Epidemiologic and Spatiotemporal Characterization of Influenza and Severe Acute Respiratory Infection in Uganda, 2010-2015

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Abstract

Rationale: Little is known about the epidemiology of severe acute respiratory infection (SARI) or influenza in sub-Saharan Africa. Characterization of influenza transmission dynamics and risk factors for severe disease and mortality is critical to inform prevention and mitigation strategies.

Objectives: To characterize the epidemiology and transmission dynamics of influenza and risk factors for influenza-associated severe respiratory infection in Uganda.

Methods: Clinicians at 12 sentinel surveillance sites prospectively collected clinical data and upper respiratory tract samples from consecutive patients who met criteria for SARI and influenza-like illness (ILI). Samples were tested for influenza A and B viruses using real-time reverse transcription–polymerase chain reaction. Spatial and spatiotemporal cluster modeling was performed to identify loci of increased influenza transmission. Morbidity and mortality were assessed through chart review in a defined subset of patients. Univariable and multivariable analyses were used to identify risk factors for severe respiratory infection, prolonged hospitalization, and in-hospital mortality.

Measurements and Main Results: From October 2010 to June 2015, 9,978 patients met case definitions for SARI and ILI and had samples tested for influenza A and B. Of the 9,978 patient samples tested, 1,113 (11.2%) were positive for influenza. Among 6,057 patients with ILI, 778 samples (12.8%) were positive, and among 3,921 patients with SARI, 335 samples (8.5%) were positive. Significant clustering of influenza cases was observed in urban and periurban areas and during rainy seasons. Among 1,405 cases of SARI with available outcome data, in-hospital mortality was 1.6%. Infection with the 2009 pandemic A/H1N1 subtype and prolonged time to presentation were independently associated with SARI among influenza cases.

Conclusions: Influenza is associated with a substantial proportion of acute respiratory infection in Uganda. As influenza vaccination programs are developed in East Africa, timing campaigns to confer protection during rainy seasons should be considered, particularly among high-risk urban populations.

Keywords: Africa South of the Sahara; acute respiratory infection; influenza; epidemiology; spatiotemporal analysis

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Severe respiratory infections are the third leading cause of death globally, with an estimated 4.25 million deaths annually (1). Seasonal influenza viruses are an important cause of severe acute respiratory infections (SARI), with 3 to 5 million cases of SARI caused by influenza and 250,000 to 500,000 deaths each year (2). As evidenced by the 2009 H1N1 pandemic, novel influenza strains are a threat to global health security, and the continued emergence of avian influenza viruses with pandemic potential remains a looming global health threat (2, 3). To improve local and international responses to emerging infections associated with severe respiratory disease, the American Thoracic Society released a research agenda underscoring the need to characterize the epidemiology and clinical syndromes associated with influenza and other emerging respiratory viruses (3).

Little is known about the clinical epidemiology, seasonality, and transmission dynamics of influenza in tropical and developing country settings (2, 4). In sub-Saharan Africa, such data are especially limited because of gaps in surveillance, laboratory and diagnostic infrastructure, and competing public health priorities (5–7). This is despite emerging data suggesting that influenza has been associated with a substantial burden of severe respiratory infection across the continent for decades (5, 6, 8). During the 2009 H1N1 pandemic, it is estimated that approximately 25% of influenza-related deaths worldwide occurred in sub-Saharan Africa, likely because of inadequate access to health care resources and limited availability of influenza vaccines and antiviral therapies (5, 6, 8).

In Uganda, the burden of severe respiratory disease associated with influenza is largely unknown. To better understand the burden and epidemiology of SARI and influenza in Uganda, the Uganda Virus Research Institute (UVRI) expanded sentinel surveillance for influenza in late 2010, with increased emphasis placed on hospitalized patients with SARI. In this study, we use this prospectively collected surveillance data to characterize the epidemiology and transmission dynamics of influenza in Uganda. We hypothesized that spatiotemporal modeling would identify the spatial and temporal loci of increased influenza transmission and that multivariable analyses would reveal specific

risk factors for disease severity, morbidity, and mortality among patients with influenza and SARI. Some of the results of this study have been reported previously in the form of an abstract (9).

