Deaths	
Cause of death, age, y	No., mean (range)	Rate,* mean (range)
All causes		
5–19	16,974 (13,300–19,282)	112 (92–126)
20–44	190,910 (108,052–233,926)	1,045 (653–1,257)
45–64	124,156 (87,355–148,521)	1,899 (1,596–2,090)
65–74	57,660 (50,294–64,230)	4,009 (3,871–4,146)
≥75	73,893 (61,318–88,604)	9,732 (9,122–10,277)
≥5	463,594 (321,917–541,780)	1,101 (837–1,250)
All respiratory		
5–19	2,887 (1,800–3,496)	19 (12–23)
20–44	44,054 (19,247–57,459)	240 (116–310)
45–64	27,206 (1,7492–33,170)	414 (319–474)
65–74	11,987 (10,558–13,156)	834 (801–870)
≥75	15,314 (13,353–17,619)	2,024 (1,882–2,189)
≥5	101,450 (63,971–122,326)	240 (166–282)
All circulatory		
5–19	1,371 (1,262–1,567)	9 (8–10)
20–44	17,681 (15,515–19,435)	97 (91–107)
45–64	34,799 (30,285–38,674)	537 (506–572)
65–74	24,890 (23,003–26,751)	1,735 (1,658–1,828)
≥75	33,975 (30,171–39,207)	4,487 (4,240–4,735)
≥5	112,716 (100,327–123,683)	269 (256–283)
Pneumonia and influenza		
5–19	1,874 (1,152–2,281)	12 (8–15)
20–44	29,615 (11,827–38,562)	162 (71–212)
45–64	13,571 (7,364–17,335)	206 (134–249)
65–74	4,973 (4,252–5,472)	346 (327–368)
≥75	7865 (6,749–9,020)	1,040 (959–1,149)
≥5	57,901 (32,332–71,860)	137 (84–165)

*Mortality rate per 100,000 person-years.

Technical Appendix Table 2. Seasonal influenza- and respiratory syncytial virus-associated deaths among persons ≥5 y of age categorized by HIV status, South Africa, 1998–2009*

Year, predominant influenza type (subtype)		Excess all causes deaths						Excess all respiratory deaths					
		Total		HIV+		HIV–		Total		HIV+		HIV–	
		No.	Rate†	No.	Rate†	No.	Rate†	No.	Rate†	No.	Rate†	No.	Rate†
Influenza viruses													
1998, A(H3N2)		8,859	21.5	2,552	68.1	6,901	18.4	3,601	8.7	1,181	31.5	2,420	6.4
1999, B		6,833	17.4	1,411	60.7	5,674	15.4	2,576	6.5	538	23.1	2,038	5.5
2000, A(H1N1)		7,292	18.3	1,707	53.2	5,927	16.1	2,823	7.0	700	21.8	2,122	5.7
2001, A(H3N2)		8,020	19.8	2,098	63.0	6,380	17.1	3,191	7.8	922	27.7	2,269	6.1
2002, B		6,450	16.7	1,158	64.5	5,472	14.9	2,351	6.1	400	31.5	1,950	5.3
2003, A(H3N2)		9,310	22.2	2,855	69.8	7,164	19.0	3,823	9.1	1,356	33.1	2,466	6.5
2004, A(H3N2)		9,784	23.1	3,120	71.4	7,486	19.7	4,021	9.4	1,495	34.2	2,526	6.6
2005, A(H1N1)		10,015	23.3	3,229	70.4	7,678	18.3	4,087	9.5	1,537	33.5	2,549	6.6
2006, A(H3N2)		10,229	23.6	3,255	68.4	7,904	19.4	4,130	9.5	1,528	32.1	2,601	6.7
2007, A(H3N2)		10,565	24.1	3,240	66.1	8,276	19.2	4,210	9.6	1,491	30.4	2,719	6.9
2008, A(H1N1)		10,746	22.2	3,143	62.5	8,531	19.7	4,241	9.5	1,419	28.2	2,821	6.1
2009, A(H3N2)		11,012	24.5	3,006	58.5	8,878	22.4	4,302	9.6	1,324	25.7	2,978	7.5
Respiratory syncytial virus													
1998	NA	292	0.7	237	13.2	55	0.1	183	0.4	154	8.5	29	0.08
1999	NA	323	0.8	273	11.7	50	0.1	224	0.5	194	8.3	29	0.08
2000	NA	363	0.9	316	11.8	47	0.1	274	0.6	245	7.6	29	0.08
2001	NA	436	1.1	384	11.5	51	0.1	358	0.8	323	9.7	35	0.08
2002	NA	514	1.2	458	12.2	55	0.1	449	1.0	410	10.9	39	0.08
2003	NA	574	1.3	516	12.6	58	0.1	518	1.2	476	11.6	42	0.08
2004	NA	615	1.4	554	12.7	60	0.1	559	1.3	516	11.8	43	0.08
2005	NA	626	1.4	565	12.3	60	0.1	561	1.3	519	11.3	42	0.08
2006	NA	621	1.4	562	11.8	59	0.1	547	1.2	506	10.6	41	0.08
2007	NA	608	1.3	551	11.2	57	0.1	521	1.1	482	9.8	42	0.08
2008	NA	589	1.3	534	10.6	55	0.1	491	1.1	454	9.0	43	0.08
2009	NA	569	1.2	515	10.0	54	0.1	461	1.0	426	8.2	42	0.08

