The epidemiological and economic burden of influenza in Kenya: implications for public health action

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Chapter 1: General Introduction

1.1 Influenza in Africa

In 2013, there were 160 million estimated cases of acute lower respiratory tract infections, including influenza-like illness, which occurred globally (1), resulting in 2.7 million deaths (2). It is estimated that a majority of these deaths, up to 90%, occur in the developing world (3-5). In Africa and Asia, acute lower respiratory tract infections are two to ten times more common and have three to seven-fold worse outcomes than in the industrialized world. Indeed they are the leading cause of death in children (6).

In Sub-Saharan Africa (SSA), data and surveillance for influenza has been limited due to a combination of factors that include limited public health infrastructure and resources, and other competing health priorities such as human immunodeficiency virus (HIV), tuberculosis (TB), and malaria (7-9). In response to the threat of avian influenza A(H5N1) that occurred in Asia in 2003, and eventually reached three African countries (Djibouti, Egypt, and Nigeria) (10), several African countries in partnership with international institutions and governments invested in the development of epidemiologic and laboratory influenza surveillance (9, 11).

As a result of the establishment of these surveillance platforms, several African countries were able to detect and monitor influenza A(H1N1)pdm09 (11). However, with the exception South Africa and Madagascar which routinely reported influenza activity to the World Health Organization (WHO) with data that suggested a strong seasonality as of 2009, data from most of the SSA countries remains inadequate to inform influenza public health policies (8). This is largely because data on the burden of influenza have not been documented. This notwithstanding, the limited published data from these countries has suggested a high burden of influenza, especially among young children <5 years (4, 11, 12), and persons with chronic medical conditions such as HIV/AIDS and TB (12-15).

Other than influenza, data from the surveillance and research platforms has been used to characterize the epidemiology of respiratory syncytial virus (RSV) and other respiratory pathogens. RSV is an important viral cause of pneumonia and bronchiolitis, and available data from SSA shows a substantial morbidity and mortality burden associated with RSV among young children <5 years (5, 12, 16), and among those who are immunocompromised (12, 13, 17).

1.2 Influenza in Kenya

1.2.1 Kenya

Kenya is a country that is situated in East Africa with a territory that lies on the equator between 5°N and 5°S covering an area of 581,309 square kilometers (18) (Figure 1.1). As of 2014, Kenya had an estimated population of 45 million inhabitants with half of the population aged below

nineteen years [median age of 19 years; 15% of the total population comprising of young children aged <5 years; and 3% comprising of elderly persons aged ≥65 years] (19, 20).

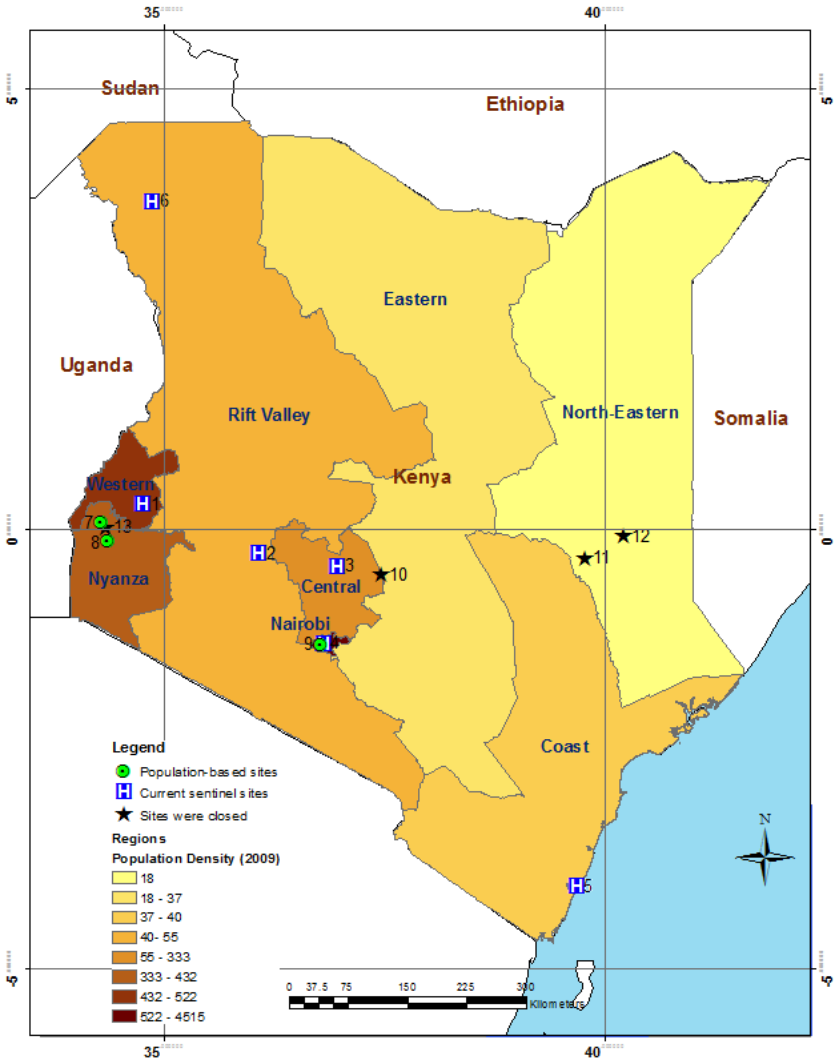

Figure 1.1: Map of Kenya showing the location of influenza surveillance sites. These are: 1) Kakamega County Referral Hospital (CRH); 2) Nakuru CRH; 3) Nyeri CRH; 4) Kenyatta NH; 5) Mombasa CRH; 6) Kakuma refugee camp; 7) Siaya CRH; 8) St. Elizabeth Hospital, Lwak; 9) Tabitha Clinic, Kibera; 10) Embu CRH; 11) Garissa CRH; 12) Dadaab refugee camp; 13) Ting'wang'i HC

There is a considerable climate variability within Kenya. The coastal tropical region is characterized by hot and humid weather year round and records average monthly temperatures as high as 29°C with an average annual rainfall of over 1,000 mm. The northern and northeastern parts of Kenya have semi-arid and desert-like conditions and experience sunny and dry weather most of the year. The climate is cooler in the areas around the capital city (Nairobi) and the central parts of Kenya, which has a relatively higher altitude, and temperatures may drop as low as 7°C during the July-August cold season. The Western parts of the country, in the close proximity to Lake Victoria experience some of the highest rainfalls levels in the Country (1250 –1700 mm annually). Overall,

the country experiences its long rains from March to May and short rains in October and November (21, 22).

Administratively, Kenya has two tiers of government as of 2013; the national government, and county governments (comprising of forty seven devolved units with semi-autonomous functions). Health, which is one of the devolved functions and currently managed by the county governments, has three major sources of financing; government (national and county) contributing 33.5%, individuals paying 39.8% out-of-pocket, and the rest 26.7% financing from donors and other private entities (23). Overall, 48% of the health facilities [hospitals (58%); health centers/nursing homes (54%); and dispensaries/clinics (46%)] in Kenya are run by the government (24). Children under five years who seek care at public health facilities are exempted from paying medical fees (25, 26).

As of 2010, Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) (accounting for 18% of the deaths), Lower respiratory infections (11%), and malaria (10%), were considered the top causes of premature death in Kenya (27). Kenya is among the countries with high prevalence of HIV in SSA. A recent population-based survey conducted in Kenya showed that the HIV prevalence was 5.6% among persons aged 15-64 years old (28, 29), and 0.9% among children aged 18 months to 14 years old (30). Nyanza province, in the Western part of Kenya, had the highest HIV prevalence of 15.1% among persons aged 15-64 years. Malaria is reported to account for 34% of the outpatient visits in Kenya (31), with a national prevalence of 8% among children aged 6 moths to 14 years in 2015. The lake endemic zone of western Kenya has the highest prevalence of malaria overall (27%), whereas the prevalence in the low risk areas is as low as <1% (32).

1.2.2 Influenza surveillance in Kenya

In Kenya, lower respiratory infections are the second largest cause of death in the general population after HIV/AIDS (2), and account for 19% of all deaths among children <5 years in 2013 (33). A large fraction of respiratory tract infections are associated with viruses, quite notably influenza A and B, and RSV (34). Whereas seasonal influenza has long been recognized as a cause of morbidity and mortality in countries with temperate climates, recent studies have shown that influenza causes a significant burden of disease in countries in the tropics as well (35, 36).

The Kenyan Ministry of Health (KMoH), with the technical support from the United States (US) Centers for Disease Control and Prevention (CDC), established a national sentinel surveillance system for influenza in 2006 (Figure 1.1). These sentinel surveillance sites are spread across the country, and were initially setup to cover each of the eight provinces in the country (now referred to as “regions” as of 2013 when a new constitution was implemented in Kenya). The objectives of the surveillance system was i) to identify circulating influenza strains, ii) to understand the epidemiology and burden of influenza in Kenya, and iii) to serve as a component of an early warning system for pandemic influenza (37). Two of these surveillance sites were setup at the two refugee

camps in Kenya (one in each of the refugee sites); Kakuma refugee camp located in the northwestern Kenya (predominantly hosting Somali and Sudanese refugees); and Dadaab which is located in the east (predominantly hosting Somali refugees) (38).

Besides conducting surveillance for the objectives listed above, three other surveillance sites were setup within defined population catchment areas (elsewhere referred to as population-based sites). This has provided an important platform for disease burden estimation for influenza and other respiratory pathogens, including RSV. The three sites are: Tabitha Clinic, an outpatient facility in Kibera (an informal settlement in Nairobi with a study population of 33,881 and covering an area of 0.38 km^2) (39); and Lwak Mission hospital, and Siaya County hospitals, both located in rural western Kenya where the Kenya Medical Research Institute (KEMRI) and CDC implement a heath demographic surveillance system covering a population of approximately 220,000 (39, 40). Using the same case definitions as for influenza surveillance, specimens collected for influenza testing at these three sites (Kibera, Lwak and Siaya) have also previously been tested for RSV and other respiratory pathogens including adenovirus, parainfluenza viruses 1, 2, and 3, human metapneumovirus, and rhino/enterovirus.

1.2.3 Transmission and clinical presentation of influenza in Kenya

Influenza is mainly transmitted from person to person by droplet spread containing up to 105 virus particles/ml (41), and is largely thought to be transmitted by direct or indirect contact with respiratory secretions in the tropics (42). The incubation period is 1-4 days (average: 2 days), and people could be infectious even before the onset of symptoms (43). Influenza infection is typically characterized by a sudden onset of fever, headache, cough, rhinorrhea, sore throat, myalgia, or fatigue (41, 44). Usually, influenza is self-limiting and could last for three to five days (41). However, influenza could also result in complications, which are more frequent in the elderly and persons with chronic illnesses such as TB, HIV/AIDS, or cardiac disease (12, 13, 15, 45). Some patients may develop a primary influenza viral pneumonia, which could result in death. But more commonly, influenza infection could result in secondary bacterial pneumonia which may occur up to two weeks after the acute viral infection (46, 47).

