Severe Acute Respiratory Illness Deaths in Sub-Saharan Africa and the Role of Influenza: A Case Series From 8 Countries

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(See the editorial commentary by Gessner on pages 843–4.)

Background. Data on causes of death due to respiratory illness in Africa are limited.

Methods. From January to April 2013, 28 African countries were invited to participate in a review of severe acute respiratory illness (SARI)–associated deaths identified from influenza surveillance during 2009–2012.

Results. Twenty-three countries (82%) responded, 11 (48%) collect mortality data, and 8 provided data. Data were collected from 37 714 SARI cases, and 3091 (8.2%; range by country, 5.1%–25.9%) tested positive for influenza virus. There were 1073 deaths (2.8%; range by country, 0.1%–5.3%) reported, among which influenza virus was detected in 57 (5.3%). Case-fatality proportion (CFP) was higher among countries with systematic death reporting than among those with sporadic reporting. The influenza-associated CFP was 1.8% (57 of 3091), compared with 2.9% (1016 of 34 623) for influenza virus–negative cases ($P < .001$). Among 834 deaths (77.7%) tested for other respiratory pathogens, rhinovirus (107 [12.8%]), adenovirus (64 [6.0%]), respiratory syncytial virus (60 [5.6%]), and *Streptococcus pneumoniae* (57 [5.3%]) were most commonly identified. Among 1073 deaths, 402 (37.5%) involved people aged 0–4 years, 462 (43.1%) involved people aged 5–49 years, and 209 (19.5%) involved people aged ≥50 years.

Conclusions. Few African countries systematically collect data on outcomes of people hospitalized with respiratory illness. Stronger surveillance for deaths due to respiratory illness may identify risk groups for targeted vaccine use and other prevention strategies.

Keywords. influenza, human; mortality; Africa South of the Sahara.

Respiratory disease remains a major cause of mortality globally. Influenza virus infections alone may cause an estimated 250 000–500 000 deaths each year [1]. However, the burden of influenza-associated mortality in different regions and settings is not well understood. Available data suggest both the respiratory disease– and influenza-associated mortality may be increased in low-income settings such as sub-Saharan Africa

[2–5]. In South Africa, influenza-associated age-standardized mortality rates among individuals aged ≥65 years, among whom the human immunodeficiency virus (HIV) prevalence is very low, were 2–4 times higher than that among individuals of the same age in the United States [6]. Severe influenza outbreaks in Madagascar and Democratic Republic of the Congo (DRC) in 2002 were also associated with high case-fatality proportions (CFPs) [7, 8]. These mortality data are supported by surveillance data from 14 African countries during 2006–2010 that found that 8.9% of hospitalizations that met the case definition for severe acute respiratory illness (SARI) were associated with influenza virus infection [9], suggesting that influenza is an important cause of severe respiratory disease in Africa.

Globally, the 2009 influenza A(H1N1) pandemic was estimated to result in nearly 300 000 deaths in the first 12 months after virus emergence. More than half of these deaths may have occurred in Southeast Asia and Africa [4]. In Madagascar, influenza-attributable mortality was 20% higher than estimates of mortality attributable to seasonal influenza from previous years in the capital city Antananarivo [10], and early data from South Africa identified a high proportion of pregnant women, as well as individuals with HIV infection and tuberculosis among fatal cases [11]. Likewise, a global pooled analysis of influenza-associated hospitalizations and deaths during the 2009 pandemic found pregnancy to be associated with a relative risk of hospitalization of 6.8 and a relative risk of death of 1.9. While HIV infection and active tuberculosis were not assessed individually by the global pooled analysis, among patients hospitalized with influenza immunocompromise was associated with a relative risk of death of 27.7 and chronic respiratory disease was associated with a relative risk of death of 7.8 [12]. Using a different modeling method, another study estimated that a much lower proportion of pandemic mortality occurred in Africa [13]. Therefore, respiratory disease–associated mortality data from multiple countries in sub-Saharan Africa are essential to better understanding the impact of pandemic and seasonal influenza.

