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A Look at the Change in the Seasonality of Influenza between Three Distinct Regions of Uganda: Central, Northwest, and Western

Sarah K. McClellan
Georgia State University

Richard Rothenberg MD MPH
Georgia State University

Gerardo Chowell PhD
Georgia State University

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A Look at the Change in the Seasonality of Influenza between Three Distinct Regions of Uganda: Central, Northwest, and Western.

By

Sarah Kyle McClellan

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Sarah Kyle McClellan

Approved:

Richard Rothenberg, MD MPH
Committee Chair

Gerardo Chowell, PhD
Committee Member

August 19, 2016

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Sarah Kyle McClellan

TABLE OF CONTENTS

List of Tables

List of Figures

A Look at the Change in the Seasonality of Influenza between Three Distinct
Regions of Uganda: Central, Northwest, and Western.

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ABSTRACT

       Influenza is suspected to be endemic in tropical climates, with peaks during and/or following cold or rainy seasons. To date, only one study has been conducted examining the epidemiology and seasonality of influenza in Uganda. The focus of this analysis is to determine whether a change in the seasonality of influenza can been seen between three distinct regions of Uganda: Central, Northwest, and Western.

       Secondary data analysis was conducted on surveillance data collected by the Uganda Virus Research Institute (UVRI) between April 2007 to September 2010 from 10 surveillance sites. Surveillance sites were grouped for this analysis into three regions: Central, Northwest, and Western. A total of 3,944 samples were collected and tested for any strain of influenza.

       The prevalence of influenza over the 4 years of surveillance was 10.1%. The majority of cases came from the Central region (81.7%) and the highest prevalence of influenza-positive samples were collected in the Central region (88.7 cases/1,000 persons).

       A clear difference in influenza activity was observed during the 2009 H1N1 pandemic. Uganda reported its first case of H1N1 in July 2009 (Relief Web). The Central region experienced its initial flux of influenza activity in July and August 2009 (**Figure 1**). However, the Northwest region did not experience a flux in activity until October 2009 (**Figure 2**). Influenza activity in the Central and Northwest regions appear to coincide with colder temperatures and both rainy seasons. The Northwest region was the only region to experience a peak corresponding with warmer weather.

       Results showed a slight change in the seasonality of influenza between the Central and Northwest regions of Uganda from surveillance data collected between April 2007 and September 2010.

Introduction

The World Health Organization (WHO) in the 2010 World Health Statistics Report classified Uganda as a low-income country. While influenza morbidity and mortality have been well-documented in high and middle income countries, little is known about the epidemiology, burden of disease, and seasonality of influenza in Africa.

Influenza surveillance began in Uganda in 2006 when WHO recognized the Uganda Virus Research Institute (UVRI) in Entebbe as a National Influenza Centre (NIC). Influenza has been described as endemic in tropical climates, however, respiratory syncytial virus (RSV) and influenza infections have been observed mainly during rainy seasons in Asian, African and South American countries with tropical climates (Shek et al., 2002). Uganda experiences two rainy seasons: March to May and October to November and hottest temperatures are felt from December to February (World Travel Guide). To date, only one study has been conducted examining the epidemiology and seasonality of influenza in Uganda (Lutwama et al., 2012).

The focus of this analysis is to determine whether a change in the seasonality of influenza can been seen between the Central, Northwest, and Western regions of Uganda. Does influenza activity peak at different times of the year in the different regions? Does one region experience more influenza than the others? Is influenza endemic? Does Uganda share similar seasonality patterns as countries in similar tropical climates?

Literature Review

A comprehensive literature review was conducted to assess available research regarding the epidemiology and seasonality of influenza in Uganda. Search terms included "influenza" and "influenza surveillance." Available research for Uganda was scarce, so the field of interest was widened to include the bordering countries of Kenya and Tanzania. Many of the articles read reported findings from Kenya. Uganda, Kenya, Tanzania and other East Africa countries share similar tropical climates.

Radin et al. (2012) explained the importance of influenza surveillance in Africa: "pandemic influenza strains can emerge and/or spread undetected in settings with less extensive surveillance systems. Pandemic influenza has the potential to cause relatively greater morbidity and mortality in resource-poor countries."

Much of East Africa experiences tropical climates. Gessner et al. (2012) published a systematic review of studies based in Kenya and concluded that, in countries nearer to the equator, "influenza seasonality is less pronounced." Influenza activity in Ghana corresponded with the countries rainy season (Bonney, 2012). In a 2013 study conducted by Balinandi et al., data was collected from August to December 2008 in Kampala and Entebbe, Uganda. This study found that 46.6% of enrollees (n=172) were positive for one of more respiratory agents. The most commonly detected virus was influenza A (n=71). The prevalence of influenza detected in Influenza-like Illness (ILI) cases (19.2%) was higher in Balinandi et al. (2013) study than previously reported observations of 12% by Lutwama et al. (2012). The higher prevalence could be due in part to the timing of the study, during months that experience heaviest reported rainfall.

Lutwama et al. (2012) conducted the first study in Uganda that looked at the epidemiology and seasonality of influenza. The study analyzed data collected by the UVRI from April 2007 to September 2010.

Many of the surveillance sites were in areas of high population and high trade. Densely crowded populations are at a higher risk for airborne disease due to the ease of transmission associated with overcrowding (Ahmed et al., 2012).

Over half of the cases were in children <5 years of age, an age group considered to be high risk for influenza infection. Thirteen percent (359/2,758) of samples tested positive for influenza. Throughout 2008-2009, the only full calendar year surveilled, Lutwama et al. (2012) found that 17.2% (279/1,620) of collected specimens tested positive for influenza. Upon further analysis, persons 5-14 years of age had the highest percentage of influenza-positive samples (19.6%, 100/509) and were more likely to test positive for influenza compared to children 0-4 years of age (OR 2.43 95% CI 1.82-3.25). The highest percentage of influenza positive specimens were received from The Surgery, a private 24-hour emergency care clinic in Kampala (77.2%, 44/57) (Lutwama et al., 2012).

The highest number of samples were collected between May and November. Influenza activity was highest during October and November. These months correspond to periods of cold weather and increased rainfall. This pattern of influenza activity during periods of cold weather and increased rainfall has previously been documented in studies conducted in Singapore (tropical climate) and Hanoi, Vietnam (subtropical climate) (Moura, Perdigão, & Siqueira, 2009).