In Kenya, the WHO recommended case definition for influenza-like illness (ILI) surveillance was used; axillary temperature ≥38°C and cough or sore throat in an outpatient of any age (37). A modified version of the WHO's Integrated Management of Childhood Illness (IMCI) definition for pneumonia was used for children aged <5 years; requiring hospitalization and the presence of cough or difficulty breathing plus one or more of the following danger signs: chest in-drawing, stridor, unable to breastfeed or drink, vomits everything, convulsions, lethargy, or unconsciousness. Among persons aged ≥5 years, the case definition used required hospitalization with an axillary temperature ≥38°C and cough, difficulty breathing or shortness of breath (37). A recent study in Kenya showed that fever and convulsions were significantly associated with increased odds of laboratory-confirmed influenza among children <5 years who were hospitalized with SARI, while

headache was associated with increased odds of laboratory-confirmed influenza among persons ≥5 years (37). Malaria is a common comorbidity among patients presenting with ILI or SARI who are sampled for influenza testing (48), especially in the malaria endemic areas of western and the coastal parts of Kenya, due to the overlap of symptoms included in the case definitions for influenza surveillance with the clinical presentation of malaria (49).

1.2.4 Influenza control strategies in Kenya

Kenya has no national influenza vaccination program in place, and only recently (in 2013) developed its first national immunization policy guidelines for all vaccine-preventable diseases, which included influenza (50). In these policy guidelines, immunization for influenza, generally based on the WHO's Strategic Advisory Group of Experts (SAGE) recommendations, was recommended for young children, healthcare workers, and persons with chronic medical conditions. However, the need for more guidance and prioritization of limited vaccination resources has recently led to the formation the Kenya National Immunization Technical Advisory Group (KENITAG), with a need and preference for data from the Kenyan setting to inform policy recommendations and priority setting. In addition, following the experience of the pandemic influenza in 2009, the KMoH together with other partners developed pandemic preparedness plans which could be activated in the event another pandemic were to emerge.

1.3 Morbidity and mortality burden of influenza in Kenya

Since 2006 when surveillance for influenza was established in Kenya, there has been limited but increasing evidence documenting the burden of influenza-associated morbidity burden (51-53). Estimation of the incidence of influenza-associated hospitalizations and outpatient visits has been made possible using surveillance platforms with well-defined catchment populations, although mostly limited to a few geographical locations in the country; namely Western Kenya, Nairobi, and Coastal Kenya. However, there are no existing estimates of the burden of influenza-associated mortality from Kenya.

As in most SSA countries, there is an absence of systematically collected robust vital statistics data in Kenya. This is in part because a large fraction of persons who die from respiratory illness may not seek care before death (54), and hence are not captured in health facility-based surveillance systems. Moreover, certain age groups such as the elderly may be particularly underrepresented in health-facility based surveillance (55, 56). Many influenza-associated hospitalizations and deaths also occur weeks after a person's initial infection, either because the person may develop a secondary bacterial co-infection or because influenza can aggravate an existing chronic illness (e.g. cardiovascular diseases) (57). Thus, many people that are hospitalized

or die from influenza-associated complications may seek medical care later in their illness when influenza is not suspected, or can no longer be detected from respiratory specimens. Studies that model excess mortality or hospitalizations during periods of known circulation of influenza viruses would therefore be useful in evaluating the population-based burden of infections caused by these viruses.

1.4 Risk factors for influenza infection and/or severe influenza in Kenya

1.4.1 The impact of HIV/AIDS and TB on influenza disease burden in Kenya

Studies conducted outside of tropical Africa and elsewhere have shown persons living with HIV/AIDS to be at an elevated risk of infection with the influenza virus (17, 58). Influenza virus infections could also lead to the worsening of pre-existing medical conditions such as HIV/AIDS, resulting in longer periods of hospitalization and death (12, 59). Additionally, it is believed that persons living with HIV/AIDS who are infected with the influenza virus could shed the virus for longer periods of time thereby facilitating transmission in the household (60). Studies conducted in South Africa had also previously shown a high mortality burden due to influenza among persons with HIV/AIDS and/or TB (12, 15, 61).

1.4.2 Seasonality and meteorological factors associated with influenza activity in Kenya

In the temperate regions, influenza epidemics exhibit clear seasonality with peaks during winter months (62, 63). In these regions lower temperature, lower solar radiation and lower specific humidity were shown to be significantly associated with increased influenza activity. This allows for a precise timing of influenza vaccination campaigns to precede periods of peak circulation. In contrast, the seasonal characteristics of influenza are more diverse in tropical and subtropical regions which are characterized by semi-annual epidemics or year-round influenza activity, often without well-defined influenza seasons (64-68).

Whereas influenza viruses have been shown to circulate for most of the year in Kenya (37), a clear description on the weather patterns and how they influence influenza circulation could help inform the mechanism of future vaccination campaigns, and highlight seasons when added diagnostic, treatment efforts or infection control mechanisms to reduce the burden of influenza might be put in place.

1.5 The need for data on Economic burden of influenza in Kenya

Other than the health impact caused by influenza virus infection, influenza illness has been shown to exert a considerable economic burden, although most of the data available come from

temperate and resource rich countries (69-72), and none from Africa. Beyond data on the absolute burden of influenza, policy-makers require information on the cost of illness to evaluate the cost-effectiveness of potential interventions. Few data can influence a policy decision to use a vaccine more than the cost of an illness to the population and the possibility of an intervention to reduce that cost.

1.6 Rationale for this thesis

The morbidity burden estimates for influenza-associated disease in Kenya are limited, and only available for a few geographical locations in the country. There also remain only cursory data on the disease burden associated with influenza-associated mortality in Africa, with none available from Kenya. Although influenza has been shown to circulate throughout the year in Kenya, the timing and meteorological determinants of increased influenza circulation are not described. Additionally, the role of chronic medical conditions such as HIV/AIDS on disease burden and transmission of influenza are not described; and data on the economic impact of the respiratory tract infections associated with influenza in Kenya do not exist.

Estimation and synthesis of these data will not only help to quantify the magnitude of the disease burden and describe the timing of influenza activity in Kenyan populations, but also will provide a basis for quantifying its economic impact, and identifying and prioritizing the segments of the population which are in need of the limited vaccination resources. These data could also be used by other tropical countries in Africa with similar cultural and geographical contexts to inform influenza prevention and control policies.

1.7 Research questions

This thesis addresses the following research questions:

i) What is the morbidity and mortality burden of influenza-associated disease in Kenya, and which segments of the population are most affected?
ii) What are the risk factors for influenza infection and/or severe influenza in Kenya?
iii) What is the cost and overall economic burden of influenza-associated disease in Kenya?

1.8 Thesis outline

The research questions listed above were addressed through several studies that were conducted in Kenya and presented in the chapters described below.

1.8.1 Morbidity and mortality burden of influenza in Kenya

In chapter 2, we review and summarize published data describing the disease burden associated with influenza in Kenya. We also discuss the various disease burden estimation methods used and provide suggestions for future research strategies that will help to generate additional data needed to inform influenza control strategies. In chapter 3, we estimate the age-specific burden, including rates for children aged <6 months, of medically-attended, and non-medically attended influenza and RSV using data collected from a population-based disease surveillance site in Western Kenya. In chapter 4, we use verbal autopsy data collected through a health demographic surveillance system (HDSS) in Western Kenya to estimate the overall and age-specific excess mortality rates associated with influenza virus and RSV during the period 2007 to 2013. We also estimate mortality rates associated with influenza and RSV among persons with respiratory illness (including pneumonia), HIV/AIDS and pulmonary TB related deaths.

1.8.2 Risk factors for influenza infection and/or severe influenza in Kenya

In chapter 4, we present data on the mortality burden due to influenza among persons with HIV/AIDS and PTB. In chapter 5, we present findings from a household-based study that was conducted in an informal settlement in Nairobi (Kibera) that examined i) the association between the HIV status of household members and their risk of introducing influenza to the home, and ii) whether the HIV status of index cases of influenza impacts the risk of developing secondary influenza-like illness (ILI) among their household contacts.

In chapter 6, we describe the patterns of periods of increased influenza circulation, over the period 2007-2013, for different regions (based on different "climatic" zones) and for Kenya as a whole. We also provide suggestions on the possible implications for future vaccination programs, and assess the relationship between three meteorological variables (temperature, rainfall, and specific humidity) and the onset of influenza activity.

1.8.3 Economic burden of influenza in Kenya

In chapter 7, we estimate the cost-per-episode, from a societal perspective, of laboratory-confirmed influenza-associated illness in Kenya using data collected from interviews with case-patients or their care-takers. Using the cost-per-episode, we estimate the annual economic burden of influenza-associated illness in Kenya by applying these costs to the annual national morbidity burden using previously published data on burden of influenza-associated disease.

1.8.4 General discussion

Finally, we provide an overall synthesis of the key findings from the studies presented in this thesis in a summary discussion in chapter 8. Here, we also discuss the possible implications of the findings presented in this thesis for other countries in East Africa and conclude with the recommendations for further research.

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Chapter 2: Influenza-associated Disease Burden in Kenya: A Systematic Review of Literature

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Abstract

Background: In Kenya data on the burden of influenza disease are needed to inform influenza control policies.

Methods: We conducted a systematic review of published data describing the influenza disease burden in Kenya using surveillance data collected until December 2013. We included studies with laboratory confirmation of influenza, well-defined catchment populations, case definitions used to sample patients for testing and a description of the laboratory methods used for influenza testing. Studies with or without any adjustments on the incidence rates were included.

Results: Ten studies reporting the incidence of medically-attended and non-medically attended influenza were reviewed. For all age groups, the influenza positive proportion ranged from 5-10% among hospitalized patients, and 5-27% among all medically-attended patients (a combination of in- and outpatients). The adjusted incidence rate of hospitalizations with influenza among children <5 years ranged from 2.7-4.7 per 1,000 [5.7 per 1,000 in children <6 months old], and were 7-10 times higher compared to persons aged ≥5 years. The adjusted incidence of all medically-attended influenza among children aged <5 years ranged from 13.0-58.0 per 1,000 compared to 4.3-26.0 per 1,000 among persons aged ≥5 years.

Conclusions: Our review shows an expanding set of literature on disease burden associated with influenza in Kenya, with a substantial burden in children under five years of age. Hospitalizations with influenza in these children were 2-3 times higher than reported in the United States. These findings highlight the possible value of an influenza vaccination program in Kenya, with children <5 years and pregnant women being potentially important targets.

2.1 Introduction

Human influenza infections are a major cause of morbidity and mortality worldwide (1-3). Although risk factor data from tropical climates are limited, young children (<5 years), pregnant women, the elderly, and persons with underlying medical conditions have been shown to be at increased risk of severe disease (1, 4). A recent study estimated that there were 20 million cases of influenza associated with pneumonia; 1 million cases of influenza associated with severe pneumonia; and 28000–111500 deaths associated with influenza among children aged <5 years globally in 2008, with 99% of these deaths occurring in the developing world (5). A summary of existing direct estimates of influenza disease burden in tropical and developing countries is needed to validate global modeling efforts that suggest a disproportionate burden in these countries.