The high prevalence of comorbid conditions, including HIV infection, tuberculosis, and pregnancy, may contribute to increased disease severity and mortality from influenza in Africa [14]. Limited access to health care may also increase mortality from respiratory diseases in Africa. HIV infection, *Mycobacterium tuberculosis* coinfection, underlying medical conditions, pneumococcal coinfection, and intensive care unit admission were associated with increased mortality among influenza virus–positive patients with SARI in South Africa [2]. South Africa also estimated that influenza-associated mortality rates were 3.8 times greater (95% confidence interval [CI], 2.2–6.6) in adults aged 25–54 years, the age group with the highest HIV seroprevalence, than in adults aged ≥65 years [15].

Specific data on rates and risk groups for influenza-associated mortality are needed to help inform target groups for vaccine policy and to help inform allocation of resources in a pandemic. Hospital-based influenza surveillance has increased dramatically in Africa in the last decade [9], and we assessed whether the current systems could provide insights into seasonal influenza–associated mortality among persons hospitalized for respiratory disease in Africa, as well as data on other etiologies of respiratory disease–associated mortality in sub-Saharan Africa.

METHODS

Between January to April 2013, we sent a standard data template to representatives of 28 (59%) of 46 World Health Organization (WHO) African Region Member States. These included all 24 countries who reported data to the WHO's FluNet 2012 and countries that we were aware were conducting systematic hospital-based SARI surveillance (Supplementary Table 1). We requested information on all SARI cases and SARI-associated deaths detected by surveillance during 2009–2012. SARI case definitions used by these countries were consistent with WHO recommendations for adults and children <5 years of age [16]; however, some countries used expanded case definitions to include 14 days of symptom duration and/or physician-diagnosed lower respiratory tract infection. WHO-recommended case definitions were updated in 2011, and many countries have recently updated SARI case definitions to reflect these recommendations. The WHO's current SARI case definition for all age groups is an acute respiratory infection with a subjective or measured temperature of ≥38°C and cough with onset in the last 10 days requiring hospitalization [17]. Variables collected in SARI surveillance included the number of subjects enrolled, the number of specimens tested for influenza virus by real-time reverse transcription–polymerase chain reaction (rRT-PCR), influenza virus rRT-PCR test results, age, and outcome of hospitalization (discharge or death). We collected additional variables for SARI-associated deaths, including sex, pregnancy status, underlying medical conditions, and results of testing for other respiratory infections. Nasopharyngeal and oropharyngeal swab specimens or nasal aspirates were collected from enrolled SARI cases to test for influenza virus and other respiratory viruses. Except for Malawi, which conducts internal quality assurance, all countries providing data participate in the WHO's External Quality Assurance Project for influenza diagnosis. Data on *Streptococcus pneumoniae* from Kenya, South Africa, and Madagascar were from blood culture or blood lytA PCR and are indicative of invasive disease [18, 19]. HIV infection, tuberculosis, and other comorbid conditions were reported according to local diagnostic and surveillance practices and were not independently verified.

Data were analyzed using SAS 9.3 (SAS Institute, Cary, North Carolina). The Wilcoxon rank sum test was used to assess statistical significance of differences in nonparametric variables. The Pearson χ^2 test was used to test for associations between

categorical variables and influenza virus infection among SARI-associated deaths.

RESULTS

Representatives from 23 of 28 countries (82%) provided information about their country's SARI surveillance. Of these 23 countries, 11 (48%) did not collect outcome data on persons hospitalized for SARI, 9 (38%) collected SARI-associated mortality data systematically either prospectively or retrospectively, 2 (8%) received reports of SARI-associated deaths from sentinel sites but not systematically, and 1 (4%) had <1 year of surveillance data. Of the 11 countries that collected mortality data either systematically or via sentinel site reports, the following 8 completed the standard template for this analysis: DRC, Kenya, Madagascar, Malawi, Rwanda, South Africa, Tanzania, and Uganda. Of these, DRC, Tanzania, and Uganda receive reports of SARI-associated deaths from sentinel sites but did not collect these data systematically; Rwanda conducted a retrospective review of medical charts and registers to identify SARI-associated deaths; and the remaining countries (Kenya, Madagascar, Malawi, and South Africa) collect SARI outcome data (including mortality) prospectively from the time of enrollment in SARI surveillance to the time of hospital discharge or death. Community deaths following discharge were not reported by any country. SARI surveillance was primarily conducted in pediatric and/or adult medical wards at surveillance hospitals, and surveillance practices varied by country in terms of the number of cases enrolled per day or the days of enrollment per week.