Radin et al. (2012) analyzed Influenza-like Illness (ILI) and Severe Acute Respiratory Infection (SARI) data collected from 15 African countries (including Uganda) from 2006-2010.

Researchers were interested in describing the age, distribution, seasonality, strain circulation, and percent of respiratory disease where influenza was detected. Twenty-one and seven tenths percent of ILI cases and 10.1% of SARI cases tested positive for influenza. Eight and nine-tenths percentage of hospitalizations for SARI were associated with influenza infection. The article concluded that "the burden of respiratory disease and influenza" was highest in children <5 years of age.

The percent of ILI positive cases was highest (34%) in the 10-14 age group and lowest (17%) in the >65 age group. The percent of SARI positive cases was highest (12%) in children 10-14 years of age and lowest (3%) among adults >65 years of age. Twelve and five tenths percent of ILI cases and 6.4% of SARI cases tested positive for influenza (Radin et al., 2012).

In an article published in the *Journal of Infectious Diseases* by McMorrow et al. (2015) all SARI cases and SARI-associated deaths detected by surveillance between 2009-2012 were analyzed. Cases were collected from 8 countries in sub-Saharan Africa including Uganda. McMorrow et al. (2015) noted that the countries with systematic death reporting reported higher all-cause (including influenza) associated case-fatality proportions (CFPs) than countries with sporadic reporting. Therefore, Uganda's reported CFP of 0.0 can be attributed to poor reporting and insufficient surveillance.

Further analysis revealed influenza-associated deaths to account for 33.3% in children 0-4 years, 35.1% in adults 18-49 years, and 31.5% in adults >50 years. Children 0-4 years of age accounted for nearly two thirds of SARI cases and over a third of all SARI-associated deaths and influenza-associated deaths. Adults >65 years of age accounted for 2.4% of SARI cases. McMorrow et al. (2015) speculated that the variance is credited to differences in health care utilization.

Another study focused on two rural Western Kenyan towns, Lwak and Siaya, looked at the coinfection of influenza and malaria among young children (Thompson et al., 2012). Bordering Lake Victoria, Lwak and Saiya make up one of the poorest areas in Kenya with high child mortality and endemic malaria. Thompson et al. (2012) found that being positive for one infection was associated with a reduced likelihood of being positive for the other. Meaning, children with influenza were less likely to have malaria than those without influenza (and vice versa).

Length of stay in hospital varied among age groups. Among children <24 months of age, coinfection was not associated with length of stay. Researchers found that "influenza only" was shown to be associated (but not significantly) with one addition day in Lwak and "malaria only" was significantly associated with a half day shorter stay in Siaya. However, in children 24-59 months, coinfection was associated with a one to three day increase in the length of in-hospital care and was associated with more severe illness than single infection (Thompson et al., 2012).

Ahmed et al. (2012) looked at respiratory viruses in Dabaab and Kakuma, refugee camps in Eastern and Northwestern Kenya, and identified the epidemiology of acute respiratory illness (ARI) among refugees. Displaced populations are at higher risks for respiratory infections for a variety of reasons including; overcrowding, malnutrition, increased stress, and poor housing conditions. From September 2007 to August 2010, Ahmed et al. (2012) tested 6,264 participants who reported to a hospital or health clinic within the camps with symptoms of ILI or SARI (case definitions were modified from WHO definitions).

Researchers found that rates peaked for most viruses between November and February. Rates were highest in children <12 months of age. Surprisingly, researchers found no association with increased hospitalizations in either camp during the 2009 H1N1 pandemic.

Ahmed et al. (2012) concluded that because at least one respiratory virus was found in 50% of specimens from participants, refugee populations are at higher risk of developing severe illnesses from respiratory infections.

Several articles have been published based on influenza surveillance data collected in Kibera, an urban slum in Nairobi, and Lwak, a rural town in Western Kenya bordering Lake Victoria.

One article examined secondary attack rates of H1N1 influenza among households in both urban (Kibera) and rural (Lwak) settings. Secondary attack rates are the spread of disease from an initial case to individuals with whom they come into contact (Epiville, Columbia U.) The proportion of secondary cases of ILI was greatest among children <5 years of age than among children ≥5 years of age in both sites (Kim et al., 2012).

Children <5 years of age were found to be 3.8 times more likely to develop a secondary case of ILI than children ≥5 years of age. More specifically, children <5 years of age who encountered lab-confirmed H1N1 patients were ~4 times more likely to develop secondary illness compared to older children in Lwak. The absolute H1N1 secondary household attack rates were 4.6% (Kibera) and 8.2% (Lwak). Setting could explain the difference in secondary household attack rates. Lwak is a rural setting, people may spend more time at home and around family compared to individuals who live in urban Kibera. Researchers also hypothesized that endemic malaria in Lwak may play a role in developing secondary illness of H1N1. Sixty-five and seven-tenths percent of ILI patients were blood smear-positive for malaria. If true, this would contradict previously discussed findings from Thompson et al. (2012) that stated "children with influenza were less likely to have malaria than children without influenza."

Another study conducted in Kibera, Kenya found that while influenza was present all year. Influenza activity peaked surrounding the rainy seasons and a smaller peak was experienced during the cold season (Breiman et al., 2015). In Lwak, Kim et al. (2012) found that influenza cases spiked during months of heavy rainfall and hotter temperatures. In Uganda, Lutwama et al. (2012) reported peaks of influenza activity corresponding with the coldest months of the year supporting Breiman et al.'s findings in Kibera.

Katz et al. (2012) reported that the incidence of acute influenza-associated lower respiratory tract infections and home-reported ILI were higher in Lwak than in Kibera. Katz et al. (2012) noted that malaria rates usually peak in Western Kenya (Lwak) in the months following heavy rainfall. The corresponding peaks in influenza activity and malaria could mean that malaria acts as a potential confounder for the influenza burden of disease.

A later study by Katz et al. (2014) reported that 9.6% of SARI cases and 14.6% of ILI cases sampled were positive for influenza. And while influenza was detected nearly every month, the highest percentage of influenza-SARI cases occurred during periods of low precipitation, relatively low temperatures, and variable humidity.