In Kenya, influenza surveillance was established partly in response to the global emerging threat of avian influenza A(H5N1) (6, 7). As is the case with other tropical and sub-tropical countries, influenza viruses circulate in Kenya for most of the year (7-9) and morbidity (hospitalization and outpatient) burden of influenza have only recently been described (10-18).

An improved understanding of disease burden in Kenya relating to morbidity, mortality, and economic losses is needed to support decisions involving the allocation of limited resources toward influenza control programs. The Kenyan Ministry of Health (KMoH) has released its first ever influenza vaccination policy (19) and this has necessitated the publication of an overview of the burden of influenza in Kenya to inform initial vaccination pilot activities.

In this article, we review existing data on the influenza disease burden in Kenya using data collected until December 2013. We summarize published data describing the health burden of human influenza collected through population-based influenza surveillance systems in Kenya. We also discuss the various disease burden estimation methods used and provide suggestions for future research strategies that will help to generate additional data needed to inform influenza control strategies.

2.2 Methods

2.2.1 Search strategy and selection criteria

Our objective is to provide a comprehensive overview of the disease burden of influenza in Kenya. We carried out a literature review with specific search terms; "Kenya" and each of the following words "Influenza", "Respiratory", "Pneumonia", "Severe Acute Respiratory Illness", and "Influenza-like Illness". We searched PubMed and EMBASE (Ovid) for studies – with no language restrictions - that contained original data and were conducted until December 2013. The search was last conducted on March 23, 2015. We created a master list of the search results from these two search databases with two variables; author names and study title. We then removed duplicates. Titles from these search results were reviewed for the presence of any of the following key words; “Kenya”, “Influenza”, “respiratory”, “pneumonia”, “influenza-like illness”, “acute lower respiratory infection”, “acute upper respiratory infection”, “mortality”, “deaths”, “hospitalization”, “hospital

admission", and "outpatient". Abstracts of articles that contained at least one of these search words were then reviewed by one researcher (GOE) and included if they contained information on disease burden of influenza in Kenya.

Only studies with original data collected before December 2013 were included. We considered studies for inclusion: (i) if they reported incidence rates of hospitalization and/or outpatient visits associated with influenza-like illness (ILI), acute respiratory illness (ARI), acute lower respiratory illness (ALRI), severe respiratory illness (SARI), and severe or very severe pneumonia using laboratory confirmed influenza cases ; (ii) if they had well-defined catchment populations or estimations of the population-at-risk [using any of population-based disease surveillance systems, health demographic surveillance systems (HDSS), national population census data, or population registration records]; (iii) if they provided the case definition used to sample patients for testing; and (iv) if they provided a description of the laboratory testing methods used. Studies that presented adjusted or unadjusted (crude) incidence rates were included in the review (see Appendix File 2.1, for a summary of the formulae used for the adjustments). All reported rate adjustments are indicated for each study. Additionally, we scanned the reference lists and titles of articles selected for review using the criteria defined above.

A flow chart with details of the process followed in selecting the articles that were reviewed, and the number of articles included –and excluded from this review is provided in Figure. 2.1.

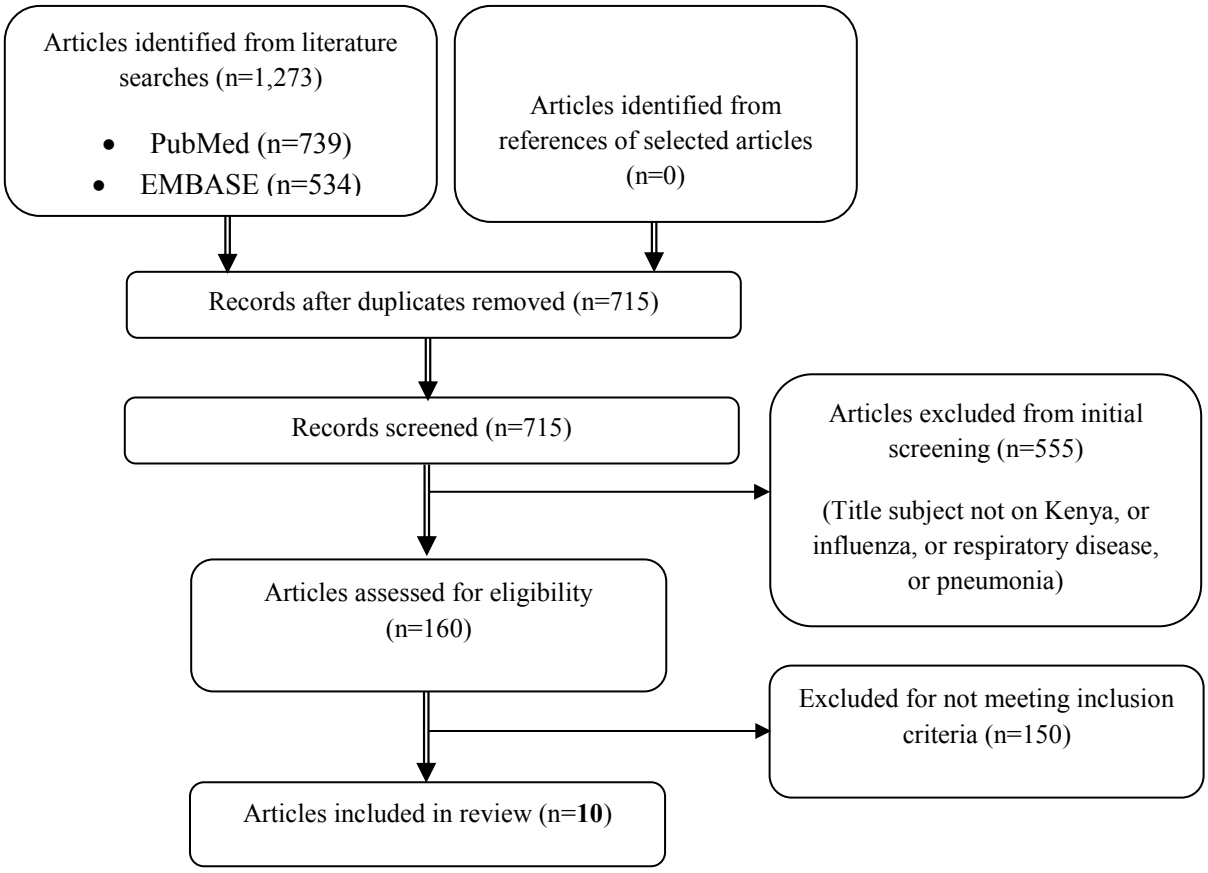

Figure. 2.1: Overview of the different phases of literature selection. The inclusion criteria was: Studies that reported incidence rates of influenza-associated illness; with well-defined catchment populations; that provided the case definition used for testing influenza; and that provided a description of the laboratory methods used for testing influenza.

2.2.2 Data extraction, analysis and reporting

Data extraction was performed by one researcher (GOE) using a template that collected details on study characteristics [title, author(s), publication year, place of study, study participants age group, syndromes used for case identification, and adjustment factors used for calculating incidence rates]. The adjustments applied to the rates were limited to one or more of the following: (i) patients who met the swabbing criteria but were not tested for influenza; (ii) cases in the community who met the specific case definition but did not seek healthcare at the study hospital/clinic; and (iii) asymptomatic detection of influenza using controls to determine illness attributable to influenza. In this review, we reported both adjusted and unadjusted influenza burden disease rates, but our primary measure was the adjusted rates as these were more accurate estimates of the disease burden.

The outcome measures that we considered were incidence of: (i) hospitalizations with influenza; (ii) medically-attended influenza (outpatient and inpatient combined); and (iii) non-medically attended influenza. We also, as a secondary measure, reported on the proportion of those who tested positive for influenza if data on incidence of influenza illness were reported. Other than the conditions defined in the inclusion criteria, no further quality assessments were applied to the reviewed articles. All incidence rates were reported per 1,000 persons or person-years. Adjusted rates reported in our paper included at least an adjustment for patients who met the swabbing criteria but were not tested, which was the most commonly applied adjustment in the studies that we reviewed.

Data from the articles reviewed were summarized as ranges (minimum - maximum), where two or more studies were involved, and presented in tables by the following domains: (i) proportions testing positive for influenza; (ii) hospitalizations with influenza; (iii) medically-attended influenza; and (iv) non-medically attended influenza.

2.3 Results

2.3.1 Search results and description of methods used

There were a total of 1,273 search records returned, including duplicates (PubMed=739; and EMBASE=534) (Figure. 2.1). After removing duplicates, there were 715 unique articles that were returned from the search and among these were 555 (78%) were on subjects not related to influenza or respiratory illness and were excluded in the first round of screening. Of the remaining 160 articles, there were 51 articles on an influenza related subject; 67 on pneumonia, and 42 on a broader respiratory subject other than influenza and pneumonia. Of these 160 articles, 10 met the inclusion criteria for this review.

Figure. 2.2 shows the location of the study sites that generated the data that were used in the analysis for articles that we reviewed. Eight of the 10 articles reviewed were based on surveillance data collected by the Kenya Medical Research Institute (KEMRI) and the Centers for Disease Control

and Prevention (CDC) (10-14, 17, 18, 20). The remaining two articles were based on data collected by the KEMRI and Wellcome Trust Research Program (15, 16). Of the ten articles reviewed, one was published in 2010 (15), five in 2012 (11-13, 16, 17), two in 2013 (10, 14), one in 2014 (18) and one in 2015 (20). Case definitions used in two of these articles included data on severe or very severe pneumonia (15, 16); six included data on severe acute respiratory illness (SARI) or acute lower respiratory illness (ALRI) (10, 11, 14, 17, 18, 20); two included data on influenza-like illness (ILI) (11, 18); and two included data on acute respiratory illness (ARI) (12, 13).