During 2009–2012, the 8 countries that provided data on SARI-associated deaths enrolled 40 355 subjects, of whom 1222 (3.0%) died during hospitalization. Complete data on influenza virus testing and age were available for 37 714 SARI cases (93.5%). Among these cases, 1073 deaths were reported (SARI CFP, 2.8%), ranging widely by country, from 0.1% in DRC to 5.5% in Madagascar. Among the 37 714 SARI cases tested for influenza virus, 3091 (8.2%) tested positive for influenza virus, ranging from 5.1% in Tanzania to 25.9% in Madagascar (Table 1).

Of 1073 SARI cases who died during hospitalization and were tested for influenza virus, 57 (5.3%) tested positive, for an overall influenza-associated CFP of 1.8% (57 of 3091), compared with 2.9% (1016 of 34 623) among influenza virus–negative SARI cases ($P < .001$). The influenza-associated CFPs ranged from 0 in Malawi, Tanzania, and Uganda to 3.6% in Madagascar. Countries with systematic death reporting had higher all-cause and influenza-associated CFPs than countries with sporadic reporting. Of the 1073 reported deaths, 402 (37.5%) were among children aged 0–4 years, 462 (43.1%) were among children and adults aged 5–49 years, and 209 (19.5%) were among adults aged ≥50 years (Table 1).

Among the 57 influenza-associated deaths, 19 (33.3%) were among children aged 0–4 years, 20 (35.1%) were among adults aged 18–49 years, and the remaining 18 (31.5%) were among adults aged ≥50 years (Table 1). The median age among influenza-associated deaths was 32 years (interquartile range [IQR], 1–56 years), compared with 28 years (IQR, 1–45 years) among SARI-associated deaths without influenza virus infection

Table 1. All-Cause and Influenza-Associated Severe Acute Respiratory Illness (SARI) Cases and Deaths During 2009–2012, by Country and Age Group

Variable	All-Cause SARI			Influenza-Associated SARI		
	Cases, No. (%)	Deaths, No. (%)	CFP, %	Cases, No. (%)	Deaths, No. (%)	CFP, %
Country						
DRC	2290 (6.1)	2 (0.2)	0.1	166 (5.4)	2 (3.5)	1.2
Kenya	10 667 (28.3)	309 (28.8)	2.9	915 (29.6)	17 (29.8)	1.9
Madagascar	645 (1.7)	34 (3.2)	5.3	167 (5.4)	6 (10.5)	3.6
Malawi	1364 (3.6)	8 (0.7)	0.6	156 (5.0)	0 (0)	0
Rwanda	3188 (8.5)	61 (5.7)	1.9	198 (6.4)	1 (1.8)	0.5
South Africa	15 199 (40.3)	615 (57.3)	4.0	1222 (39.5)	31 (54.4)	2.5
Tanzania	3548 (9.4)	38 (3.5)	1.1	181 (5.9)	0 (0)	0
Uganda	813 (2.2)	6 (0.6)	0.7	86 (2.8)	0 (0)	0
Age, y						
0–4	23 995 (63.6)	402 (37.5)	1.7	1782 (57.7)	19 (33.3)	1.1
5–17	3009 (8.0)	47 (4.4)	2.2	320 (10.4)	0 (0)	0.0
18–49	7912 (21.0)	415 (38.7)	5.5	727 (23.5)	20 (35.1)	2.8
50–64	1866 (4.9)	132 (12.3)	7.5	165 (5.3)	10 (17.5)	6.1
≥65	932 (2.5)	77 (7.2)	8.9	97 (3.1)	8 (14.0)	8.2
Overall	37 714	1073	2.8	3091	57	1.8

Abbreviations: CFP, case-fatality proportion; DRC, Democratic Republic of the Congo.