Methods

Surveillance Methods and Laboratory Testing

Health facilities designated as sentinel surveillance sites for influenza in Uganda were chosen in accordance with World Health Organization guidelines for influenza surveillance, as described previously (10, 11). Sentinel surveillance sites are located in geographically diverse locations throughout Uganda, including both urban and rural districts. From 2010 to 2015, surveillance for both SARI and influenza-like illness (ILI) was performed at five sites. ILI and SARI surveillance alone was performed at four and three sites, respectively (*see* Figure E1 in the online supplement).

The full UVRI protocol for SARI and ILI case identification has been published (10). Briefly, ILI was defined as an outpatient ≥ 2 months of age, with a measured fever (temperature $>38^{\circ}\text{C}$) and either cough or sore throat within 10 days of symptom onset. SARI was defined as a hospitalized individual 2 months to <5 years of age, with recent onset of cough or difficulty breathing within 10 days of symptom onset plus an additional clinical indicator of respiratory distress; or a hospitalized individual ≥ 5 years of age, with fever (either measured or subjective) presenting with cough or shortness of breath within 10 days of symptom onset.

Clinicians interviewed eligible patients, examined medical records to collect clinical and demographic data, and completed a study questionnaire. Naso- and/or oropharyngeal swab samples were collected from suspected cases and were shipped to the UVRI National Influenza Center using an established protocol (10). Testing for influenza A and B viruses was performed via real-time reverse transcription–polymerase chain reaction (RT-PCR) using primers provided by the U.S. Centers for Disease Control and Prevention (10). For influenza A–positive samples, subtyping was performed for seasonal A/H1, A/H3, A/H5, and 2009 pandemic A/H1N1 (A/H1N1pdm09).

Epidemiologic Analysis

Epidemiologic and laboratory data were abstracted into a standardized data-entry screen. Data were cleaned by removing patients who did not meet case definitions for ILI or SARI. The SPSS statistical package (version 23.0; IBM Corp., Armonk, NY) was used for data analysis. Fischer exact or chi-square tests were used to compare categorical variables, and medians were compared using the Wilcoxon-Mann-Whitney *U* test. Univariable analysis and multivariable logistic regression models were used to calculate odds ratios and 95% confidence intervals (*see* online supplement).

Spatial and Spatiotemporal Analyses

To identify loci of increased influenza transmission, we used space-time and spatial-only scan statistic models included in the SaTScan software package (version 9.4.2; Boston, MA) to detect clusters with greater than expected numbers of influenza cases of the same subtype (12). Originating at defined locations, the spatial statistic applies a likelihood function to circular scanning windows of increasing size and compares expected with observed case numbers inside and outside the scan window to detect clusters (12, 13). For the space-time analysis, a cylinder of variable height representing the number of days in a potential cluster is incorporated into the window. Case dates and locations were defined as the date of illness onset and the subcounty of residence (an intermediate unit between districts and villages), respectively.

A Poisson distribution was assumed to determine expected case numbers with subcounty populations obtained from 2014 Uganda national census data (14). The maximal spatial and temporal cluster magnitudes were set as 50 km and 3 months, respectively. Clusters were considered significant at $P \leq 0.05$ (*see* online supplement). Clusters were visualized using QGIS (version 2.12.2 QGIS; Open Source Geospatial Foundation Project). In all subcounties in which influenza cases were reported, we compared the demographic characteristics of subcounties located within significant space-time and/or spatial clusters with those located outside such clusters using chi-square tests and Student's *t* tests.

Ethics Statement

In the context of public health surveillance and routine clinical care, verbal consent was obtained from suspected cases ≥ 18 years of age and from parents or legal guardians for cases < 18 years of age. The study was approved by the Research Ethics Committee at UVRI and the Institutional Review Board at Columbia University Medical Center. The study's funders had no role in study design, data analysis and interpretation, manuscript preparation, or decision to publish.

Results

Descriptive Epidemiology and Seasonality

From October 1, 2010, to June 28, 2015, 10,142 suspected ILI and SARI cases were identified. Of these, 9,978 (98.4%) fulfilled case definitions for ILI (6,057; 60.7%) or SARI (3,921; 39.3%) and had naso- and/or oropharyngeal samples collected and tested for influenza A and B by RT-PCR. One hundred fifty cases were excluded because their age was < 2 months, and 14 cases were excluded from two surveillance sites that were active for only 1 year of the study period.