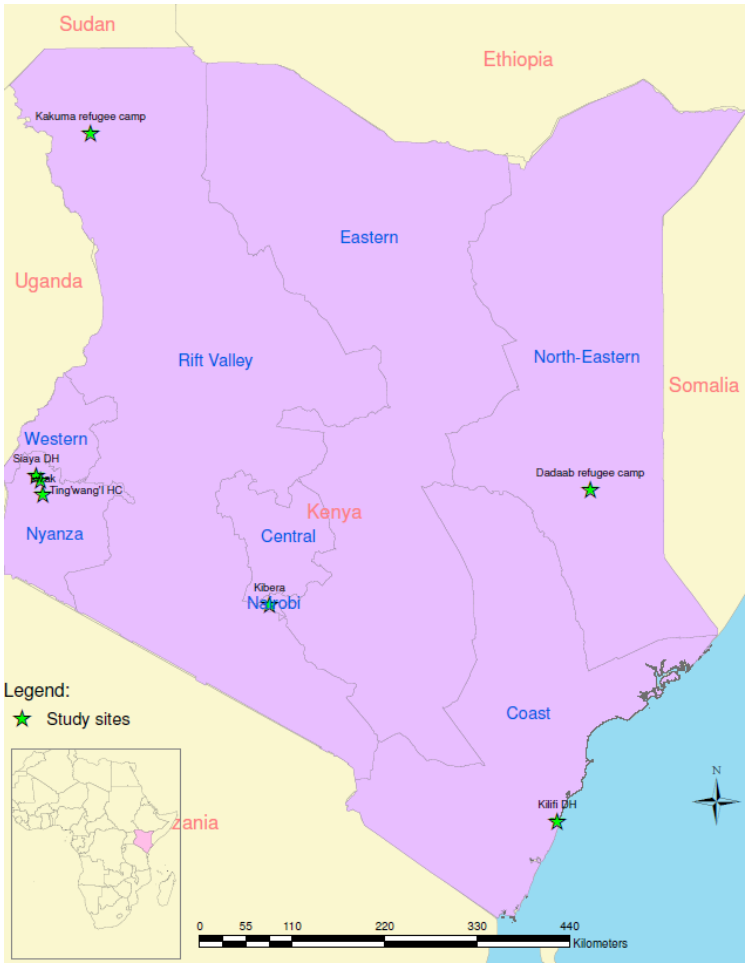

Figure. 2.2: Map of Kenya showing the study sites which generated data that was used in the reviewed papers

The case definitions for the respiratory syndromes used in identifying the cases to be tested for influenza varied (Appendix Table 2.1). Six of the articles reviewed used mid-year population data from well-defined catchment areas as denominators, either from a HDSS, refugee camp records, or national census data for estimation of incidence while the rest used person-time years of follow-up calculated from a population-based surveillance system. All ten articles that reported influenza A and/or B testing, used reverse transcriptase polymerase chain reaction (RT-PCR) testing methods. The data reported in all the papers reviewed were collected year-round, and all (except one (15)) of

the papers had multiple years of data included. All – except one (15) - of the articles included data collected during the 2009 pandemic period.

Most (9/10) of the articles reported data on the proportions of patients who tested positive for influenza (Appendix Table 2.2). Six of the nine articles reported rates of hospitalization with influenza (Table 2.1), four reported rates of medically-attended influenza (both in- and outpatients) (Table 2.2), and two reported incidence of non-medically attended SARI or ILI (10, 18) (Table 2.3). None of the studies reviewed had data on influenza mortality in Kenya.

2.3.2 Proportions testing positive for influenza

The proportions of those who tested positive for influenza A and/or B varied among the studies included (Appendix Table 2.2). These ranged from 4.9% to 26.7% for all medically-attended patients [4.9% to 13.7% among children <5 years; 14.0% to 20.5% among persons ≥5 years; and 9.8% to 26.7% in studies that reported proportions among patients of all ages]. Among hospitalized patients who were tested, the proportion of those who tested positive for influenza A and/or B ranged from 5% to 10%.

2.3.3 Incidence rate of hospitalization with influenza

Incidence rates of hospitalization with influenza varied among the studies, which were implemented during different years, and used varying case definitions, and adjustments factors (Table 2.1 and Appendix Table 2.3). There were six studies that reported incidence rates of hospitalization with influenza. Two studies conducted among children with severe or very severe pneumonia reported similar incidence rates among children <5 years [0.8 cases per 1,000 in the first study, and 0.6 cases per 1,000 (95% CI 0.5-0.7) in the second study] (15, 16). No adjustments for people with pneumonia who were not tested were reported in these two studies. Unadjusted rates of influenza among hospitalized children in the age group <5 years were also reported in a study conducted in two refugee sites. These unadjusted rates ranged 4.2-5.6 cases per 1,000 for influenza A viruses and 1.1- 1.4 for influenza B viruses.

Adjusted incidence rates of hospitalization with influenza among children of the age group of <5 years who presented with SARI ranged from 2.7-4.7 per 1,000 (10, 18). Adjusted incidence rates of hospitalization with influenza among persons aged ≥5 years who presented with SARI ranged from 0.2-0.4 per 1,000 among persons aged ≥5 years, and were lower compared to those of children in the age group of <5 years. In Western Kenya there was a high incidence rate of hospitalization with influenza among children <6 months [5.7(95% CI 2.4-13.8) per 1,000] (18).

2.3.4 Incidence rate of medically-attended influenza

Over the study period covered in our review, there were three publications that reported broader medically-attended (combining in- and outpatients) influenza incidence rates. Two of the publications were based on medically-attended ALRI (11, 14); and another on medically-attended ARI (13). Two studies reported medically-attended influenza incidence rates only for outpatients (18, 20). The adjusted incidence rates of medically-attended influenza ranged from 21.8-58.0 per

1,000 child-years for children in the age group of <5 and 4.3-26.0 for persons aged ≥5 years (Table 2.2 and Appendix Table 2.4).

A study that was conducted in a peri-urban informal settlement in Nairobi (Kibera) and a rural site in Western Kenya (Lwak) among patients who sought care for ALRI as inpatients and/or outpatients, reported higher adjusted incidence rates for influenza among children <5 years in the rural site [40.5 (95% CI 31.2-52.6)] compared to the urban site [22.0 (95% CI 17.7-26.6)]. However, similar results were reported among persons ≥5 years [15.8 (95% CI 14.1-17.7) vs. 12.0 (95% CI 10.3-13.3)] in the rural and urban sites respectively (11) (Appendix Table 2.4).

2.3.5 Incidence rate of non-medically attended influenza

Only two of the studies reviewed (both conducted in Western Kenya) estimated non-medically attended incidence rates of influenza (two reported non-medically attended SARI in Siaya (10, 18); and one reported non-medically attended ILI (18)). The incidence of influenza with non-medically attended severe ARI ranged from 2.9-5.1 per 1,000 among children <5 years, and 0.4-0.8 among persons aged ≥5 years. In the one study that estimated incidence of influenza among non-medically attended ILI cases, there were an estimated 30.1 cases of influenza per 1,000 (95% CI 27.3-33.3) among children <5 years and 5.4 cases per 1,000 (95% CI 4.9-6.0) among persons aged ≥5 years (18) (Table 2.3 and Appendix Table 2.5).

2.4 Discussion

We have provided a comprehensive summary of available data on disease burden of influenza in Kenya and we show that influenza is an important cause of respiratory infection-associated morbidity, especially among younger children under the age of five years. Indeed, both adjusted and unadjusted incidence rates of hospitalization with influenza (10, 17, 18), and outpatient visits (18) were higher than those that have been reported in United States and European countries during similar time periods (21-32).

We also note that the published literature on the burden of influenza in Kenya is limited but expanding. Eight of the ten papers that we reviewed were published within the last three years (2012 - 2014) – including two studies that published data on the post- pandemic A(H1N1) period. This could be attributed to the interest generated by the threat of avian and pandemic influenza.

Our review showed that there were an estimated 2.7-4.7 cases of influenza per 1,000 among children <5 years who were hospitalized with severe acute respiratory illness (SARI). These were 7-10 times higher compared to those in persons aged ≥5 years. A study that estimated disease burden among hospitalized children <6 months in Western Kenya reported that there were 5.7 cases of influenza per 1,000 (18). This is consistent with data from several other countries (22, 23, 33), and shows a considerable burden of disease in young infants for whom influenza vaccination is not recommended, and also highlights the rationale for targeting pregnant mothers for influenza vaccination (34). Whereas pregnant mothers have been shown to be at increased risk of complications associated with influenza (35), vaccinating them may not only be beneficial to them

but could also offer protection to their young infants - for whom no influenza vaccine is currently licensed - through breastfeeding and trans-placental antibody transfer (36, 37).

The incidence rates of hospitalization with influenza among children <5 years reported at the two refugee sites (Kakuma and Dadaab) – without adjustments for eligible cases who were not tested - were higher than rates reported elsewhere in Kenya. This could be due to the unique challenges experienced by the populations in refugee settings, such as population density, which could make them more vulnerable to exposure to respiratory infections (38, 39). While the incidence rates of hospitalization with influenza are similar to those reported in South Africa (40), Asia (41-46), Latin America (47), some of the reported rates were up to seven times higher than rates reported in the United States (21-26) and Europe (27, 28). The incidence rates of hospitalization with influenza children <6 months in Kenya, for example, were 2-3 times higher than rates reported in the United States (23).

The adjusted incidence of medically-attended (outpatient + inpatient) influenza among children <5 years ranged from 21.8 to 58.0, and 4.3 to 26.0 per 1,000 among persons aged ≥5 years in different studies. These rates were similar to rates reported in Asia (48), but up to 2-4 times higher than annual estimates reported in Europe (29-31), and up to 2-8 times higher than rates reported in the United States (32).

The incidence of non-medically attended severe ARI associated with influenza suggested a burden of disease that was similar to the medically-attended burden. As reported in the health utilization survey conducted in Western Kenya, 52% of children <5 years and 66% of persons ≥5 years who reported to have had pneumonia did not seek care at a hospital (49). The similarity between the medically-attended and non-medically attended incidence not only underscores the fact that there is a considerable burden of non-medically attended influenza, but also highlights the low levels of health-care seeking for respiratory illness in Kenya (49). These findings also suggest that surveillance limited to the health care setting will not capture the entire burden of influenza severe respiratory illness in contexts such as Kenya.

The studies reviewed included various adjustments for patients who met the case definitions but were not tested for influenza (10-12, 18); for those who sought health-care at a facility other than the one used for estimating the incidence rates (13, 14); and for asymptomatic detection of influenza among controls (13, 14). The first two adjustments would serve to increase the crude incidence to account for persons who met the case definition and were not tested for influenza or those who did not seek care; while the latter would drive the rate downwards by only accounting for the cases for which the virus was the likely cause disease. Other than the case definition for ILI developed by the World Health Organization (WHO) which was more commonly applied across the different studies (50), the case definitions used for SARI, ALRI and ARI also substantially varied across the studies reviewed. In order to facilitate disease burden comparisons over time, it would have been helpful if researchers also presented their data using standard case definitions as recommended by WHO (51); and unadjusted rates in addition to those where adjustments were applied. These standardizations, in addition to presenting data in age groups that may be aggregated to WHO recommended age categories [<2, 2-4, 5-14, 15-49, 50-64, and ≥65 years] (51) would help to facilitate comparisons across studies and across countries (52).

All the articles reviewed utilized data generated from well-defined catchment areas managed by either the KEMRI and CDC, or the KEMRI and Wellcome Trust research collaboration; indeed a majority of the articles reviewed included KEMRI and CDC co-authors who are also authors on this paper. Additionally, all the papers that we reviewed included in their analysis data that were collected year-round and a majority of them had multiple years of data used in estimating incidence rates. This consideration is important because – other than considering that influenza circulates in Kenya year-round (7) – it minimizes the risk of overestimating the disease burden by only sampling during epidemic periods.

Six of the ten studies reviewed utilized mid-year population denominators, derived from HDSS or National census data (12), for the estimation of incidence rates. As opposed to using denominators derived from individual follow-up (person-time) in population-based surveillance systems, denominators based on mid-year population could potentially underestimate the incidence rates as they may not accurately reflect the actual population dynamics relating to births, migrations and deaths, especially if smaller populations are involved (53). However, using either of these two denominator types to estimate incidence rates would normally yield nearly identical results for large populations. Taken in the context of the resources required to set-up and run a population-based surveillance system, denominators derived from mid-year population numbers may be useful for disease burden estimation in Kenya for the foreseeable future.