Table 2. Underlying Medical Conditions Reported Among Deaths Due to Severe Acute Respiratory Illness (SARI) Detected by Surveillance During 2009–2012 in 8 African Countries, Overall and by Influenza Virus Status

Condition	All-Cause Deaths, Proportion (%)		Influenza Virus–Positive Deaths, Proportion (%)		Influenza Virus–Negative Deaths, Proportion (%)		P Value[a]
	With Data	Died	With Data	Died	With Data	Died	
HIV infection	580/1073 (54.1)	419/580 (72.2)	33/57 (57.9)	23/33 (69.7)	547/1016 (53.8)	396/547 (72.4)	.74
Tuberculosis	661/1073 (61.6)	103/661 (15.6)	38/57 (66.7)	8/38 (21.1)	623/1016 (61.3)	95/623 (15.2)	.34
Asthma	1056/1073 (98.4)	18/1056 (1.7)	55/57 (96.5)	2/55 (3.6)	1001/1016 (98.5)	16/1001 (1.6)	.24
Other	720/1073 (67.1)	112/720 (15.6)	41/57 (71.9)	9/41 (22.0)	679/1016 (66.8)	103/679 (15.2)	.24

Abbreviation: HIV, human immunodeficiency virus.

[a] For comparison of the prevalence of the condition among influenza virus–positive and influenza virus–negative deaths due to SARI.

(P = .05). The influenza-associated CFP varied by age group and was highest among adults aged ≥65 years (8.2%) and lowest among children aged 5–17 years (0%; $P < .001$). Persons aged ≥65 years accounted for just 2.5% of SARI cases but 7.2% of SARI-associated deaths and 14.0% of influenza-associated deaths due to SARI.

Among 1073 SARI-associated deaths, data on underlying medical conditions were incomplete (Table 2). Despite the limited availability of data, 532 deaths (49.6%) were reported to have an underlying medical condition (including HIV infection and *M. tuberculosis* infection). Among 1073 deaths, HIV status was reported for 580 (54.1%), and, of these, 419 (72.2%) were infected with HIV. Thirty-three of 57 influenza virus–positive deaths (57.9%) had HIV status information, and, of these, 23 (69.7%) were HIV infected. A total of 547 of 1016 influenza virus–negative deaths (53.8%) had HIV status reported, and 396 (72.4%) were HIV infected ($P = .74$). Among the 661 deaths (61.6%) with data, tuberculosis was reported for 103 (15.6%), and there was no difference in the prevalence of tuberculosis among influenza virus–positive and influenza virus–negative deaths ($P = .34$). Information on asthma was available for 1056 SARI-associated deaths (98.4%) but was rarely identified in both influenza virus–positive (3.6%) and influenza virus–negative deaths (1.6%; $P = .24$). Information on other medical conditions was reported for 720 deaths (67.1%). Among children and adults with a reported underlying medical condition, HIV infection was most commonly reported among all ages (419 of 532 cases [78.8%]), followed by malnutrition (11 of 96 [11.5%]) and tuberculosis (8 of 96 [8.3%]) for children aged 0–4 years and tuberculosis (95 of 436 [21.8%]) and diabetes (25 of 436 [5.7%]) for children and adults aged ≥5 years. Of the 245 deaths among women of childbearing age, pregnancy status was provided for 237 (96.7%), of whom 7 (3.0%) were pregnant at the time of death. None of the 7 pregnant women with SARI identified in routine surveillance who died were infected with influenza virus.

Among the 57 influenza-associated deaths, 9 (15.8%) were confirmed as involving influenza A(H1N1)pdm09 infection, 19 (33.3%) as involving influenza A(H3N2) infection, and 20 (35.1%) as involving influenza B infection; nonsubtyped influenza A infection was detected in 9 (15.8%). There were no statistically significant differences in the distribution of deaths by influenza virus subtype by age group ($P = .72$).