Compared with patients with ILI, those with SARI were more likely to be male ($P < 0.001$), to be of a younger median age (median age [interquartile range], 1 [0.7–3] yr vs. 2 [1–6] yr, $P < 0.001$), and to be young children aged 2 months to 4 years (81.2% vs. 69.3%; $P < 0.001$) (Table 1). Among all patients, $< 1\%$ (76 of 9,978; 0.76%) reported any history of influenza vaccination.

Of the 9,978 samples tested for influenza, 1,113 were positive (11.2%); 778 of 6,057 samples (12.8%) were from patients with ILI, and 335 of 3,921 samples (8.5%) were from patients with SARI. Among all influenza-positive samples, 851 (76.5%) were influenza A, 261 (23.5%) were influenza B, and 1 (0.1%) was influenza A and B coinfection. Among influenza A cases, 493 (57.9%) were A/H3N2, 351 (41.2%) were A/H1N1pdm09, 5 (0.7%) were unsubtypeable, and 2 (0.2%) were A/H1N1pdm09 and A/H3N2 coinfection.

The dominant circulating influenza virus types and subtypes varied between surveillance years (Figure E2). Across all years, peaks in influenza activity occurred consistently during the biannual rainy

Table 1. Characteristics of patients with ILI and SARI identified by sentinel surveillance program for influenza in Uganda, October 2010–June 2015

Patient Characteristics	ILI (n = 6,057)	SARI (n = 3,921)
Sex		
Male	2,963 (48.9)	2,125 (54.2)
Female	3,090 (51.1)	1,796 (45.8)
Age, yr		
2 mo–4	4,183 (69.3)	3,186 (81.2)
5–14	1,145 (19.1)	404 (10.3)
15–34	515 (8.6)	140 (3.6)
35–54	150 (2.6)	128 (3.3)
55–64	22 (0.3)	24 (0.6)
> 65	5 (0.1)	39 (1.0)
Age, yr, median (IQR)	2 (1–6)	1 (0.7–3)
Year of diagnosis		
2010*	381 (6.3)	64 (1.6)
2011	891 (14.8)	84 (2.1)
2012	1,440 (23.9)	776 (19.8)
2013	1,400 (23.2)	1,113 (28.4)
2014	1,466 (24.3)	1,419 (36.1)
2015†	458 (7.5)	465 (12.0)
Sentinel site		
Arua	66 (1.1)	470 (12.0)
Entebbe	1,579 (26.1)	971 (24.8)
Fort Portal	NS	612 (15.6)
Kawaala	1,607 (26.5)	NS
Kibuli	NS	32 (0.9)
Kisenyi	421 (7.0)	NS
Kiswa	242 (4.0)	NS
Kitebi	1,253 (20.7)	NS
Koboko	791 (13.1)	80 (2.0)
Mbarara	27 (0.4)	584 (14.9)
Nsambya	NS	49 (1.2)
Tororo	68 (1.1)	1,123 (28.6)
Signs and symptoms		
Measured temperature $> 38^{\circ}\text{C}$	6,057 (100.0)	340 (5.7)
Cough	5,780 (96.3)	3,640 (92.8)
Sore throat	553 (9.2)	122 (3.1)
SOB	2,584 (43.1)	2,611 (66.6)
Diarrhea	1,947 (41.0)	1,114 (29.5)
Vomiting	1,855 (30.9)	605 (17.3)
Headache	3,333 (70.0)	704 (18.0)
Myalgia	1,514 (31.8)	419 (11.1)
Confusion	NA	155 (4.4)
Stridor	NA	392 (11.7)
Chest indrawing	NA	965 (27.6)
Nasal flaring	NA	2,027 (57.9)
Reported history of influenza vaccination		
Yes	0 (0.0)	76 (1.9)
No or unknown	6,057 (100.0)	3,845 (98.1)
Influenza positive		
Yes	778 (12.8)	335 (8.5)
No	5,279 (87.2)	3,586 (91.5)

Definition of abbreviations: ILI = influenza-like illness; IQR = interquartile range; NA = clinical features not present because they are criteria for SARI case definition; NS = surveillance for ILI or SARI not performed at surveillance site; SARI = severe acute respiratory infection; SOB = shortness of breath. Data are presented as No. (%) unless indicated otherwise.