Another study conducted in Kibera and Lwak, Kenya looked at the unrecognized burden of influenza in young children (McMorrow et al., 2015). Eight and three-tenths percent of acute lower respiratory illness patients tested positive for influenza along with 11.4% of ILI patients. Children with ILI in Kibera were more likely to have influenza compared to children in Lwak (19.1% vs 9.4%). The highest rates of influenza-associated hospitalizations in Lwak were seen in the 6-23 month age group (8.4 hospitalizations/1,000 person-years) and the 0-5 month age group (7.6 hospitalizations/1,000 person-years). Hospitalizations were rarely reported in Kibera (McMorrow et al., 2015).

The Bondo district of Western Kenya is a rural, poor area supported mostly by subsistence farming and fishing. Feikin et al. (2012) found children <5 years of age to experience much higher rates of influenza-associated hospitalizations when compared to older children and adults (143.7 vs. 36.7 cases/100,000 persons).

Most of the influenza-positive results were reported between May and October but monthly numbers peaked in July and August, months of dry and relatively cool temperatures in Western Kenya. In the second year of surveillance, researchers observed a second peak in January and February during the dry and warmer months (Feikin et al., 2012). Another study based in Western Kenya reported highest numbers of acute respiratory infection (ARI) admissions and influenza cases between the months of September and March but noted that influenza circulated year-round (Makokha et al., 2016).

Emukule et al. (2014) looked at the burden of influenza and respiratory syncytial virus (RSV) among inpatients and outpatients in rural Western Kenya. Data was collected from August 2009 to July 2012. Influenza was detected in 8% of SARI cases and 14% of ILI cases. Researchers also found that influenza-positive percentages were lower during hotter months.

Another study by Emukule et al. (2016) examined timing, associations with climatic factors, and other implications for influenza vaccination campaigns in Kenya. It was found that characteristics of influenza seasonality are less predictable in tropical sub-Saharan regions where influenza activity is best described as semiannual epidemics or have a year-round presence. Increased influenza activity was reported during months of heavy rainfall.

The guinea pig model of influenza was developed in 2006 and provides a general understanding of influenza infectiousness, development, and transmission in guinea pigs. Guinea pigs were used because most influenza viruses do not easily transmit among mice

14

(Lowen et al., 2014). Researchers found that influenza transmission via a "respiratory droplet or aerosol route" occurs best under cold, dry conditions. Feikin et al. (2012) found that lower specific humidity was significantly associated with influenza activity but oddly found no significant association with rainfall. After adjusting for site, humidity was significantly negatively associated with influenza and "cold-dry" weather was significantly positively associated with influenza infection which supports the findings of Lowen et al. (2014) guinea pig model.

While a review of literature by Tamerius et al. (2011) found four studies that support Feikin et al.'s findings, Lowen & Steel (2014) reported that in areas within 10 degrees of the equator, influenza activity peaked during months of high specific humidity and rainfall. Lowen & Steel (2014) concluded that while humidity and temperature may serve as predictors of influenza activity in temperate regions, other drivers may prove more accurate in tropical climates.

Tanzania, a Uganda-bordering country, also experiences a tropical climate with highest temperatures reported between November and February, lowest temperatures between May and August and two rainy seasons, mid-March to May and November to January. Humidity averages ~45% throughout the year (Mmbaga et al., 2012). Mmbaga et al. (2012) analyzed surveillance data from Tanzania with the objective of describing the epidemiology, seasonality, and burden of disease for influenza.

Data was collected between May 2008 and November 2010. Of the 61% of cases identified as ILI, 8.2% test positive for influenza. The highest proportion (34.8%) of influenza positive ILI cases were found among 5-18-year old's. Thirty-one percent of cases consisted of SARI patients. Of the 31% of SARI patients, 7.3% tested positive for influenza. The highest

proportion (23.5%) of influenza-positive SARI cases were found in children <1 year of age (Mmbaga et al., 2012).

Influenza activity in Tanzania peaked between February and June, a period of lower temperatures and increased rainfall. In 2009, a second peak was observed between August and October largely a result of the H1N1 pandemic. The low level of influenza activity in the beginning and end of each year corresponds with periods of slightly higher temperatures and humidity (Mmbaga et al., 2012).

Influenza seasonality has been studied in tropical climates but it is still poorly understood. Studies have been conducted aimed at identifying drivers or determinants of increased influenza activity. French Guiana is an equatorial country, similarly to Uganda, and experiences two distinct weather periods; a "dry season" and a "wet season." The dry season lasts from August to December while the wet season includes a short rainy season between January and February and a major rainy season from April to July (Mahamat et al., 2013). Data collection began before the 2009 H1N1 pandemic and continued during and after the pandemic. Results of this study showed that increased influenza activity coincided with the onset of both rainy seasons with a main peak coinciding with the major rainy season but was present throughout the year. The study also looked at specific humidity as a possible driver for influenza inactivity. Analysis revealed that "an increase of 1g/kg in standard humidity resulted in a significant decrease of 11% in ILI incidence 3 weeks later, after adjustment for rainfall." (Mahamat et al., 2013).

The two possible drivers (rainfall and humidity) were independently associated with ILI incidence. A study conducted in neighboring Brazil, found that in tropical regions there was a statistically significant association between the occurrence of ARI (including influenza) and

rainy seasons. Most influenza-positive samples (93%) were collected around the peak of Brazil's rainy season (Moura, Perdigão, & Siqueira, 2009).

The epidemiology and seasonality of influenza in Africa is a relatively new area of interest. To date, the seasonality of influenza is murky but data from available literature suggests influenza activity to be associated with the onset of rainy seasons and cooler temperatures. Other potential drivers such as humidity and elevation have been proposed. Further analysis needs to be done on comprehensive surveillance data to support such claims.

Methods

Secondary data analysis was conducted on surveillance data collected by the Uganda Virus Research Institute (UVRI) between April 2007 and December 2010 from 10 surveillance sites; 5 public hospitals and 5 general outpatient clinics (4 public and 1 private). Surveillance sites covered 6 districts and 4 geographically distinct regions across Uganda (Lutwama et al., 2012). The dataset was previously analyzed in an article published in 2012 by Lutwama et al. in the *Journal of Infectious Diseases*.

Analysis was conducted using SAS 9.4 (SAS Institute, Cary, North Carolina). A chi-squared test was performed to determine whether there was a significant difference between the categorical variable *Region* and the categorical variable *Outcome of Influenza*. Districts were grouped into one of three regions; the Central region which included Wakiso, Kampala, and Tororo, the Northwest region made up of Koboko and Arua, and lastly the Western region of Kabarole and Mbarara.