Other respiratory pathogens were identified by culture or PCR testing only in Kenya, Madagascar, and South Africa. Specimens from 834 deaths in these countries were tested for the presence of at least 1 other respiratory pathogen: 247 deaths (30%) involved children aged 0–4 years, and 587 (70%) involved persons aged ≥5 years. Among the 247 deaths in children aged 0–4 years tested for other pathogens, 145 (59%) tested positive for a respiratory pathogen, with influenza virus detected in 14 (6%) and ≥1 respiratory pathogen other than influenza virus detected in 131 (53%). Among those aged 0–4 years, the most commonly identified respiratory pathogens other than influenza virus were rhinovirus (35 cases [14.2%]), respiratory syncytial virus (33 [13.4%]), and adenovirus (32 [13.0%]; Table 3). Among deaths involving children aged 0–4 years, those testing negative for influenza virus were more likely to have another respiratory virus identified than those who tested positive for influenza virus ($P = .014$).

Among the 587 deaths in persons aged ≥5 years who were tested, 243 (41%) tested positive for a respiratory pathogen, with influenza virus detected in 37 (6%) and ≥1 respiratory pathogen other than influenza virus detected in 206 (35%). The most commonly identified respiratory pathogens other than influenza virus in this age group were rhinovirus (72 cases [12.3%]), *S. pneumoniae* (48 [8.2%]), and adenovirus (32 [5.5%]; Table 3).

DISCUSSION

Hospital-based surveillance for severe respiratory disease in Africa has expanded dramatically in the last decade, yet data on etiologies of mortality are very sparse. Our aim was to assess the capacity of SARI surveillance to collect mortality data and provide initial insights of the characteristics of SARI and influenza-confirmed deaths, rather than to accurately document the

Table 3. Respiratory Pathogens Observed Among 834 Deaths Due to Severe Acute Respiratory Illness Detected by Surveillance During 2009–2012 in 3 African Countries, by Age and Influenza Virus Status

Age, Pathogen	All-Cause Deaths, No. (%)	Influenza Virus–Positive Deaths	Influenza Virus–Negative Deaths
0–4 y			
Any	247	14	233
Adenovirus	32 (13.0)	1 (7.1)	31 (13.3)
Parainfluenza virus 3	13 (5.3)	0 (0)	13 (5.6)
Respiratory syncytial virus	33 (13.4)	2 (14.3)	31 (13.3)
Rhinovirus	35 (14.2)	0 (0)	35 (15.0)
S. pneumoniae	9 (3.6)	0 (0)	9 (3.9)
Other[a]	23 (9.3)	0 (0)	23 (9.9)
None	116 (47.0)	11 (78.6)	105 (45.1)[b]
≥5 y			
Any	587	37	550
Adenovirus	32 (5.5)	5 (13.5)	27 (4.9)[c]
Parainfluenza virus 3	11 (1.9)	0 (0)	11 (2.0)
Respiratory syncytial virus	27 (4.6)	1 (2.7)	26 (4.7)
Rhinovirus	72 (12.3)	4 (10.8)	68 (12.4)
S. pneumoniae	48 (8.2)	5 (13.5)	43 (7.8)
Other[d]	19 (3.2)	0 (0)	19 (3.5)
None	381 (64.9)	23 (62.2)	358 (65.1)

Abbreviation: *S. pneumoniae*, *Streptococcus pneumoniae*.

[a] Bocavirus (n = 1), coronavirus (n = 2), enterovirus (n = 4), human metapneumovirus (n = 8), and parainfluenza viruses (1, 2, and not subtyped; n = 8).

[b] $P = .014$, by the Fisher exact test.

[c] $P = .04$, by the Fisher exact test.