*Data representative of surveillance from October to December 2010.

†Data representative of surveillance from January to June 2015.

seasons of March–May and September–November (Figure 1). During these time periods, the average monthly rainfall is 129 and 118 mm, respectively, compared with an average of 58 mm across the remaining

months of the year (15). In 2012, influenza virus activity peaked during September–November, with the majority of cases influenza B (175 of 260; 67.3%). In 2013, influenza A/H3N2 predominated (154 of

Figure 1. Influenza cases in Uganda by month, October 2010–June 2015. Data available for 1,111 cases. Vertical dotted lines indicate time-periods composing the biannual rainy seasons. Colored solid lines represent influenza types and subtypes identified: A/H3N2 (blue), A/H1N1pdm09 (red), A/uns subtypeable (green), B (purple). A/H1N1pdm09 = 2009 pandemic A/H1N1.

242; 63.6%), with peaks in activity during March–May and August–September. In 2014, influenza A/H1N1pdm09 (231 of 399; 57.9%) and A/H3N2 (156 of 399; 39.1%) predominated, both peaking in August–September and March–May.

Risk Factors for Influenza

On univariable analysis, patients 5–14 and 15–34 years old, those with illness onset during the rainy season, and those with subjective or measured fever, headache, and myalgia were more likely to test positive for influenza. Influenza-positive cases were less likely to report diarrhea (Table 2). In multivariable analysis, influenza positivity remained independently associated with age 5–14 years and the absence of diarrhea and was also associated with illness onset during the rainy season (Table 2).

Risk Factors for Severe Respiratory Infection among Influenza Cases

On univariable analysis, influenza cases with severe respiratory infection (SARI) were more likely than those with mild disease (ILI) to be adults 35–54 years of age (Table 3). Cases with severe disease were

also more likely to have a prolonged time to presentation (≥ 3 d after symptom onset) and to be infected with the influenza A/H1N1pdm09 subtype. The association between influenza A/H1N1pdm09 infection and severe disease persisted when cases from the immediate postpandemic year of 2010 were excluded. In multivariable models, severe disease remained independently associated with the age group 35–54 years, influenza A/H1N1pdm09 infection, and prolonged time to presentation (Table 3). When stratified by age, severe disease remained independently associated with A/H1N1pdm09 infection and delayed presentation to care among patients 2 months to 4 years of age (Table E1).

Risk Factors for Prolonged Hospitalization and Mortality

To analyze the effect of influenza infection on hospital length of stay and mortality in patients admitted with SARI, we reviewed the charts of a subset of enrolled patients at four geographically diverse sentinel sites from 2012 to 2014. This subset represented 35.8% of all SARI cases (1,405 of 3,921).

Among these patients, 1.6% (23 of 1,405) died in the hospital. The median duration of hospitalization was 4 days (interquartile range, 2–5 d). In univariable analysis, patients with SARI with prolonged hospitalization (≥ 5 d) were more likely to be male and more likely to be >65 years of age. These associations persisted in the multivariable analysis (Table E2). Among patients 5–14 years of age, influenza positivity was associated with prolonged hospitalization, but this association was not observed when all patients were analyzed (Tables E2 and E4). In univariable analysis of mortality, patients with SARI who died in the hospital were also more likely to be male and more likely to be 35–54 years of age. These associations persisted in the multivariable analysis (Table E3). There was no significant association between influenza positivity and in-hospital mortality (Tables E3 and E5).