Outcome of Influenza was binarily coded, positive results for any strain of influenza (A, B, or unsubtypeable) were coded 1 and negative results were coded 2. A chi-squared test was also performed comparing from where samples were collected, *Healthcare* and *Outcome of Influenza*. For this analysis, all hospitals were grouped together and all other health care facilities were grouped as "health clinics."

An analysis of variances (ANOVA) was conducted to determine significance among the three regional means. An ANOVA was selected because the independent variable (*Region*) has 2 or more levels and was compared with the dependent variable (*Outcome of Influenza*) which is an interval and nominal variable (binary outcome). The ANOVA showed a significant

difference between groups, so a post-hoc comparison test (Tukey) was run. The post-hoc

comparison test showed which groups were significantly different.

Graphs showing the number of cases throughout the 4 years of surveillance were created

using Excel 2016 and tables were built in Word 2016.

A multiple variable logistic regression was run comparing *Outcome of Influenza* with

Sex, Region, and *Healthcare*.

Approval for an expedited exempt secondary data analysis was granted by the

Institutional Review Board at Georgia State University.

Results

A total of 3,944 samples were collected and tested for any strain of influenza; 81.7% (n=3,223) from the Central region, 17.6% (n=693) from the Northwest region, and 0.7% (n=28) from the Western region. Of the 3,944 samples collected, 399 tested positive for any strain of influenza. The Central region accounted for 87.7% (n=350) of all influenza-positive samples and 12.0% (n=48) of all influenza-positive samples came from the Northwest region. In the 4 years of surveillance, only 1 case (<1%) was reported from the Western region (February 2010) (**Table 1**). Due to the small reporting size from the Western region, further analysis is unavailable.

Samples were collected from only the Central region in 2007 (n=491). Of the samples tested, 62 (12.6%) tested positive for any strain of influenza. Samples collected in 2007 made up 12.4% of the total collected samples throughout the 4 years of surveillance (**Table 1**).

In 2008, samples were collected from all three regions (n=802). Of the samples tested, 138 (17.2%) tested positive for any strain of influenza. Of the 138 influenza-positive samples, 87.7% (n=121) came from the Central region, 12.3% (n=17) came from the Northwest region and 0 were collected from the Western region. Samples collected in 2008 made up 20.3% of total collected samples (**Table 1**).

In 2009, samples were only collected from the Central and Northwest regions (n=855). Of the samples tested, 74 (8.7%) samples tested positive for any strain of influenza. Of the 74 influenza-positive samples, 77.0% (n=57) came from the Central region and 23.0% (n=17) came from the Northwest region. Samples collected in 2009 made up 21.7% of the total collected samples (**Table 1**).

In 2010, samples were collected from all three regions (n=1,796). Of the samples tested, 125 (7.0%) tested positive for any strain of influenza. Of the 125 influenza-positive samples, 88.0% (n=110) came from the Central region, 11.2% (n=14) came from the Northwest region, and 0.8% (n=1) came from the Western region. Samples collected in 2010 made up 45.5% of the total collected samples throughout the 4 years of surveillance (**Table 1**).

The prevalence of influenza for the 4 years of surveillance was 10.1% (399/3,944). The highest prevalence was seen in the Central region (88.7 cases/1,000 persons), followed by the Northwest (12.2 cases/1,000 persons) and Western (0.3 cases/1,000 persons) regions (**Table 2**).

The analysis of variances (ANOVA) showed a significant difference in means for *Outcome of Influenza* between *Regions*, $F(2, 3941) = 81.69$, $p=0.0040$ ($\alpha=0.05$) (**Table 3**). Based on the post-hoc comparison test (Tukey), the only significant difference in means was between the Central and Northwest regions. The Western region did not differ significantly from either of the other regions (**Table 4**).

A significant difference between *Healthcare* and *Outcome of Influenza* was also found. A higher percentage of cases were reported from hospitals (75.33%) then health clinics (24.67%). The chi-square statistical value was 12.45 with an associated p-value of 0.0004 ($\alpha=0.05$) (**Table 5**).

A multiple variable logistic regression was conducted to estimate the probability of the outcome. Results showed a significant difference between *Healthcare* and *Outcome of Influenza*. Over all three regions, the odds of receiving a positive diagnosis in a hospital was 1.37 (CI 1.10, 1.71) times higher than receiving a positive diagnosis in a health clinic, after adjusting for *Sex* and *Region* (**Table 6**).

When only looking at the Central and Northwest region, the odds of receiving a laboratory confirmed diagnosis for influenza in a hospital was 1.39 (CI 1.11, 1.74) times more likely than receiving a positive diagnosis for influenza in a health clinic, after adjusting for *Sex* and *Region*.   Further analysis showed that the odds of receiving a positive diagnosis for influenza in the Central region was 0.71 (CI 0.520, 0.958) times lower compared to receiving a positive diagnosis for influenza in the Northwest region. In other words, receiving a positive influenza diagnosis in the Northwest region was 1.42 times higher than receiving a positive diagnosis for influenza in the Central region, after adjusting for *Sex* and *Healthcare* (**Table 6**).

The Central region was the only region to contribute surveillance data in all 4 years. In 2007, there was an increase in influenza cases from May to November, peaking in October (n=11). In 2008, influenza activity increased from July to December, with a clear peak in November (n=39). This peak in November 2008 had the highest number of influenza cases in all 4 years of surveillance and in all 3 regions. In 2009, the number of cases spiked in July and August (n=13). Influenza activity increased from May to November of 2010, peaking in June (n=27). Following June 2009, at least one influenza-positive sample was collected every month from the Central region (**Figure 1**).

Surveillance data from the Northwest region showed a consistent level of activity from June to November 2008, with peaks in August and October (n=5). The largest peak in influenza cases occurred in October 2009 (n=14). Following June 2010, at least one influenza-positive sample was collected every month (except for September) from the Northwest region with a peak in November (n=5) (**Figure 2**).

Differences in seasonality within regions and/or year-round occurrence in Uganda was graphed. The Northwest region was the only region to experience one yearly peak during

Uganda's summer months (December – February). All other peaks coincided with either cold or

rainy months (**Figure 3**).