[d] Bocavirus (n = 1), enterovirus (n = 7), human metapneumovirus (n = 5), and parainfluenza viruses (1, 2, and not subtyped; n = 6).

burden of influenza-associated mortality. We found that few countries that conduct influenza surveillance are systematically collecting data on outcomes of hospitalization, and available information on deaths is sparse and incomplete. Likewise, data on the presence of comorbidities were incomplete. We also found that pregnant women were underrepresented in SARI data from all countries. We found a wide range in CFPs for SARI and influenza across countries, which may reflect differences in case definitions, criteria for hospitalization, quality of hospital care, or quality of surveillance, including proper handling of biological specimens and ascertainment of deaths. Countries where deaths are reported from sites sporadically had lower CFPs than those that reported deaths systematically, suggesting that sporadic reporting may fail to capture a large number of SARI-associated deaths. Reports of hospitalizations and deaths from low-income and middle-income settings during the 2009 A(H1N1) pandemic include La Reunion (255 hospitalizations and 6 deaths; CFP, 2.4%), Argentina (11 086 hospitalizations and 580 deaths; CFP, 5.2%), and Chile (1585 hospitalizations and 134 deaths; CFP, 8.5%) [20]. The majority of published data on SARI CFPs from African countries is focused on children. A meta-analysis of 11 African studies in children aged 0–59 months found an average in-hospital CFP of 3.9% (95% CI, 2.7%–5.5%) among children hospitalized with acute lower respiratory tract infections [3]. Comparison with CFP estimates among respiratory disease–associated hospitalizations from the region suggests incomplete death reporting in this analysis.

Despite the incomplete data, we were able to draw some important conclusions. First, in-hospital respiratory mortality and influenza-associated mortality occur predominantly in very young individuals and those 18–49 years. Second, a viral pathogen could be identified in 38% of deaths tested for influenza virus and other respiratory pathogens. In particular, our data highlight the role that respiratory syncytial virus and adenovirus may play in respiratory mortality in the region. Third, HIV infection and tuberculosis are important factors in severe respiratory disease in Africa.

The low number of deaths among pregnant women is unexpected, given their increased risk of influenza-associated death during the pandemic [12, 21] and increased risk of severe disease from seasonal influenza [22], and it may reflect inadequate surveillance in antenatal clinics and maternity wards. Owing to high fertility rates, >9% of African women of childbearing age are estimated to be pregnant at any given time [23], suggesting that current surveillance may not adequately identify severe disease in pregnant women.

From the data collected here nearly two thirds of enrolled SARI cases were children 0–4 years of age, while adults aged ≥65 years accounted for just 2.4% of SARI cases. Some but not all of this difference may be explained by population demographic characteristics in Africa; >40% of the population of Africa in 2013 is <15 years of age, and just 3.4% are aged ≥65 years [24]. There may be differences in access to care among elderly persons in Africa that result in fewer elderly individuals with respiratory illness being hospitalized. Our analysis demonstrates that elderly persons who are hospitalized have a greater risk of death from respiratory disease, especially influenza, than young children. A systematic review of the case-fatality risk from the 2009 A(H1N1) pandemic found significant variation in risk by age group, ranging from approximately 1 death per 100 000 symptomatic cases in children aged 0–19 years to approximately 1000 deaths per 100 000 symptomatic cases in persons aged ≥65 years [25]. These estimates support our finding of an increased CFP among hospitalized elderly individuals, although only 15.8% of the influenza-associated deaths reported here involved influenza A(H1N1) infections (Table 1). Despite this, children aged 0–4 years accounted for over one third of all SARI-associated deaths and one-third of influenza-associated deaths due to SARI in this analysis, a finding consistent with prior studies in low-income settings [3, 26]. Likewise, adults

aged 18–49 years accounted for over one third of all SARI-associated deaths and one third of influenza-associated deaths due to SARI, which may be explained by the high prevalence of HIV in this age group.

In this analysis, HIV status was not reported for nearly half of enrolled SARI-associated deaths. Despite this limitation, these data clearly demonstrate that HIV infection is common among SARI-associated hospitalizations and deaths with and without influenza virus coinfection; however, we are unable to demonstrate a statistical association of HIV infection with death among hospitalized SARI cases. Our coauthors from South Africa have found that HIV-infected patients with influenza were 4 times more likely (95% CI, 1–12) to die than HIV-uninfected patients with influenza [2]. Data on tuberculosis were also missing from many deaths; however, when reported, tuberculosis was common among SARI-associated deaths but was not found more commonly among SARI-associated deaths with influenza.