Spatial and Spatiotemporal Analyses

We sought to identify, as a surrogate for transmission, spatial and spatiotemporal loci associated with greater than expected numbers of influenza cases stratified by

Table 2. Risk factors for influenza positivity among patients with SARI and ILI in Uganda

Patient Characteristics	Influenza Positive [No. (% total)] (n = 1,113)	Influenza Negative [No. (% total)] (n = 8,865)	Univariable OR (95% CI)	Multivariable OR (95% CI)
Sex				
Male	581 (52.3)	4505 (50.8)	Reference 0.944 (0.83–1.07)	
Female	530 (47.7)	4355 (49.2)		
Age, yr				
2 mo–4	737 (66.8)	6632 (75.1)	Reference 1.72 (1.47–2.00) 1.35 (1.06–1.72) 0.81 (0.53–1.25) 1.10 (0.43–2.78) 1.15 (0.45–2.94)	Reference 1.59 (1.06–2.38) 1.07 (0.53–2.17)
5–14	248 (22.5)	1300 (14.7)		
15–34	85 (7.7)	567 (6.4)		
35–54	23 (2.0)	255 (2.9)		
55–64	5 (0.5)	41 (0.5)		
>65	5 (0.5)	39 (0.4)		
Age, yr, median (IQR)	3 (1–6)	2 (0.9–4)		
Year of diagnosis				
2010*	60 (5.4)	385 (4.4)		
2011	79 (7.1)	896 (10.1)		
2012	261 (23.5)	1955 (22.1)		
2013	243 (21.9)	2270 (25.7)		
2014	399 (36.0)	2487 (28.1)		
2015†	67 (6.1)	855 (9.6)		
Sentinel site				
Arua	36 (3.2)	500 (5.6)		
Entebbe	296 (26.6)	2238 (25.2)		
Fort Portal	64 (5.8)	548 (6.2)		
Kawaala	257 (23.1)	1350 (15.2)		
Kibuli	2 (0.2)	28 (0.3)		
Kisenyi	28 (2.5)	393 (4.4)		
Kiswa	33 (3.0)	211 (2.4)		
Kitebi	197 (17.7)	1056 (11.9)		
Koboko	52 (4.7)	819 (9.2)		
Mbarara	32 (2.9)	579 (6.5)		
Nsambya	3 (0.3)	45 (0.5)		
Tororo	102 (10.0)	1089 (12.6)		
Illness onset during rainy season				
Yes	629 (56.7)	4758 (53.8)	1.13 (0.99–1.28)	1.30 (1.03–1.65)
No	480 (43.3)	4090 (46.2)		
Signs and symptoms				
Subjective fever within 10 d				
Yes	59 (17.6)	476 (13.3)	1.40 (1.04–1.88)	1.12 (0.63–1.96)
No	276 (82.4)	3110 (86.7)		
Measured temperature > 38°C				
Yes	787 (70.7)	5154 (58.3)	1.72 (1.51–1.98)	1.15 (0.64–2.00)
No	326 (29.3)	3690 (41.7)		
Cough				
Yes	1057 (95.8)	8363 (95.0)	1.21 (0.89–1.66)	
No	46 (4.2)	443 (5.0)		
Sore throat				
Yes	72 (6.5)	603 (6.9)	0.95 (0.74–1.23)	
No	1028 (93.5)	8194 (93.1)		
SOB				
Yes	581 (52.6)	4614 (52.3)	1.01 (0.89–1.15)	
No	523 (47.4)	4204 (47.7)		
Diarrhea				
Yes	251 (26.0)	2810 (37.3)	0.59 (0.51–0.69)	0.66 (0.49–0.87)
No	715 (74.0)	4727 (62.7)		
Vomiting				
Yes	252 (24.0)	2208 (26.2)	0.89 (0.77–1.04)	
No	796 (76.0)	6214 (73.8)		
Headache				
Yes	586 (60.7)	3451 (46.9)	1.75 (1.53–2.01)	1.33 (0.95–1.84)
No	379 (39.3)	3914 (53.1)		
Myalgia				
Yes	283 (29.9)	1650 (22.5)	1.47 (1.27–1.71)	0.99 (0.66–1.48)
No	662 (70.1)	5677 (77.5)		

Definition of abbreviations: CI = confidence interval; ILI = influenza-like illness; IQR = interquartile range; OR = odds ratio; SARI = severe acute respiratory infection; SOB = shortness of breath.

*Data representative of surveillance from October to December 2010.

†Data representative of surveillance from January to June 2015.