Only one study reported rates among children <6 months, and a few reported data on those aged ≥50 years (11, 12) which is in part explained by the lower health-seeking behavior among older persons in Kenya (49), and perhaps also by a diminished likelihood that older patients will report the fever required to meet the WHO SARI case definition. Understanding the disease burden, especially in the high risk groups which include pregnant women, and people with underlying medical conditions; as well as understanding the socio-economic (direct and in-direct) burden of influenza in Kenya would be helpful to public-health and influenza control programs and understanding the impact of influenza. For example a recent study conducted in Western Kenya showed a substantial burden of influenza (3-times higher) among HIV-infected adults aged ≥18 compared to their HIV-negative counterparts (13). Another study in South Africa reported 4–8 times greater incidence of acute lower respiratory tract infection (LRTI) with influenza among HIV-infected compared to HIV-uninfected persons (40).

Our study was subject to limitations. First, we may have missed some articles as we limited our review to only published data searched the PubMed and EMBASE databases. However, we believe that the likelihood of finding additional data relevant to our study in other databases is very low. Second, most of the published data summarized in our review included data from the 2009 pandemic influenza period and may have served to overestimate the seasonal influenza disease burden. Third, the reviewed papers were limited to respiratory surveillance only. For some populations (particularly young infants) presentation may be fever without respiratory symptoms. As such, the true burden among children may have been underestimated. Fourth, the clinical threshold to hospitalize in Kenya may not be comparable to US or Europe and therefore hospitalization rates should be interpreted with caution when making these comparisons. Fifth, most of the studies presented data on incidence of influenza without presenting either the age-specific denominators or age-specific numbers of cases. Taken together with the fact that there were varied case definitions and adjustments applied, this made it difficult for us to calculate meta-

analytic rates of influenza disease burden in Kenya. Lastly, while not a direct limitation of our methods, the absence of data on influenza mortality remains a gap that needs to be addressed in order to inform influenza vaccine policy.

In conclusion, our literature review provides a comprehensive summary of available data on the disease burden of influenza in Kenya over the past 8 years, and shows a substantial medically- and non-medically attended disease burden among children aged <5 years. Additional research gaps identified in the review include the lack of influenza mortality and socio-economic disease burden data. While these additional data would be very helpful to policy makers and other stakeholders to inform prevention and treatment policies, the current data in Kenya indicate an important burden of influenza in young children that might be reduced with a targeted vaccination program including children and pregnant women. However, any decision about influenza vaccination must look at its burden relative to other respiratory pathogens such as respiratory syncytial virus – when a vaccine becomes available - and even non-respiratory vaccine preventable diseases.

Table 2.1: Average annual incidence rates of hospitalization with influenza for different respiratory syndromes (per 1,000 persons or person-years) in Kenya

Author(s)	Syndrome type	Adjustment used	Study site	Age group	Incidence[a] Range[b]
Berkley et al. (2010)(15) and Onyango et al. (2012)(16)	Hospitalized Severe or very severe pneumonia	None stated	Kilifi	< 1 year	1.5-2.4
				<5 years	0.6-0.8
Ahmed et al. (2012)(17)	Hospitalized SARI	None stated	Kakuma & Dadaab refugee camp	< 1 year	10.3-12.3
				< 5 years	4.2-5.6
Fuller et al. (2013)(10) and Emukule et al. (2014)(18)	Hospitalized SARI	Healthcare seeking; those with syndrome who did not have swabs tested for influenza virus	Siaya, Western Kenya	<6 months	5.7
				<5 years	2.7-4.7
				≥5 years	0.2-0.4
				All ages	0.7-1.1
Feikin et al. (2012)(12)	Hospitalized ARI	Rates adjusted for those hospitalized with ARI who did not have swabs tested for influenza	Bondo, Western Kenya	<1 year	1.4
				<5 years	1.4
				All ages	0.6
All studies	All syndromes	With or without any adjustment	All study sites	<6 months	5.7
				<1 year	1.4-12.3
				<5 years	0.6-5.6
				≥5 years	0.2-0.4
				All ages	0.6-1.1

Abbreviations: SARI=Severe acute respiratory illness; ARI=Acute respiratory illness.
[a]Incidence reported per 1,000 persons or person-years; [b]Range is the minimum-maximum in cases where two or more studies were involved

Table 2.2: Average annual incidence rates of medically-attended influenza A and/or B (hospitalized and outpatient) per 1,000 persons or person-years in Kenya

Author(s)	Syndrome type	Adjustment used	Study site	Age group	Incidence[a] Range[b]
Katz et al. (2012)(11)	In- and outpatient ALRI	Adjusted for those with ALRI who were not tested for influenza	Kibera and Lwak	< 1 year	32.8-42.1
				<5 years	22.0-40.5
				≥5 years	12.0-15.8
				All ages	13.7-23.0
Feikin et al. (2013)(14)	In- and outpatient SARI	Adjusted for healthcare seeking by extrapolating from those with ARI[‡] at household visit who sought care at a clinic besides the study clinic and for the pathogen-attributable fraction (PAF[¥])	Lwak, Western Kenya	<5 years	58.0
Breiman et al. (2015)(20)	Outpatient SARI	Adjusted for healthcare seeking for SARI at the study clinic and for the pathogen-attributable fraction (PAF[¥]).	Kibera	<5 years	13.0
Feikin et al. (2012)(13)	In- and outpatient ARI	Adjusted for healthcare seeking by extrapolating from those with ARI[‡] at household visit who sought care at a clinic besides the study clinic and for the pathogen-attributable fraction (PAF[¥])	Lwak, Western Kenya	≥5 years	26.0
Emukule et al. (2014)(18)	Outpatient ILI	Adjusted for those with ILI who were not tested for influenza	Ting'wang'i, Western Kenya	<6 months	16.2
				<5 years	21.8
				≥5 years	4.3
				All ages	7.2
All studies	All syndromes	With any adjustment	All study sites	<6 months	16.2
				< 1 year	32.8-42.1
				<5 years	21.8-58.0
				≥5 years	4.3-26.0
				All ages	7.2-23.0

Abbreviations: SARI=Severe acute respiratory illness; ALRI=Acute lower respiratory illness; ILI=influenza-like illness; ARI=Acute respiratory illness

[a]Incidence reported per 1,000 persons or person-years; [b]Range is the minimum-maximum in cases where two or more studies were involved; [‡]ARI in home was defined as cough, difficulty breathing or chest pain and reported fever; [¥]Adjusted rates downward for asymptomatic detection of influenza in controls.

Table 2.3: Non-medically attended average annual incidence rates of Influenza reported for different respiratory syndromes (per 1,000 persons or person-years) in Kenya

Author(s)	Syndrome type	Adjustment used	Study site	Age group	Incidence[a] Range[b]
Fuller et al. (2013)(10); Emukule et al. (2014)(18)	Non-medically attended SARI	Adjusted for persons with pneumonia who did not seek care from health utilization survey (HUS)	Siaya	<6 months	6.2
				<5 years	2.9-5.1
				≥5 years	0.4-0.8
				All ages	0.9-1.4
Emukule et al. (2014)(18)	Non-medically attended ILI	Adjusted for persons with ARI who did not seek care from HUS	Ting'wang'i	<6 months	22.3
				<5 years	30.1
				≥5 years	5.4
				All ages	9.1

[a]Incidence reported per 1,000 persons or person-years; [b]Range is the minimum-maximum in cases where two or more studies were involved

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Appendix File 2.1: Summarized equations for the adjustment factors accounting for persons who were not tested for influenza, those who did not seek healthcare, and for asymptomatic detection of influenza

Equation 1. Incidence rate of influenza-associated hospitalization/outpatient visit

$$IR = \frac{Flu_{cases}}{PoY}$$

Where:

IR = Unadjusted incidence rate of influenza-associated hospitalizations/outpatient visits
Flu_{cases} = Total number of cases who tested positive for influenza
PoY= Person-time of surveillance in years/Mid-year population

Equation 2a. Adjustment for those who met the specific case definition but were not tested for influenza

$$AdjIR = \left(IR \times \frac{1}{P_{flutest}}\right)$$

Where:

$AdjIR$ = Incidence adjusted for those who were not tested for influenza
IR = Unadjusted (crude) incidence rate of influenza-associated hospitalizations/outpatient visits
$P_{flutest}$ = Proportion of hospitalized patients who met the specific case definition and were tested for influenza

Equation 2b. Adjustment for those who did not seek healthcare

$$AdjIR = \left(IR \times \frac{1}{P_{case}}\right)$$

Where:

$AdjIR$ = Incidence adjusted for those who were not tested for influenza
IR = Unadjusted (crude) incidence rate of influenza-associated hospitalizations/outpatient visits
P_{case} = Proportion of cases in the community who met the specific case definition and sought healthcare at the study hospital/clinic

Equation 2c. Adjustment for asymptomatic detection of influenza

$$AdjIR = (IR \times PAF)$$

Where:

$AdjIR$ = Incidence adjusted for those who were not tested for influenza
IR = Unadjusted (crude) incidence rate of influenza-associated hospitalizations/outpatient visits
PAF = Pathogen-attributable fraction defined as (OR-1)/OR
OR = The odds ratio of detection of influenza among cases compared to asymptomatic controls from a case-control analysis

Note: Refer to the individual published papers for further details on specific adjustments used.

Appendix Table 2.1: Case definitions use for respiratory syndromes in reviewed articles