* Estimated from stage 1 model (excess deaths irrespective of HIV status) and stage 2 model (excess deaths by HIV status).
†Mortality rates per 100,000 person-years

Technical Appendix Table 3. Sensitivity analysis of seasonal influenza- and respiratory syncytial virus-associated mortality implemented over one month incremental shift of the respiratory syncytial virus season among persons ≥45 y of age in South Africa, 1998–2009

Shift of RSV* season (in months)	Mean annual excess deaths							
	All causes		All respiratory		All circulatory		Pneumonia and influenza	
	Influenza	RSV	Influenza	RSV	Influenza	RSV	Influenza	RSV
+0†	6,442	0	2,523	0	2,647	0	1,450	0
+1	6,478	1,709	2,609	209	2,730	470	1,499	149
+2	5,811	3,661	2,309	1,329	2,406	1,598	1,244	1,089
+3	6,500	2,668	2,548	1,136	2,686	1,473	1,444	903
+4	6,635	0	2,652	167	2,796	107	1,539	201
+5	6,103	0	2,504	0	2,553	0	1,451	0

*RSV, respiratory syncytial virus.
†Actual data with no shift of the RSV season.

Technical Appendix Table 4. Sensitivity analysis comparing the results of seasonal and pandemic influenza- and respiratory syncytial virus-associated deaths between the count model (main model; equation 1) and the rate model, South Africa, 1998–2009*

	Mean annual excess number of deaths					
	Seasonal influenza, mean 1998–2009		Influenza A(H1N1)pdm09, 2009		Respiratory syncytial virus, mean 1998–2009	
Cause of death, age, yr	Count model (95% CI)	Rate model	Count model (95% CI)	Rate model	Count model (95% CI)	Rate model
All causes						
5–19	127 (91–171)	131	682 (455–910)	699	61 (29–87)	62
20–44	1,966 (1,160–2,770)	1,926	1,820 (1,201–2,403)	1,801	449 (66–863)	445
45–64	2,447 (1,499–3,408)	2,434	1,301 (867–1,735)	1,317	NED	NED
65–74	1,664 (1,185–2,181)	1,680	279 (186–373)	285	NED	NED
≥75	2,888 (2,138–3,557)	2,879	31 (20–42)	32	NED	NED
All respiratory						
5–19	96 (60–137)	95	626 (417–835)	615	39 (13–61)	38
20–44	778 (416–1,144)	791	936 (624–1,248)	927	389 (269–516)	386
45–64	1,106 (696–1,562)	1,088	729 (486–972)	734	NED	NED
65–74	626 (416–852)	629	159 (106–212)	161	NED	NED
≥75	1,005 (704–1,323)	1,012	16 (10–21)	16	NED	NED
All circulatory						
5–19	28 (7–48)	27	7 (0–13)	7	8 (0–30)	8
20–44	252 (127–375)	254	252 (168–336)	257	NED	NED
45–64	854 (619–1,081)	860	404 (269–539)	399	NED	NED
65–74	749 (536–955)	738	75 (51–103)	74	NED	NED
≥75	1,270 (971–1,511)	1,289	13 (8–17)	13	NED	NED
Pneumonia and influenza						
5–19	86 (55–120)	88	449 (297–586)	444	35 (16–52)	36
20–44	569 (317–823)	565	548 (365–731)	560	257 (178–340)	252
45–64	612 (378–923)	626	421 (281–562)	416	NED	NED
65–74	299 (179–430)	307	90 (54–126)	91	NED	NED
≥75	620 (438–870)	605	3 (0–12)	3	NED	NED

*NED, no estimated deaths.

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