Table 3. Risk factors for SARI among patients with influenza in Uganda

Patient Characteristics	Influenza–SARI [No. (% total)] (n = 335)	Influenza–ILI [No. (% total)] (n = 778)	Univariable OR (95% CI)	Multivariable OR (95% CI);
Sex				
Male	188 (56.1)	397 (51.1)		
Female	147 (43.9)	380 (48.9)	0.82 (0.63–1.06)	
Age, yr				
2 mo–4	240 (71.2)	491 (63.9)	Reference	Reference
5–14	56 (16.7)	194 (25.3)	0.59 (0.42–0.83)	0.60 (0.43–0.84)
15–34	18 (5.4)	71 (9.2)	0.52 (0.30–0.89)	0.51 (0.30–0.88)
35–54	13 (3.9)	10 (1.3)	2.66 (1.15–6.15)	2.63 (1.13–6.13)
55–64	3 (0.9)	2 (0.3)	3.07 (0.50–18.48)	
>65	5 (1.5)	0 (0.0)		
Age, yr, median (IQR)	2 (1–5)	3 (1–7)		
Influenza type and subtype				
Influenza A	265 (79.1)	586 (75.3)	1.24 (0.91–1.69)	
A/H3N2	136 (40.6)	357 (45.9)	0.81 (0.62–1.05)	
A/H1N1pdm09	128 (38.2)	223 (28.7)	1.54 (1.12–2.01)	1.53 (1.16–2.02)
A/H3N2 + H1N1pdm09*	1 (0.3)	1 (0.1)		
A/unsubtypable	0 (0.0)	5 (0.7)		
Influenza B	70 (20.9)	191 (24.6)	0.81 (0.60–1.11)	
Influenza B + A/H3N2*	0 (0.0)	1 (0.1)		
Illness onset during rainy season				
Yes	190 (56.7)	424 (54.8)	1.08 (0.83–1.40)	1.08 (0.83–1.40)
No	145 (43.3)	350 (45.2)		
Time from illness onset to presentation				
≥3 d	126 (37.6)	220 (28.4)	1.52 (1.15–1.98)	1.40 (1.06–1.85)
Time, d, median (IQR)	2 (1–3.2)	2 (1–3.0)		

Definition of abbreviations: A/H1N1pdm09 = 2009 pandemic A/H1N1; CI = confidence interval; ILI = influenza-like illness; IQR = interquartile range; OR = odds ratio; SARI = severe acute respiratory infection.

*Each type or subtype was analyzed as a separate case in univariable and multivariable analyses.

influenza subtype. The space-time analysis identified 25 clusters, 14 (56.0%) of which were statistically significant, accounting for 32.0% (356 of 1,113) and 29.6% (329 of 1,113) of all influenza cases, respectively. The spatial-only analysis identified 70 clusters, 38 (54.3%) of which were statistically significant, accounting for 76.3% (849 of 1,113) and 65.9% (733 of 1,113) of all influenza cases, respectively. Both analyses identified large, significant influenza clusters centered in urban and periurban subcounties of Kampala and Entebbe that occurred temporally during rainy season months.

In the space-time analysis, five significant influenza A/H3N2 clusters were identified (Tables E6 and E13–E15; Figure 2). The primary cluster (that with the highest likelihood ratio) was localized to urban and periurban subcounties in Entebbe and Kampala from April to May 2013 (51 cases; log-likelihood ratio [LLR], 115.21; $P < 0.001$). For influenza A/H1N1pdm09, four significant clusters were identified, with the primary cluster localized to urban subcounties in Entebbe and Kampala from April to June 2014

(74 cases; LLR, 192.50; $P < 0.001$) (Figure 3). Five significant influenza B space-time clusters were identified, and the primary cluster was localized to Entebbe and Kampala from September to November 2012 (94 cases; LLR, 306.22; $P < 0.001$).

From 2010 to 2015, significant spatial clusters of all influenza subtypes were identified in urban and periurban subcounties of Entebbe and Kampala (Tables E7–E12). In 2014, the spatial-only statistic also identified significant A/H1N1pdm09 clusters in rural subcounties of eastern, western, and northern Uganda.

Subcounties located within significant clusters were more likely to be classified by the Uganda Bureau of Statistics as urban areas (cities, municipalities, and town councils) (11 of 25 [44.0%] vs. 14 of 68 [20.6%]; $P < 0.001$) and had a significantly higher mean population density (4,265 vs. 2,549 persons/km²; $P < 0.001$) (14). Districts located within significant clusters had a higher mean annual rainfall compared with those located outside such clusters (1,350 vs. 1,052 mm, $P = 0.006$).