Discussion

The largest percentage of samples was collected from the Central region (81.7%). The Central region also provided the largest percentage of influenza cases (87.7%) and was the only region involved in all 4 years of surveillance (**Table 1**). The Central region comprises of Uganda's two major cities, Kampala (the capital) and Entebbe. In April 2007, surveillance started in Kampala, at Mengo hospital. The number of sites gradually increased over the next 4 years as well as the number of samples collected at each site (Lutwama et al., 2012).

The prevalence of influenza for the 4 years of surveillance was 10.1% (**Table 2**). Balinandi et al. (2013) reported a higher prevalence of influenza than the current study. One explanation for the differences in prevalence is timing. Balinandi et al.'s (2013) study was conducted from August to December 2008 in Kampala and Entebbe. That period corresponds with Uganda's second rainy season. The timing and higher prevalence supports the notion that influenza activity in Uganda increases relative to rainfall.

Although, more samples were tested in 2009 (n=855) than in 2008 (n=802), the higher percentage of influenza-positive samples was found in 2008 (17.2%) compared to 2009 (8.7%) (**Table 1**). WHO's report "Pandemic (H1N1) 2009 in the African Region; Update 63" reported 251 confirmed cases of H1N1 in Uganda. This official number is much larger than the 74 influenza-positive samples for any strain of influenza reported during the study period resulting in a highly underestimated H1N1 burden of disease experienced in Uganda (**Table 1**).

In its final year, surveillance was conducted at all 10 sites (5 hospitals and 5 general outpatient clinics) (Lutwama et al., 2012). The largest number of samples was also collected during the final year of surveillance and accounted for nearly half (45.5%) of the total number of samples collected during all 4 years (**Table 1**).

There was a significant difference in the percentages of collected samples between regions. A significantly higher percentage of samples was collected from the Central region (81.7%) compared to the Northwest (17.6%) and Western (0.7%) regions (**Table 2**).

There was also a significant difference in means between *Region* and *Outcome of Influenza* (**Table 3**). Further analysis (post-hoc Tukey), revealed a significant difference in means between the Central and Northwest regions (**Table 4**). The Central region accounted for 87.7% of all influenza cases while the Northwest region accounted for 12% (**Table 1**).

One plausible explanation for the significant difference in the percentages of collected samples between regions and the number of cases reported in each region could be that the Central region was the only region to contribute surveillance data all 4 years or because there were more surveillance sites in the Central region compared to the other two regions.

Population density also may have played a role in both the percentages of collected samples between regions and the number of cases reported in each region. Population density surrounding the surveillance sites located in the Northwest and Western regions (91-500 persons/km^2) is much less compared to the population density surrounding the surveillance sites in the Central region (501-4,600 persons/km^2) (Lutwama et al., 2012). The Central region consists of two urban cities, Kampala (the capital) and Entebbe, and the Northwest and Western regions are mostly rural.

Analysis showed significant differences in the type of healthcare facility where people received influenza-positive diagnoses. Results showed that people were more likely to receive an influenza-positive diagnosis from a hospital than from a health clinic (**Table 6**). One explanation for this could be that people are more fearful of influenza-like symptoms, which are similar to symptoms of malaria. This increased fear may result in an increased likelihood of

seeking treatment at a hospital. The odds of receiving an influenza-positive diagnosis was not significantly different between sexes.

A clear difference in influenza activity was observed during the 2009 H1N1 pandemic. Uganda reported its first case of H1N1 in July 2009 (Relief Web). The surveillance data analyzed showed the Central region experiencing its initial flux in July and August 2009 (**Figure 1**). The data also shows that the Northwest region did not experience a flux in activity until October 2009 (**Figure 2**). The delay in influenza activity onset in the Northwest region could be due to the flow of travel into and throughout Uganda. Central Uganda is a bustling metropolis. H1N1 could have arrived by plane or boat explaining why Entebbe and Kampala experienced a flux in activity months before the Northwest region.

Influenza activity in the Central region appears to coincide with cooler temperatures and both rainy seasons. In every year of surveillance, influenza activity in the Central region decreased around the warmer months (December to February). Activity tended to increase following Uganda's first rainy season (March to May) and throughout the rest of the year. Peaks in activity occurred in October 2007 (n=11), November 2008 (n=39), August 2009 (n=19), and June 2010 (n=27) (**Figure 1**).

The November 2009 peak in activity coincided with the second rainy season. Similar correlations between increased influenza activity and rainfall have been observed in Kenya (Breiman et al., 2015) (Emukule et al., 2016) and Ghana (Bonny et al., 2012). The second largest peak was observed in June 2010 during the colder months. Increased influenza activity in colder temperatures has been previously reported by researchers (Breiman et al., 2015) (Katz et al., 2012) in Kenya and Tanzania (Mmbaga et al., 2012).

A plausible explanation for the spike in influenza activity during the cold and/or rainy seasons could be caused by changes in social behaviors and not the change in weather. People stay indoors more when it is cold or rainy thus allowing for greater opportunity for the spread of influenza. Per Lowen & Steel (2014), influenza transmission occurs best under cold, dry conditions and the virus half-life is increased as well. Feikin et al. (2012) also found that lower specific humidity was significantly associated with influenza activity but found no significant association with rainfall.

Surveillance data from the Northwest region was sporadic. Activity in the Northwest region appeared to coincide with the colder months and second rainy season. Peaks in activity occurred in August and October 2008 (n=5), October 2009 (n=14), and surprisingly February 2010 (n=4) (**Figure 2**). Due to the sporadic nature of reporting this data may not accurately represent influenza activity in the Northwest region of Uganda.

The August and October 2008 peaks in activity concurred with the end of Uganda's winter and beginning of the second rainy season. The peak observed in February 2010 is surprising because it corresponds with the end of Uganda's summer months.

There have been several studies conducted in Kenya that reported results supporting increased influenza activity during warmer months as seen in the Northwest region in 2010. Kim et al. (2012) found that influenza activity increased in warmer weather. Katz et al. (2012) reported highest influenza-associated SARI cases in times of less rainfall and Feikin et al. (2012) described a second peak in influenza activity during Western Kenya's dry and warm season.