Authors(s)	Syndrome	Case definitions used
Berkley et al. (2010)	Hospitalized Severe or very severe pneumonia	Severe pneumonia was defined as cough OR difficult breathing AND lower chest wall in-drawing and no signs of very severe pneumonia. Very severe pneumonia was defined as cough OR difficult breathing AND at least one of (hypoxia, inability to drink or breast feed, inability to sit, or impaired consciousness at admission).
Onyango et al. (2012)	Hospitalized Severe or very severe pneumonia	Severe pneumonia was defined as cough OR difficulty breathing AND lower-chest-wall in-drawing. Very severe pneumonia was defined as cough OR difficulty breathing AND one or more of (cyanosis, prostration, unconsciousness, or an oxygen saturation level <90%).
Ahmed et al. (2012)	Hospitalized SARI	For children > 1 week and < 2 months old, SARI was defined as an admission to the pediatric ward with any of the following: respiratory rate > 60 per minute, severe chest in-drawing, nasal flaring, grunting, fever ≥ 38°C, hypothermia < 35.5°C, or pulse oxygenation < 90%. For children 2 months to < 5 years of age, SARI was defined as cough or difficulty breathing and any one of the following: respiratory rate > 50/min for infants 2 months to < 1 year old or > 40/min for children 1 to < 5 years old, chest in-drawing or stridor in a calm child, unable to drink or breast feed, vomiting, convulsions, lethargic or unconscious, or pulse oxygen saturation < 90%. For older children and adults ≥ 5 years of age, SARI was defined as fever ≥ 38°C, and cough or sore throat, and shortness of breath or difficulty breathing.
Fuller et al. (2013)	Hospitalized SARI	For children <5 years as cough or difficulty breathing and any one of the following: IMCI‡ danger sign, tachypnea for age group, nasal flaring, grunting, oxygen saturation <90%, chest in-drawing, or stridor in a calm child. In patients aged ≥5 years, SARI was defined as any hospitalized case with cough, difficulty breathing, or chest pain during the previous 14 days.
Emukule et al. (2014)	Hospitalized SARI	Defined as cough or difficulty breathing or pleural chest pain within the last 14 days for persons of all ages.
Feikin et al. (2012)	Hospitalized ARI	Acute cough, difficulty in breathing or pleuritic chest pain.
Feikin et al. (2013)	In- and outpatient ALRI	For patients aged ≥5 years, ALRI was defined as cough, difficulty breathing or chest pain and either documented axillary temperature ≥38°C or oxygen saturation <90%.
Katz et al. (2012)	In- and outpatient ALRI	For in- and out-patient children <5 years ALRI was defined as cough OR difficulty breathing, AND at least one of (maternal report of IMCI‡ danger sign, lower-chest wall in-drawing, stridor, oxygen saturation <90%). For in- and out-patients aged ≥5 years, ALRI was defined as cough OR difficulty breathing OR chest pain, AND a documented axillary temperature of ≥38.0°C OR and oxygen saturation level of ≤90%.
Breiman et al. (2015)	Outpatient SARI	For in- and out-patient children <5 years SARI was defined as cough OR difficulty breathing, AND at least one of (unable to drink/breastfeed, vomits everything, convulsions, lethargic or unconscious, stridor when calm, and lower chest wall in-drawing, as well as an additional criterion of oxygen saturation <90%).
Katz et al. (2012) Emukule et al. (2014)	In- and outpatient ILI Outpatient ILI	Defined as axillary temperature ≥38°C AND cough or sore throat in an outpatient within the past 14 days for persons of all ages. Defined as axillary temperature ≥ 38°C and cough or sore throat for persons of all ages.
Feikin et al. (2012)	In- and outpatient ARI	Cough or difficulty breathing or chest pain and documented axillary temperature ≥38°C or oxygen saturation <90% or hospitalization.
Fuller et al. (2013)	Non-hospitalized SARI	Those with pneumonia who did not seek care in health utilization survey (HUS). In this HUS, pneumonia was defined as: cough or difficulty breathing for more than two days or a diagnosis of 'pneumonia' by a healthcare worker.
Emukule et al. (2014)	Non-hospitalized SARI	Those with pneumonia who did not seek care in health utilization survey (HUS). In this HUS, pneumonia was defined as: cough and difficulty in breathing for more than two days (excluding the past 14 days) within the preceding 12 months or a diagnosis of 'pneumonia' by a healthcare worker.
Emukule et al. (2014)	Non-medically attended ILI	Those with acute respiratory illness (ARI) who did not seek care in a HUS. In this HUS, ARI was defined as: cough and difficulty in breathing within the last 14 days.

‡Inability to drink or breastfeed, vomiting everything, convulsions, lethargy or unconscious

Appendix Table 2.2: Proportion testing positive for influenza A and/or B among hospitalized patients and in- and outpatients seen with different respiratory syndromes in Kenya

Author(s)	Study period	Syndrome type	Study site	Age group	Influenza positive n/N(%)
Berkley et al. (2010)	Jan to Dec, 2007	Hospitalized severe or very severe pneumonia	Kilifi	<5 years	44/779(5.8)[a]
Onyango et al. (2012)	Jan, 2007 to Dec, 2010	Hospitalized severe or very severe pneumonia.	Kilifi	<5 years	99/2,002(4.9)
Ahmed et al. (2012)	Sep, 2007 to Aug, 2010	Hospitalized SARI	Kakuma and Dadaab	<5 years	410/4,449(9.2)[a]
Emukule et al. (2014)	Aug, 2009 to Jul, 2012	Hospitalized SARI	Siaya	All ages	348/5,507(7.9)
Feikin et al. (2012)	Mar, 2007 to Feb 2010	Hospitalized ARI	Bondo	<5 years	83/1,213(6.8)
				≥5 years	121/866(14.0)
				All ages	204/2079(9.8)
Katz et al. (2012)	Mar, 2007 to Feb 2010	In- and outpatient ALRI	Kibera	All ages	319/1197(26.7)
			Lwak	All ages	359/1,641(21.9)
Feikin et al. (2013)	Mar, 2007 to Feb 2010	In- and outpatient SARI	Lwak	<5 years	27/408(6.6)[a]
Breiman et al. (2015)	Mar, 2007 to Feb 2011	Outpatient SARI	Kibera	<5 years	112/818(13.7)
Feikin et al. (2012)	Mar, 2007 to Feb 2010	In- and outpatient ARI	Lwak	≥5 years	249/1216(20.5)[a]
Emukule et al. (2014)	Aug, 2009 to Jul, 2012	Outpatient ILI	Ting'wang'i	All ages	206/1,632(13.7)

Abbreviations: SARI=Severe acute respiratory illness; ALRI=Acute lower respiratory illness; ILI=influenza-like illness; ARI=Acute respiratory illness

Appendix Table 2.3: Average annual incidence rates of influenza-associated hospitalizations for different respiratory syndromes (per 1,000 persons or person-years) in Kenya

Author(s)	Study period	Syndrome type	Adjustment used	Study site	Age group	Incidence* (95% CI)
Berkley et al. (2010)	Jan to Dec, 2007	Hospitalized Severe or very severe pneumonia	None stated.	Kilifi[¢]	< 1 year	2.40[a]
					1-<2 years	1.00[a]
					2-4 years	0.40[a]
					<5 years	0.80[a]
Onyango et al. (2012)	Jan, 2007 to Dec, 2010	Hospitalized severe or very severe pneumonia.	None stated.	Kilifi	<1 years	1.5(1.2-2.0)
					<5 years	0.6(0.5-0.7)
Ahmed et al. (2012)	Sep, 2007 to Aug, 2010	Hospitalized SARI	None stated.	Kakuma refugee camp	< 1 year	12.3(7.7-19.5)[a]
					1-4 years	4.2(2.9-6.1)[a]
					< 5 years	5.6(4.2-7.5)[a]
				Dadaab refugee camp	< 1 year	10.3(6.8-15.6)[a]
					1-4 years	2.9(2.1-4.2)[a]
					< 5 years	4.2(3.2-5.5)[a]
Fuller et al. (2013)	Aug, 2009 to Jul, 2010	Hospitalized SARI	Rates adjusted for risk factor and healthcare-seeking for SARI (See the online appendix of the published paper).	Siaya	<5 years	3.9(3.1-4.7)
					≥5 years	0.3(0.2-0.4)
				Kenya	<5 years	4.7(3.5-6.2)
					≥5 years	0.2(0.2-0.3)
					All ages	1.1(0.9-1.6)
	Aug, 2010 to Jul, 2011	Hospitalized SARI	Rates adjusted for risk factor and healthcare-seeking for SARI (See the online appendix of the published paper).	Siaya	<5 years	3.0(2.2-3.7)
					≥5 years	0.4(0.3-0.5)
				Kenya	<5 years	3.0(2.3-3.9)
					≥5 years	0.2(0.2-0.4)
					All ages	0.7(0.5-0.9)
Emukule et al. (2014)	Aug, 2009 to Jul, 2012	Hospitalized SARI	Rates adjusted for those hospitalized with SARI who did not have swabs tested for influenza virus.	Siaya	<6 months	5.7(2.4-13.8)
					6-11 months	4.7(1.8-11.9)
					12-23 months	4.5(2.3-8.6)
					2-4 years	1.4(0.7-2.8)
					<5 years	2.7(1.8-3.9)
					≥5 years	0.3(0.2-0.4)
					All ages	0.7(0.5-0.9)
Feikin et al. (2012)	Mar, 2007 to Feb 2010	Hospitalized ARI	Rates adjusted for those hospitalized with ARI who did not have swabs tested for influenza.	Bondo	<1 year	1.4(0.9-1.8)
					<5 years	1.4(1.2-1.7)
					All ages	0.6(0.5-0.6)

Abbreviations: SARI=Severe acute respiratory illness; ARI=Acute respiratory illness.

*Incidence reported per 1,000 persons or person-years; [£]SARI in the community was defined as: cough or difficulty breathing AND one of (chest wall in-drawing, vomiting everything, lethargic, convulsions, or inability to drink or breast feed); [a]Influenza A; [¢]95% CI not provided.

Appendix Table 2.4: Average annual incidence rates of medically-attended influenza A and/or B (hospitalized and outpatient) per 1,000 persons or person-years in Kenya

Author(s)	Study period	Syndrome type	Adjustment used	Study site	Age group	Incidence* (95% CI)
Katz et al. (2012)	Mar, 2007 to Feb 2010	In- and outpatient ALRI	Rates adjusted for those with ALRI at the study clinic who were not tested for influenza.	Kibera	< 1 year	32.8(21.4-50.2)
					1-<2 years	26.2(18.3-37.5)
					2-4 years	17.1(12.6-23.1)
					<5 years	22.0(17.7-26.6)
					≥5 years	12.0(10.3-13.3)
					All ages	13.7(12.2-15.2)
				Lwak	< 1 year	42.1(22.7-78.3)
					1-<2 years	43.9(26.0-74.1)
					2-4 years	40.1(28.3-56.7)
					<5 years	40.5(31.2-52.6)
					≥5 years	15.8(14.1-17.7)
					All ages	23.0(20.8-25.5)
Feikin et al. (2013)	Mar, 2007 to Feb 2010	In- and outpatient SARI	Rates were adjusted for healthcare seeking by extrapolating from those with ARI‡ at household visit who sought care at a clinic besides the study clinic and for the pathogen-attributable fraction (PAF¥).	Lwak	<5 years	58.0(38.0-78.0)
Breiman et al. (2015)	Mar, 2007 to Jul, 2011	Outpatient SARI	Adjusted for healthcare seeking for SARI at the study clinic and for the pathogen-attributable fraction (PAF¥).	Kibera	<5 years	13.0(6.0-20.0)
Feikin et al. (2012)	Mar, 2007 to Feb 2010	In- and outpatient ARI	Rates were adjusted for healthcare seeking by extrapolating from those with ARI‡ at household visit who sought care at a clinic besides the study clinic and for the pathogen-attributable fraction (PAF¥).	Lwak	≥5 years	26.0(22.8-29.2)[a]
Emukule et al. (2014)	Aug, 2009 to Jul, 2012	Outpatient ILI	Rates adjusted for those with ILI at the outpatient clinic who did not have swabs tested for influenza.	Ting'wang'i	<6 months	16.2(3.5-73.8)
					6-11 months	37.7(14.7-96.7)
					12-23 months	31.8(15.6-64.4)
					2-4 years	17.2(10.3-28.9)
					<5 years	21.8(15.1-31.6)
					≥5 years	4.3(2.8-6.4)
					All ages	7.2(5.5-9.4)

Abbreviations: SARI=Severe acute respiratory illness; ALRI=Acute lower respiratory illness; ILI=influenza-like illness; ARI=Acute respiratory illness
*Incidence reported per 1,000 persons or person-years; ‡ARI in home was defined as cough, difficulty breathing or chest pain and reported fever; ¥Adjusted rates downward for asymptomatic detection of influenza in controls; [a]Influenza A.