Discussion

This study represents one of the largest epidemiologic investigations of influenza and SARI in sub-Saharan Africa and describes a substantial burden of respiratory disease caused by influenza in Uganda. Unique contributions of this study include ascertaining the incidence and subtypes of circulating influenza viruses and characterizing risk factors for severe disease such as A/H1N1pdm09 infection and delayed presentation to care. We also identified urban and periurban areas as high-risk loci for influenza transmission and the biannual rainy seasons as temporal periods during which influenza transmission is likely increased. Significant methodologic contributions of this study include the use of a large, relatively complete prospective surveillance data set, spatiotemporal modeling, and analysis of a defined patient subset for morbidity and mortality, all of which are advances in characterizing acute respiratory disease in sub-Saharan Africa.

Compared with data for developed countries in North America, Europe, and

Figure 2. Spatiotemporal influenza clusters in Uganda detected by SaTScan space-time scan statistic, 2010–2015. Both significant and nonsignificant clusters are included. *Large circular lines* indicate geographic area of each influenza cluster and do not signify the number of cases in the cluster; *smaller solid circles* indicate the location of subcounties composing each cluster. A/H1N1pdm09 = 2009 pandemic A/H1N1.

Asia, limited data exist on the burden and epidemiology of influenza in sub-Saharan Africa, despite the emergence of modeling data suggesting that nearly 30% of global mortality during a future pandemic would occur in the region (16, 17). Similarly, the macroeconomic impact of seasonal influenza epidemics in the labor-intensive economies of sub-Saharan Africa is estimated to be substantial, and in the context of a pandemic would likely be considerably higher than in high-income countries (18). Although vaccination remains one of the most effective pandemic mitigation and control strategies, a

recent systematic review estimated influenza vaccine coverage in sub-Saharan Africa at <1% (19). In Uganda, baseline influenza vaccination rates are similarly low, with <1% of our study sample reporting a history of vaccination. At present, the national influenza vaccination program is in development, and vaccination is obtained primarily through private clinics. To inform national vaccine policy development and pandemic preparedness in this vulnerable region, identification of the epidemiologic and virologic features associated with severe disease and the spatiotemporal

factors associated with increased transmission is needed.

In our study, influenza cases in Uganda were clustered in urban and periurban areas. In urban settings, high population density and increased amounts of shared space are conducive to the transmission of influenza, as evidenced by explosive urban outbreaks and large urban disease clusters in North America and Asia during the 2009 influenza A/H1N1 pandemic (20–22). Similar to the remainder of sub-Saharan Africa, Uganda has experienced rapid urbanization over the past 40 years. The urban population is estimated at 15–20% and is projected to increase by 5% per year over the next

Figure 3. Significant spatiotemporal influenza clusters in urban and periurban subcounties of Kampala and Entebbe detected by SaTScan space-time scan statistic, 2010–2015. Large circular lines indicate geographic area of each influenza cluster; smaller solid circles proportionally indicate the number of influenza cases in subcounties composing each cluster. A/H1N1pdm09 = 2009 pandemic A/H1N1.

5 years (23). In Uganda, >60% of urban residents live in informal settlements or slums, where dwellings have high occupancy rates in all-purpose rooms (24, 25). The high number of these communities in Kampala and Entebbe may have facilitated influenza transmission, because several large slums are located within significant clusters identified in our analyses. Further elucidation of influenza transmission dynamics in these unique and vulnerable settings is needed.

From 2010 to 2015, peaks in influenza activity in Uganda occurred consistently during the months comprising the biannual rainy seasons, and significant influenza clusters were identified during these time periods. Patients with SARI and ILI were also more likely to be infected with influenza when presenting during rainy season months. In temperate climates, low humidity and ambient temperature are thought to enable the airborne survival of influenza viruses while simultaneously promoting indoor crowding and person-to-person transmission, thereby leading to winter-month peaks in influenza activity

(26). Emerging modeling data suggest that high ambient temperatures, humidity, and precipitation may facilitate influenza transmission in tropical and subtropical climates during rainy seasons through an as-yet-undefined biological mechanism (27). As the most commonly used formulations, nonadjuvant, trivalent influenza vaccines induce a neutralizing antibody response that wanes over time (28). Although future investigations are needed, timing campaigns to confer protection during rainy seasons with incorporation of Southern Hemisphere targeted vaccine formulations should be considered (29).