In **Figure 3**, surveillance data from all three regions was combined. Influenza activity is shown to decrease around the beginning of each year (corresponding with warmer temperatures). Activity started to pick up around May every year following Uganda's first rainy season and

continued throughout the rest of each year with increases observed during the cold and rainy months.

Several studies support the notion that influenza is present year-round in tropical climates (Breiman et al., 2015) (Katz et al., 2012) (Makokha et al., 2016). A year-round presence makes predicting seasonality hard (Emukule et al., 2016). The Centers for Disease Control and Prevention (CDC) defines *endemic* as "the constant presence and/or usual prevalence of a disease or infectious agent in a population within a geographic area." In this study, influenza activity appeared to reach endemic levels following June 2009. At least one influenza-positive sample was reported every month following June 2009. Predicting influenza seasonality is hard in climates such as Uganda's because influenza may prove endemic in tropical climates.

Limitations

The surveillance data used in this analysis has several limitations. The high percentage of samples collected from the Central region (81.7%) limits generalizability. Analysis and figures were created depicting influenza activity in the Central and Northwest regions. Analysis was not possible for the Western region because only 1 case of influenza was collected during the study period. The findings in this study may not be generalizable to the whole of Uganda because of the bias towards higher reporting regions.

Data collection started at the onset of influenza surveillance in Uganda. This explains why samples were only collected from the Central region in 2007 because that is where surveillance first started. Differences in seasonality may be more pronounced between regions if analysis was to be conducted on newer and more comprehensive surveillance data.

Another limitation is the country of interest. Uganda is a low-income country and research funding is limited. It would have been beneficial to conduct a regression model comparing the surveillance data with corresponding day-to-day reports of rainfall and temperature. However, day-to-day weather statistics are not available. Because of the lack of access to daily weather statistics, the surveillance data was grouped into months and compared to seasonal trends for rainfall and temperature. Having access to daily weather statistics could better explain the ups and downs in activity depicted in **Figures 1, 2, & 3** (i.e. the spike in activity seen in February 2010 in the Northwest region.)

Lastly, the surveillance data used for this analysis highly underestimates the burden of disease experienced in Uganda during the 2009 H1N1influenza pandemic. The World Health Organization's 2009 report on the H1N1 pandemic in the African region reported 251 confirmed

cases in Uganda. This official number is much larger than the 74 influenza-positive samples of

any strain of influenza reported in this data set (**Table 1**).

Future Research

Future research should focus on improving surveillance methods, such as consistent reporting, unified case definitions, and increasing the number of surveillance sites. **Figure 3** shows that influenza may prove endemic in Uganda, however the only way to know for sure is to improve surveillance.

Viboud et al. (2006) explained that successful and accurate modeling of the influenza burden in tropical countries relies heavily on high-quality surveillance data. McMorrow et al. (2015) found that countries with more comprehensive reporting reported higher numbers. It can be surmised that with improved surveillance, future studies may report higher incidence and/or prevalence of influenza in Uganda either seasonally or year-round. Improvements may also lead to more reliable predictions for future outbreaks.

Improved surveillance would provide more accurate depictions of influenza seasonality allowing for the development of more successful immunization campaigns. As previously discussed, many spikes in influenza activity coincide with Uganda's rainy seasons. If this timing is to be trusted, then perhaps launching vaccination campaigns before and during Uganda rainy seasons may reduce the number of cases and overall spread of influenza.

Air travel has been shown to play a leading role in the pandemic spread of disease around the world (Kenah et al., 2011). In countries like Brazil that experience increased tourist activity during certain months each year, launching immunization campaigns before and during tourist seasons would better protect locals from catching anything tourists may bring with them.

Extending influenza surveillance into prenatal clinics and maternity wards would provide better estimates for the burden of disease in pregnant women (McMorrow et al., 2015). Maternal immunization has been shown to reduce influenza-associated illness in infants (Katz et al.,

2012). Nankabirwa et al. (2010) found that a mother's education level may increase the likelihood of vaccination and improve utilization of primary health care services. Launching immunization campaigns targeting pregnant women could increase immunizations in both new mothers and youths.

Broadening case definitions may capture more cases of influenza (McMorrow et al., 2015). Also, integrating influenza surveillance into broader programs (i.e. pneumonia surveillance) may also prove more sustainable. However, resource limited populations may need to develop more specific case definitions that maximize case detection (Makokha et al., 2016). Barriers to hospitalization of ill children also plays a critical role in hospital-based surveillance. Barriers include: cost of transportation, cost of stay, and the parent's inability to stay in the hospital with children because of work and/or care for others.

The association between hospitalization and death in young children is another barrier experienced by parents. This association makes parents more reluctant to seek hospital-based care for children (McMorrow et al., 2015). Improving perceptions of hospitals may improve detection, treatment, and increase immunizations.

Although the influenza burden of disease seems to be higher in youths, another population to consider are individuals $\geq$50 years of age. Current understandings of influenza activity and the burden of disease in this age group may be underestimated due to the lower healthcare seeking behaviors observed in this age group in Africa (Emukule et al., 2015). Mmbaga et al. (2012) emphasized the need to shift from hospital-based surveillance to population-based surveillance when studying the elderly in Africa.

Conclusions

Although there is a limited amount of knowledge surrounding the epidemiology, burden of disease, and seasonality of influenza in Africa, increased influenza activity has been shown surrounding Uganda's colder months and rainy seasons. Trends in influenza activity differed surrounding the 2009 H1N1 pandemic between the Central and Northwest regions. This difference can be explained by the flow of travel into and throughout Uganda. Further analysis found that people were more likely to receive an influenza-positive diagnosis from a hospital rather than a health clinic. The majority of influenza-positive samples (87.7%) were collected in the Central region limiting the generalizability of this analysis.

Influenza has been shown to be endemic in tropical climates like Uganda and the findings from this study support such ideas. At least one influenza-positive sample was collected every month following June 2009 till the end of the study period. Data showed how influenza reporting improved throughout the surveillance period and future improvements in surveillance may further reveal influenza to be endemic within the Ugandan population.