Appendix Table 2.5: Non-medically attended average annual incidence rates of Influenza reported for different respiratory syndromes (per 1,000 persons or person-years) in Kenya

Author(s)	Study period	Syndrome type	Adjustment used	Study site	Age group	Incidence* (95% CI)
Fuller et al. (2013)	Aug, 2009 to Jul, 2010	Non-medically attended SARI	Percent of pneumonia case hospitalized from health utilization survey (HUS).	Siaya	<5 years	4.2(2.7-7.3)
					≥5 years	0.6(0.3-1.2)
				Kenya	<5 years	5.1(3.5-8.1)
					≥5 years	0.4(0.2-0.8)
					All ages	1.4(0.9-2.4)
	Aug, 2010 to Jul, 2011	Non-medically attended SARI	Percent of pneumonia case hospitalized from HUS.	Siaya	<5 years	3.2(2.1-5.5)
					≥5 years	0.8(0.5-1.6)
				Kenya	<5 years	3.3(2.4-5.2)
					≥5 years	0.5(0.3-0.9)
					All ages	0.9(0.6-1.6)
Emukule et al. (2014)	Aug, 2009 to Jul, 2012	Non-medically attended SARI	Adjusted for persons with pneumonia who did not seek care, using the results of a 2005 HUS.	Siaya	<6 months	6.2(2.9-13.2)
					6-11 months	5.0(2.2-11.4)
					12-23 months	4.8(2.7-8.6)
					2-4 years	1.6(0.9-2.7)
					<5 years	2.9(2.1-4.0)
					≥5 years	0.5(0.4-0.7)
					All ages	1.2(0.9-1.4)
Emukule et al. (2014)	Aug, 2009 to Jul, 2012	Non-medically attended ILI	Adjusted for persons with ARI who did not seek care, using the results of a 2005 HUS.	Ting'wang'i	<6 months	22.3(15.0-33.2)
					6-11 months	52.1(40.4-67.1)
					12-23 months	43.8(36.3-53.0)
					2-4 years	23.8(20.7-27.4)
					<5 years	30.1(27.3-33.3)
					≥5 years	5.4(4.9-6.0)
					All ages	9.1(8.5-9.8)

*Incidence reported per 1,000 persons or person-year.

Chapter 3: The Burden of Influenza and RSV among inpatients and outpatients in Rural Western Kenya, 2009 -2012

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Abstract

Background: In Kenya, detailed data on the age-specific burden of influenza and RSV are essential to inform use of limited vaccination and treatment resources.

Materials and Methods: We analyzed surveillance data from August 2009 to July 2012 for hospitalized severe acute respiratory illness (SARI) and outpatient influenza-like illness (ILI) at two health facilities in western Kenya to estimate the burden of influenza and respiratory syncytial virus (RSV).

Incidence rates were estimated by dividing the number of cases with laboratory-confirmed virus infections by the mid-year population. Rates were adjusted for healthcare-seeking behavior, and to account for patients who met the SARI/ILI case definitions but were not tested.

Results: The average annual incidence of influenza-associated SARI hospitalization per 1,000 persons was 2.7 (95% CI 1.8-3.9) among children <5 years and 0.3 (95% CI 0.2-0.4) among persons ≥5 years; for RSV-associated SARI hospitalization, it was 5.2 (95% CI 4.0-6.8) among children <5 years and 0.1 (95% CI 0.0-0.2) among persons ≥5 years.

The incidence of influenza-associated medically-attended ILI per 1,000 was 24.0 (95% CI 16.6-34.7) among children <5 years and 3.8 (95% CI 2.6-5.7) among persons ≥5 years. The incidence of RSV-associated medically-attended ILI was 24.6 (95% CI 17.0-35.4) among children <5 years and 0.8 (95% CI 0.3-1.9) among persons ≥5 years.

Conclusions: Influenza and RSV both exact an important burden in children. This highlights the possible value of influenza vaccines, and future RSV vaccines, for Kenyan children.

3.1 Introduction

Acute lower respiratory tract infections account for an estimated 1.9 million deaths in children <5 years of age annually, up to 90% of which occur in the developing world (1-3). In Africa and Asia, acute lower respiratory tract infections are two to ten times more common than in the USA (4), and have three to seven-fold worse outcomes than in the industrialized world (5). A large fraction of human respiratory tract infections are associated with viruses including influenza A and B, and respiratory syncytial virus (RSV) (6). Safe and effective vaccines for influenza are available (7, 8), but very limited quantities of influenza vaccine are currently being used in Kenya, and elsewhere in Africa (9). Efforts are on-going to develop a vaccine for RSV (10). However additional and more detailed data on burden of disease may be required before these vaccines are used more widely.

While some data suggest a significant burden of hospitalized influenza in Kenya, many of the data come from persons seeking medical care during the period of the 2009 influenza A(H1N1)pdm09 pandemic with few data from either the pre- or post-pandemic periods (11-13). The age-specific burden of influenza has also not clearly been defined among infants <6 months, or among those aged 6-12 months. Such data could be used to inform whether vaccination of pregnant women to protect infants <6 months of age (for whom no influenza vaccine is currently licensed) through maternal antibody transfer and/or vaccination of children older than six months of age may be viable vaccination strategies for Kenya. Data on the burden of RSV have also been limited to those seeking medical care – focused on children <5 years - at the Coastal and Western areas of Kenya (14-17).

To address these gaps we estimated the age-specific burden and seasonality of medically-attended, and non-medically attended influenza and RSV in western Kenya during the period 2009-2012.

3.2 Methods

Since August 2009 the Kenya Medical Research Institute and the Centers for Disease Control and Prevention (KEMRI/CDC) have conducted hospital-based surveillance for severe acute respiratory illness (SARI) at Siaya District Hospital (SDH) and outpatient surveillance for influenza-like illness (ILI) at Ting'wang'i Health Centre (THC) in western Kenya. Both facilities are located in Karemo Division, where KEMRI/CDC implements a Health Demographic Surveillance System (HDSS), with an approximate population of 80,000 (18). Karemo's population is culturally homogenous, and almost entirely rural (19). The area is endemic for malaria with a high child mortality rate (212 deaths per 1000 live births in 2008) (19) and a high HIV prevalence, which in 2008 was estimated at 14% among persons aged ≥18 years (20).

3.2.1 Data collection and case definitions

From August 2009 to July 2012, trained nurses and clinical officers enrolled all consenting patients who were admitted to SDH with SARI or sought outpatient healthcare at THC for ILI. ILI was defined as axillary temperature ≥38°C and cough or sore throat with an onset with the past 14 days in an outpatient for persons of all ages. SARI was defined as hospitalization with cough or difficulty

breathing or pleural chest pain with an onset within the last 14 days. Hospitalized SARI patients were followed up for the duration of their hospitalization until they were discharged, transferred or died. We also estimated rates of non-medically attended ILI and SARI using the proportion of persons that sought care for acute respiratory infections (ARI), and pneumonia, respectively, from a health utilization survey implemented in Western Kenya in 2005 (21). In this survey, ARI was defined more narrowly than ILI as cough and difficulty in breathing within the last 14 days (21). Pneumonia was defined as ARI lasting for more than two days (excluding the past 14 days) within the preceding 12 months or a diagnosis of 'pneumonia' by a healthcare worker. Data processing and management procedures have been described previously (13).

3.2.2 Specimen collection and laboratory methods

Patients meeting SARI and ILI case definitions were enrolled in medical facility-based surveillance and nasopharyngeal (NP) and oropharyngeal (OP) swabs were collected, combined into a single viral transport media, and tested by real-time reverse transcription polymerase chain reaction (rtRT-PCR) for influenza A and B viruses and RSV (12, 13).

Patients admitted to the hospital for any reason were offered voluntary counseling and testing for HIV. Details of HIV testing at SDH have also been described previously (22).

3.2.3 Data analysis

3.2.3.1 Descriptive Analyses

We used univariate analysis methods including mean, median and proportions to describe demographic characteristics and laboratory outcomes of patients. Chi-square tests were used to assess associations for categorical variables. Mann-Whitney rank sum tests were used to test for differences in the age distribution between patients who were tested and those who were not tested for influenza viruses and RSV.

3.2.3.2 Estimating the incidence rates of hospitalized SARI, and influenza and RSV-associated SARI

As SDH is the only hospital located within Karemo Division, age-specific incidence rates (for 11 age groups: <6 months, 6-11 months, 12-23 months, 2-4 years, 5-17 years, 18-34 years, 35-49 years, ≥50 years, <5 years, ≥5 years, all ages) of hospitalized SARI were estimated by dividing the number of cases enrolled in the HDSS for each age group, by the mid-year population in each age group residing in the Karemo Division who were enrolled in HDSS. Similarly, the age-specific incidence rates of Influenza and RSV-associated SARI hospitalizations were calculated by dividing the number laboratory-confirmed influenza or RSV cases enrolled in the HDSS for each age group, by the mid-year population in each age group. Rates of influenza and RSV-associated SARI were adjusted for patients who met the SARI case definition but from whom NP/OP swabs were not collected and tested (for each age group, the adjusted number of cases was equal to the number of laboratory-confirmed cases divided by the proportion of patients with SARI who were tested). We compared incidence rates of influenza and RSV for residents living within 0-5 kilometers (KM), 0-10 KM, and 0-20 KM of the hospital. We did this in order to assess whether rates of hospitalized influenza and RSV declined with inclusion of persons who lived within Karemo Division but farther from the hospital (Figure 3.1).

3.2.3.3 Estimating the incidence rates of outpatient ILI, and Influenza and RSV-associated ILI

We estimated age-specific incidence of outpatient influenza and RSV virus infections for the 11 aforementioned age groups. To do this we examined the outpatient registers for children <5 years and persons ≥5 years at all seven outpatient facilities in Karemo Division to obtain the area of residence (village and sub-location) for each outpatient visit for a two-year period. From each outpatient facility we calculated the number and proportion of patients seen who were residents of Karemo Division by month and age (< 5 years and ≥5 years). We summed the number of patients seen at the seven facilities who were residents of Karemo and calculated the proportion of those who visited THC. We determined that approximately 10% (12,464/128,967) of outpatient visits among Karemo residents between 2010 and 2011 occurred at THC (11% and 9% for children <5 years and persons ≥5 years, respectively). The crude incidence rates (outpatient medically-attended ILI; influenza-associated ILI; and RSV-associated ILI) were calculated by dividing the number of cases by the mid-year population in each age group residing in the Karemo Division who were enrolled in HDSS.

After calculating crude rates by age group, we calculated adjusted rates by dividing the crude rates by the proportions of patients who visited THC in each age group (0.11 for children <5 years and 0.09 for persons ≥5 years). Influenza and RSV-associated incidence rates were then further adjusted for ILI patients who did not have NP/OP swabs collected (for each age group, the adjusted number of cases was equal to the number of laboratory-confirmed cases divided by the proportion of patients with ILI who were tested) (Figure 3.1).