Identification of influenza subtypes associated with severe disease is crucial to facilitate their inclusion in candidate vaccines. Influenza disease severity in our study was associated with A/H1N1pdm09 infection, and this association persisted beyond the immediate postpandemic period. Our findings are consistent with the results of a large, population-based cohort study of influenza surveillance in the United States (30).

In this study, initiated during the first season after the 2009 pandemic, patients infected with A/H1N1pdm09 were more likely to have severe disease, compared with those infected with other influenza A subtypes and influenza B (30). In sub-Saharan Africa, limited data exist on the severity of infection caused by different influenza virus subtypes (31). A 2010 study from South Africa reported an excess number of deaths during years when influenza A/H3N2 was the dominant circulating subtype (32). However, this study analyzed prepandemic A/H1N1 subtypes, and a 2014 study from South Africa did not report differences in disease severity according to influenza virus subtype (32). Further studies are needed to better characterize the association between influenza subtypes and disease severity in the region. Because influenza-negative patients with SARI experienced rates of prolonged hospitalization and in-hospital mortality similar to those of influenza-positive patients with SARI, increased capacity for multiplexed respiratory diagnostics is also needed in sub-Saharan

Africa to support molecular epidemiologic studies and to improve surveillance for other epidemic-prone pathogens.

Among influenza cases in Uganda, severe respiratory infection was associated with delayed presentation to care. In sub-Saharan Africa, data on influenza-specific health-seeking behaviors are limited and are challenged by its presentation as a nonspecific febrile illness (6). However, a 2008 study from Uganda that analyzed pneumonia-associated deaths among children <5 years of age found that the majority of caregivers waited >24 hours (median, 48 h) before bringing patients to trained health care providers, with one-third of patients dying at home (33). Caregivers who delayed seeking care were unaware of the “danger signs” of severe respiratory disease and were more likely to administer empiric antimalarial therapy at home before presentation to a health facility (33).

Although most of the patients in our study were children, elderly patients with SARI (age, ≥ 65 yr) were more likely to experience prolonged hospitalizations, and nonelderly adults (35–54 yr of age) were found to be at high risk of SARI-associated in-hospital mortality and influenza-associated severe respiratory infection. Similar data have been reported from South

Africa, where a high prevalence of comorbid illness among elderly adults and advanced HIV infection among nonelderly adults likely contributed to higher rates of influenza-associated mortality in these age groups (32, 34).

Limitations

This study has several limitations. Our clinical epidemiologic analyses were limited because we did not have data on coexisting medical problems, including HIV status, among the cases enrolled in the surveillance cohort. Our analysis of short-term outcomes for patients with SARI was also limited to approximately 30% of cases. Although surveillance sites were chosen according to established standards and data were collected prospectively, the sentinel nature of influenza surveillance in Uganda may have resulted in ascertainment bias. Epidemiologic data from sentinel programs are inherently reflective of each site’s catchment population, and some sites enrolled only cases with SARI or ILI. Similarly, in our spatiotemporal analyses, detection of urban and periurban clusters may have been biased by the location of sentinel sites and the proportion of cases with ILI or SARI enrolled at each site, because cases with ILI in the cohort were

more likely to be influenza positive. However, through the use of Poisson modeling methods, we were able to compare observed and expected numbers of influenza cases at the subcounty level, and our analyses consistently detected large, significant clusters in urban and periurban areas throughout the study period.

Conclusions

Influenza is an important cause of acute respiratory infection in Uganda. Specific epidemiologic and virologic factors increase the risk of severe respiratory infection and poor outcomes, and urban and periurban areas appear to be high-risk loci for influenza transmission, particularly during the rainy seasons. Additional studies examining the epidemiology and transmission dynamics of influenza in sub-Saharan Africa are urgently needed to expand the evidence base for prevention and mitigation strategies in the region. ■

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