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Tables and Figures

Table 1. Frequencies and percentages of influenza outcomes by region and year

Region	Influenza n (%)	Pos (%)	Neg (%)	2007 Pos (%)	Neg (%)	%	2008 *1 Pos (%)	Neg (%)	%	2009 *123 Pos (%)	Neg (%)	%	2010 *2 Pos (%)	Neg (%)	%
Central	3223 (81.7)	350 (87.7)	2873 (81.0)	62 (100)	429 (100)	100	121 (87.7)	551 (83.0)	83.8	57 (77.0)	557 (71.3)	71.8	110 (88.0)	1336 (80.0)	80.5
Northwest	693 (17.6)	48 (12.0)	645 (18.2)	n/a	n/a	n/a	17 (12.3)	112 (16.9)	16.1	17 (23.0)	224 (28.7)	28.2	14 (11.2)	309 (18.5)	18.0
Western	28 (0.7)	1 (0.25)	27 (0.76)	n/a	n/a	n/a	0	1 (00.1)	00.1	0	0	0	1 (0.8)	26 (1.5)	1.5
				62 (12.6)	429 (87.4)	100	138 (17.2)	664 (82.8)	100	74 (8.7)	781 (91.3)	100	125 (7.0)	1671 (93.0)	100
Total	3944	399 (10.1)	3545 (89.9)	491 (12.4)			802 (20.3)			855 (21.7)			1796 (45.5)		

*Missing data on self-reported Date Onset of symptoms

Table 2. Results of the Chi-Square test between *Region* and *Outcome of Influenza*

Frequency Percent	Region	Influenza Positive	Negative	Total
	Central	350 8.87%	2873 72.84%	3223 81.72%
	Northwest	48 1.22%	645 16.35%	693 17.57%
	Western	1 0.03%	27 0.68%	28 0.71%
	Total	399 10.12%	3545 89.88%	3944 100.00%
	Frequency Missing = 126			

Statistic	DF	Value	Probability
Chi-Square	2	11.0313	0.0040

Table 3. Results of the Analysis of Variances (ANOVA) between *Outcome of Influenza* and *Region*

	Source	DF	Sum of Squares	Mean Square	F value	Pr > F
Btw Grps	Model	2	1.00	0.50	5.53	0.0040
Within Grps	Error	3941	357.63	0.09		
Total	Corrected Total	3943	358.63			

Table 4. Results of the post-hoc comparison test (Tukey) between *Outcome of Influenza* and *Region*

Comparisons significant at the 0.05 level are indicated by ***				
Region Comparison	Differences Between Means	Simultaneous 95% Confidence Intervals		
Western-Northwest	0.033550	-0.102596	0.169695	
Western-Central	0.072880	-0.061174	0.206934	
Northwest-Central	0.039330	0.009757	0.068904	***

Table 5. Results of the Chi-Square test between *Healthcare* and *Outcome of Influenza*

Frequency Percent	Healthcare	Influenza		
		Positive	Negative	Total
	Hospital	294 6.96%	2890 68.37%	3184 75.33%
	Clinic	136 3.22%	907 21.46%	1043 24.67%
	Total	430 10.17%	3797 89.83%	4227 100%
	Frequency Missing = 62			

Statistic	DF	Value	Probability
Chi-Square	1	12.4519	0.0004

Table 6. Odds Ratios after adjusting for *Region*, *Healthcare*, and *Sex* between all three regions and between the Central and Northwest regions

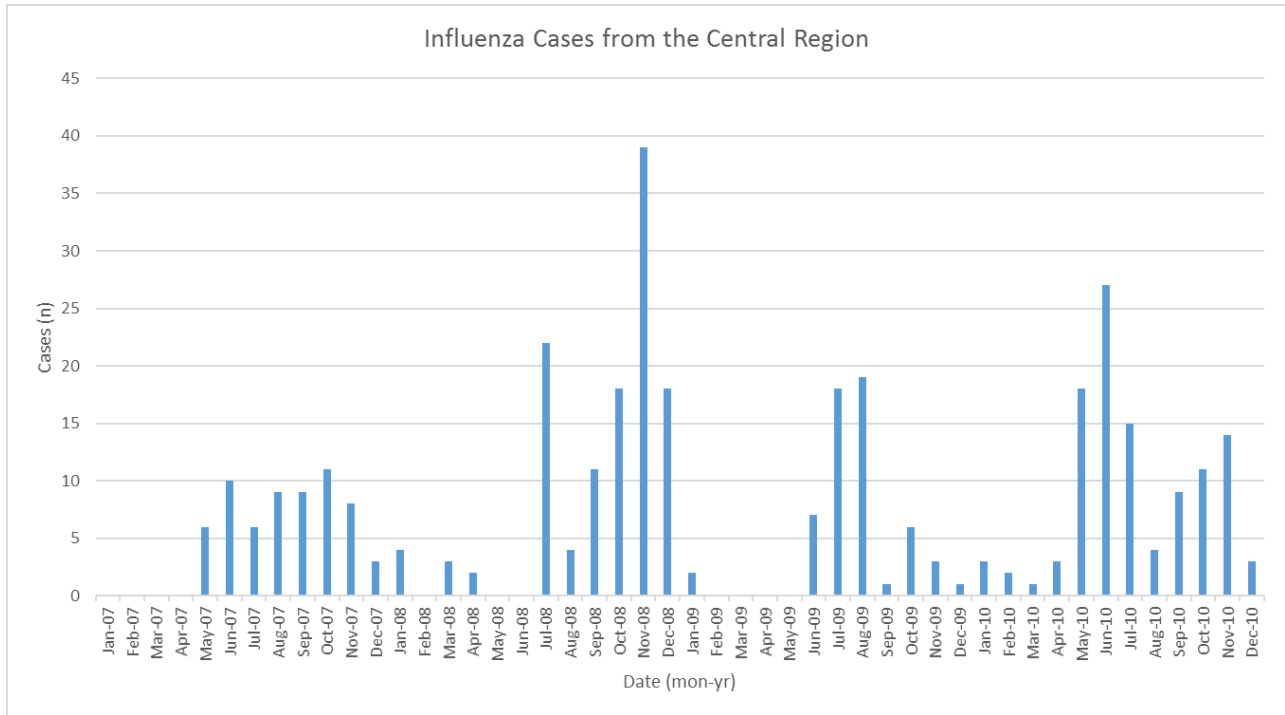| Comparisons significant at the 0.05 level are indicated by ***			
Variable	OR (95% CI) *all three regions	OR (95% CI) *Central vs Northwest regions	
Region	0.686 (0.513, 0.916)	0.706 (0.520, 0.958)	***
Healthcare	1.369 (1.095, 1.711)	1.385 (1.106, 1.735)	***
Sex	0.826 (0.676, 1.009)	0.821 (0.672, 1.004)	