There were several important limitations of this analysis. Because almost 90% of all deaths were reported from Kenya and South Africa, our findings may not be representative. In South Africa, a country with systematic reporting and a relatively high CFP in this analysis, retrospective review of respiratory deaths in sentinel hospitals found that as many as 1 in 3 respiratory deaths were not enrolled in SARI surveillance [27]. Some countries in our study reported very few or no SARI-associated deaths, which limits confidence in conclusions drawn from these data. Also, substantial differences existed in how SARI, HIV status, *M. tuberculosis* coinfection, and other underlying medical conditions were diagnosed or defined for surveillance purposes. It is likely that very severely ill patients would not have been enrolled into surveillance, especially if informed consent was required, as was the case in several countries. This may explain why 149 of 1222 reported deaths (12%) did not have influenza virus test results. Another limitation is the ability to attribute death to any one pathogen. Although influenza viruses are less commonly found in asymptomatic persons, other viruses, such as rhinoviruses and adenoviruses, are frequently isolated from nasopharyngeal or oropharyngeal swab specimens in asymptomatic persons, especially children [28–31]. The relative contribution of these pathogens to mortality may also be affected. Nasopharyngeal or oropharyngeal swab specimens may not be the ideal specimens for detecting some respiratory pathogens [32]. Also, the methods of testing for some non–influenza virus pathogens differed by site. For example, South Africa diagnosed *S. pneumoniae* infection on the basis of lytA PCR of blood samples, while Kenya used blood cultures to diagnose invasive *S. pneumoniae* infection. Our study is limited in its ability to assess the true role of pathogens other than influenza virus since data on the number of cases tested for each pathogen were not available.

Sentinel surveillance sites are often limited in their population catchment and may not capture an adequate number of respiratory disease– and influenza-associated deaths. Because of the logistics of specimen collection, transport, and analysis, many countries are only able to support a small number of sites, which may not be representative of the population. Limited access to care in many African settings may further reduce the number of persons hospitalized with respiratory infections, including influenza. Many cases of SARI may be due to secondary complications such as bacterial pneumonia after initial influenza virus infection, when influenza virus shedding has decreased or ceased. Moreover, influenza-associated deaths with a nonrespiratory presentation, including heart attack and stroke, are unlikely to be tested for influenza virus even if hospitalized. Many complications of influenza, especially postinfluenza pneumonia and death, happen >1 week after initial infection [33, 34] and therefore may occur at home after discharge. Vital registration data in South Africa indicate that as many as 50% of respiratory disease–associated deaths occur outside of hospitals [35].

Because of these limitations many countries have used other methods to estimate influenza-associated mortality. Some sites have conducted thorough community-based mortality reviews in which persons meeting the case definition of influenza-associated death are counted in a defined population [36, 37]. Excess mortality modeling is commonly used to assess deaths due to influenza in populations with accurate vital statistics or International Classification of Diseases–coded hospitalization data, with or without adjustment for influenza virus circulation [6, 38, 39]; however, few countries in Africa have complete vital registration data, and many countries do not experience clear seasonal peaks in influenza transmission, which may limit the utility of such methods. Many countries in Africa have health and demographic surveillance sites where all births and deaths are recorded and where deaths are assessed by verbal autopsy. It is possible that an assessment of trends in mortality at these sites, combined with virological data on influenza virus circulation patterns, may provide more-accurate estimates of influenza-associated deaths when vital statistics are not available.

In conclusion, stronger surveillance for respiratory deaths may help to identify risk groups for targeted vaccine use and other prevention strategies. Among those tested, respiratory viruses other than influenza virus and *S. pneumoniae* were commonly identified in SARI-associated deaths of all ages; however, nasopharyngeal carriage may overestimate mortality from some of these pathogens. Surveillance in antenatal clinics and/or maternity wards should be strengthened to better capture pregnant women, given the WHO's recent decision to prioritize them for influenza vaccination [40]. Sentinel surveillance may provide some information on characteristics of influenza-associated deaths but will likely underestimate influenza-associated mortality. Alternative methods should be used to estimate influenza-associated mortality in Africa, depending on the availability of vital statistics, accurate hospitalization data, and other forms of demographic and health surveillance.

Supplementary Data

Notes

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