Figure 1. Graph depicting the number of influenza cases collected from the Central region of Uganda (2007-2010).
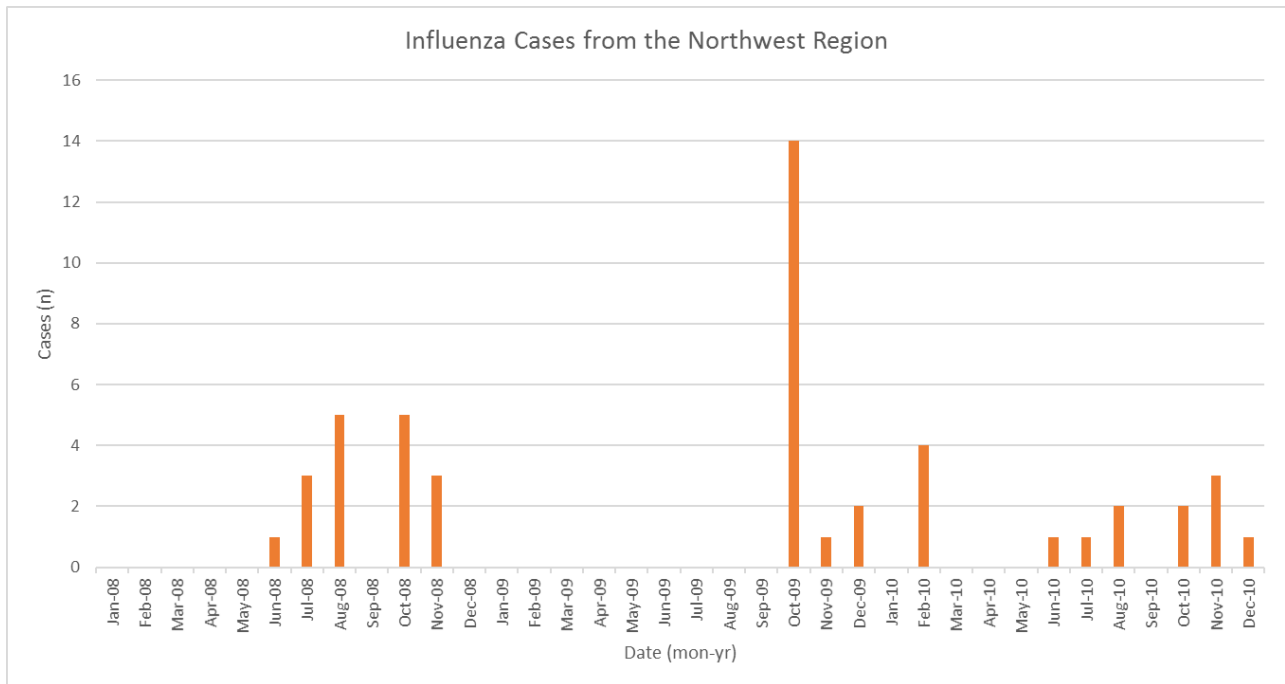

Figure 2. Graph depicting the number of influenza cases collected from the Northwest region of Uganda (2008-2010).
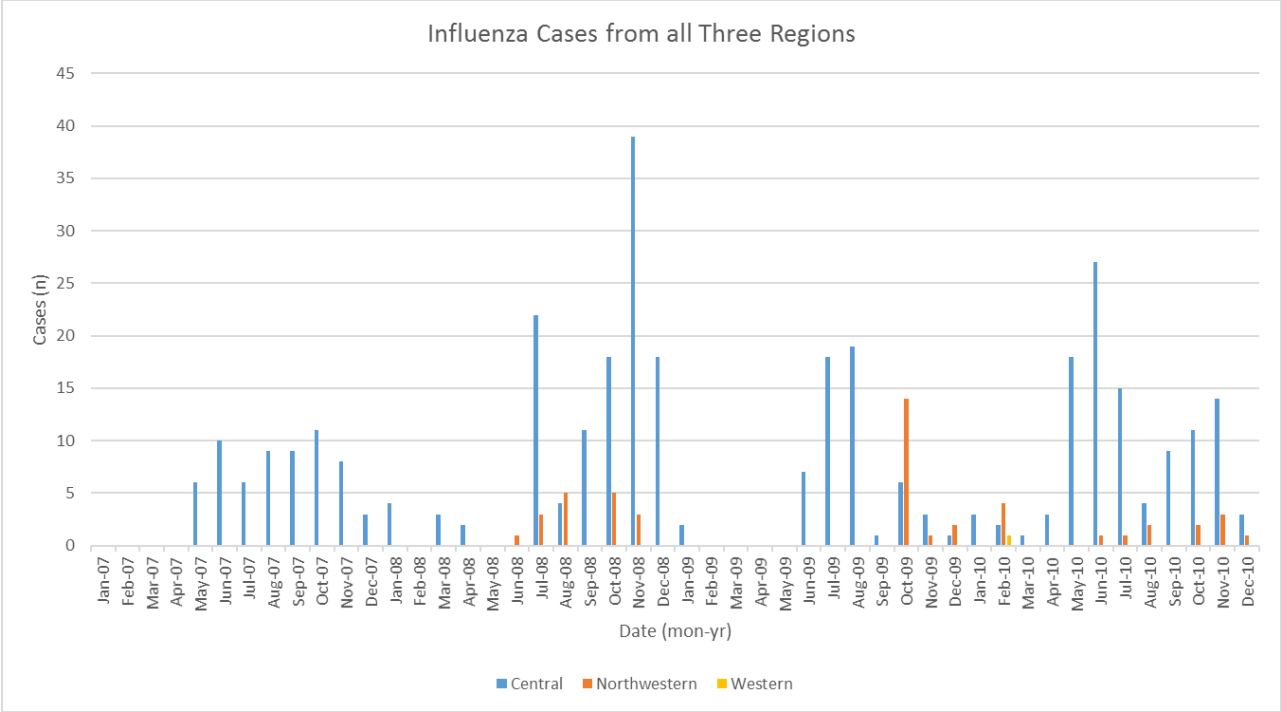
Figure 3. Graph depicting the number of influenza cases collected from all three regions of Uganda (2007-2010).