3.2.3.4 Estimating non-medically attended incidence rates of influenza and RSV

We calculated the total (hospitalized and non-hospitalized) incidence of influenza and RSV-associated SARI by dividing the hospitalized SARI-associated incidence rates by the proportion of reported cases of pneumonia who went to hospital based on data from a 2005 Health Utilization Survey. In this survey, health utilization was reported for two age groups – children <5 years and persons ≥5 years. Forty eight percent (95% CI 35-62) of the children aged <5 years and 34% (95% CI 23-48) of persons aged ≥5 years were reported to have sought care for pneumonia at a hospital. As there was no health utilization reported for the finer age categories among children <5 years and persons ≥5 years, we used the same adjustment factor reported in the survey for children <5 years (48%) for all the age categories under five years (<6 months, 6-11 months, 12-23 months, 2-4 years, and <5 years). Similarly, we used the same health utilization adjustment factor (34%) reported for persons ≥5 years for all the age groups among persons aged five years or older (5-18 years, ≥18 years, and ≥5 years). The incidence of non-hospitalized SARI associated with influenza and RSV was then calculated by subtracting the hospitalized influenza and RSV-associated SARI incidence from the total incidence of influenza and RSV-associated SARI calculated using health utilization survey data for each age group (Figure 3.1).

We took a similar approach to estimate non-medically attended ILI associated with influenza and RSV. In this survey, 42% (95% CI 33-51) of the children aged <5 years and 44% (95% CI 40-53) of

persons aged ≥5 years reported to have sought care for ARI at a health facility. We used an adjustment factor of 42% for all the age groups under the age of five years and 44% for the age groups among patients aged five years or older. Total age-specific incidence rates of influenza and RSV-associated ILI were calculated by dividing the medically-attended ILI incidence rates by the proportion of reported cases of ARI in the health utilization survey who went to any facility.

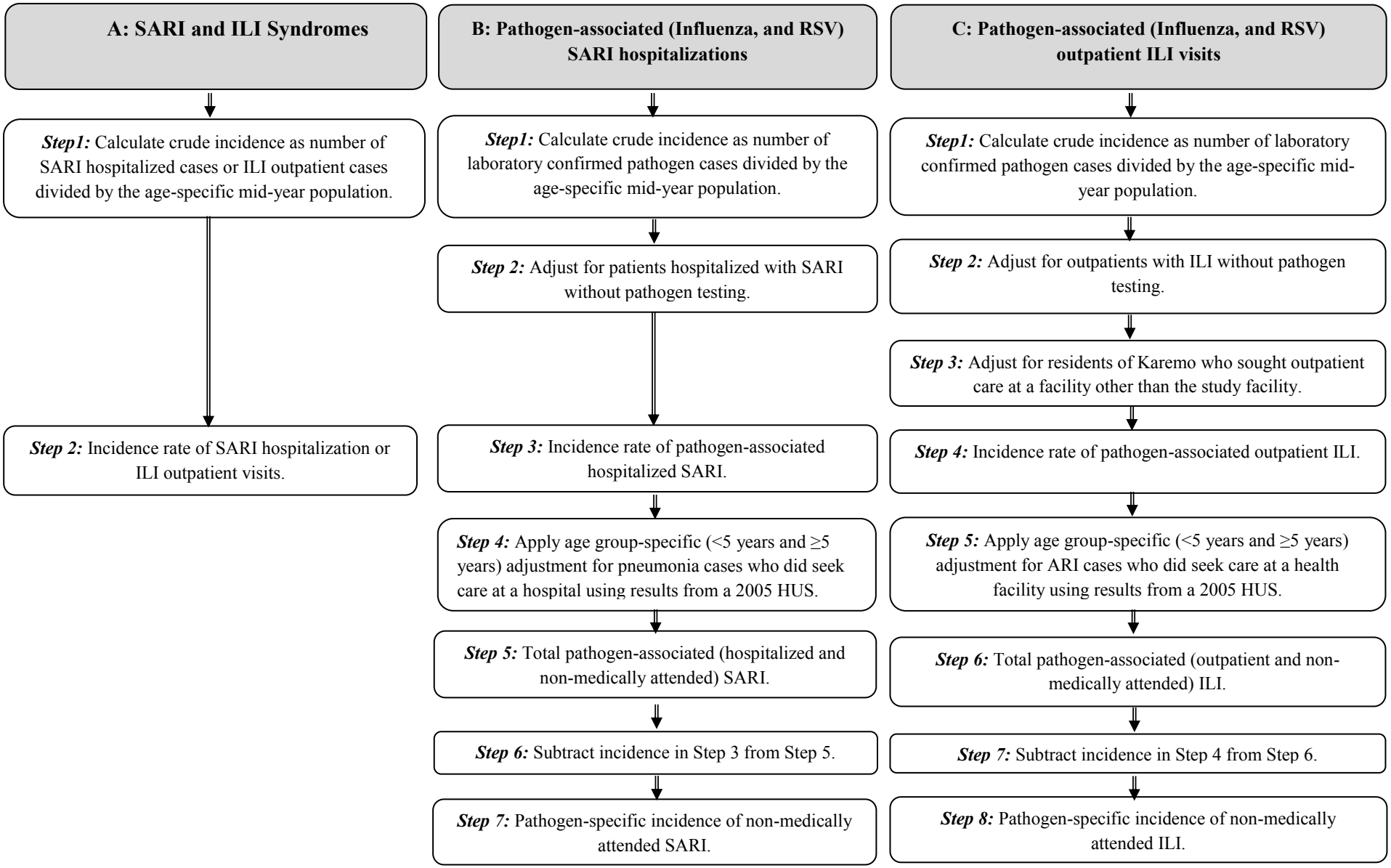

Figure 3.1: Flow diagram of the steps used for the calculation of incidence rates.

The age-specific incidence of non-medically attended ILI associated with influenza and RSV was calculated by subtracting the adjusted incidence of medically-attended influenza and RSV estimated from ILI surveillance at THC from the total incidence of influenza and RSV-associated ILI calculated using health utilization survey data, for each age group (Figure 3.1). Incidence rates were reported per 1000 persons, and the Poisson approximation method was used to calculate the 95% confidence intervals (CIs) around point estimates (23), separately for each age group. Data analysis was performed using Stata version 12.1 (Stata Corp, College Station, Texas).

3.3 Ethical considerations

This study was approved by both the Ethical Review Committee of the Kenya Medical Research Institute (KEMRI SSC-1801) and Institutional Review Board of CDC-Atlanta (CDC IRB #3308). Written informed consent was obtained from all participants or caretakers/guardians of all minors prior to enrolment in the study and sample collection.

3.4 Results

3.4.1 Descriptive analyses

We enrolled 5507 patients hospitalized with SARI at SDH, and 1632 patients with ILI at THC. Most (SARI=75%, ILI=77%) were children <5 years old. Although the study case definition was different from the current WHO case definition for SARI, seventy percent of the SARI cases included in this study also met the new WHO case definition [25% among children <5 years (30% in children < 6 months); and 47% in persons ≥5 years] (24). The median age was 1.6 years and 2.4 years for SARI and ILI patients, respectively, and 50% of the SARI patients and 53% of the ILI patients were female. Of the enrolled patients, 4387 (80%) of those with SARI and 1508 (92%) of those with ILI were tested for influenza and RSV (Table 3.1). When we compared SARI patients who were tested with those who were not, those tested were more likely to be male (50% vs. 46%; $p<0.05$), and the median age among those tested was 1.6 years compared to 1.5 years among those not tested ($p<0.001$). Similarly, ILI patients who were tested for influenza viruses or RSV were significantly older than those not tested (median age 2.4 years vs. 1.8 years; $p<0.001$). Case-fatality was significantly higher in SARI patients who were not tested for influenza or RSV than in those who were tested (18% vs. 4%; $p<0.001$).

Influenza viruses were detected in 348/4387 (8%) of the SARI patients (Table 3.1); 253 (6%) were positive for influenza A, 97 (2%) were positive for influenza B and 2 (0.1%) were positive for positive for both influenza A and B. The most commonly detected subtypes during the study period were influenza A(H1N1)pdm09 and influenza A(H3N2). RSV was detected in 437 (10%) of the SARI patients who were tested (12% in children <5 years; 4% in persons ≥5 years old). HIV-infected patients were as likely as non-HIV infected patients to test positive for these viral pathogens when we adjusted for age ($p=0.284$ for influenza; and $p= 0.957$ for RSV). The case-fatality proportion was

similar for SARI patients who tested positive compared to those who tested negative for influenza [13/348 (4%) vs. 171/4039 (4%); p=0.66] and RSV [14/437 (3%) vs. 170/3950 (4%); p=0.28], respectively. The median age among the SARI patients was significantly higher in influenza positive patients compared to RSV positive patients [3.0 vs. 1.1 years; p<0.001].

Of the 1508 ILI patients tested, 206 (14%) tested positive for influenza viruses; [159 (11%) were positive for influenza A; 51 (3%) for influenza B; and 4 (0.3%) were positive for both influenza A and B]. The most commonly detected subtypes during the three years were influenza A(H1N1)pdm09 and influenza A(H3N2). RSV was detected in 138 out of 1,508 patients (10%) [11% in children <5 years; 6% in persons ≥5 years old] (Table 3.1). Similarly, the median age among ILI patients was significantly higher in the influenza positive patients compared to RSV positive patients [4.4 vs. 2.4; p<0.001].

Influenza-virus-positive cases were detected throughout the study period with the influenza-positive proportions observed to be lower in the hotter months between December and January every year. RSV peaked more predictably during May-July of each year (Figure 3.2). Influenza A(H1N1)pdm09 was the dominant influenza virus in circulation during late 2009 and early 2010, and again during late 2010 and early 2011. Influenza A(H3N2) was the dominant influenza virus in circulation during the periods May 2010 to October 2010 and also from January 2012 to July 2012. Influenza B viruses were detected mostly between April 2011 and December 2011 (Figure 3.3).

3.4.2 Incidence of hospitalized SARI, and influenza and RSV-associated SARI

The estimated average annual incidence rate of SARI hospitalizations among children <5 years of age was 43.6(95% CI 40.1-47.3) [106.2(95% CI 88.6-127.3) in children < 6 months; 120.2(95% CI 101.7-142.0) in children 6-11 months; 67.6(95% CI 58.1-78.8) in children 12-23 months; and 16.9(95% CI 14.3-20.0) in children 2-4 years] and 2.4(95% CI 2.0-2.8) among persons aged ≥5 years cases per 1000 persons (Table 3.2). The average annual adjusted incidence of influenza-associated hospitalized SARI was 0.7 per 1000 persons (95% CI 0.5-0.9) and was higher among children aged <5 years [2.7 (95% CI 1.8-3.9)] compared to persons aged ≥5 years [0.3 (95% CI 0.2-0.4)] (Table 3.3). Influenza-associated hospitalizations were 5.7(95% CI 2.4-13.8) in children <6 months; 4.7(95% CI 1.8-11.9) in children aged 6-11 months; and 4.4(95% CI 2.3-8.5) in children aged 12-23 months. The incidence of influenza-associated SARI hospitalizations was not significantly different among residents of Karemo living within 5 KM of SDH [2.6 (95% CI 1.5-4.7)] compared to residents living within 10 KM of SDH [2.4 (95% CI 1.6-3.7)] and those living with 20 KM of SDH [2.7 (95% CI 1.8-3.9)] (Figure 3.4).

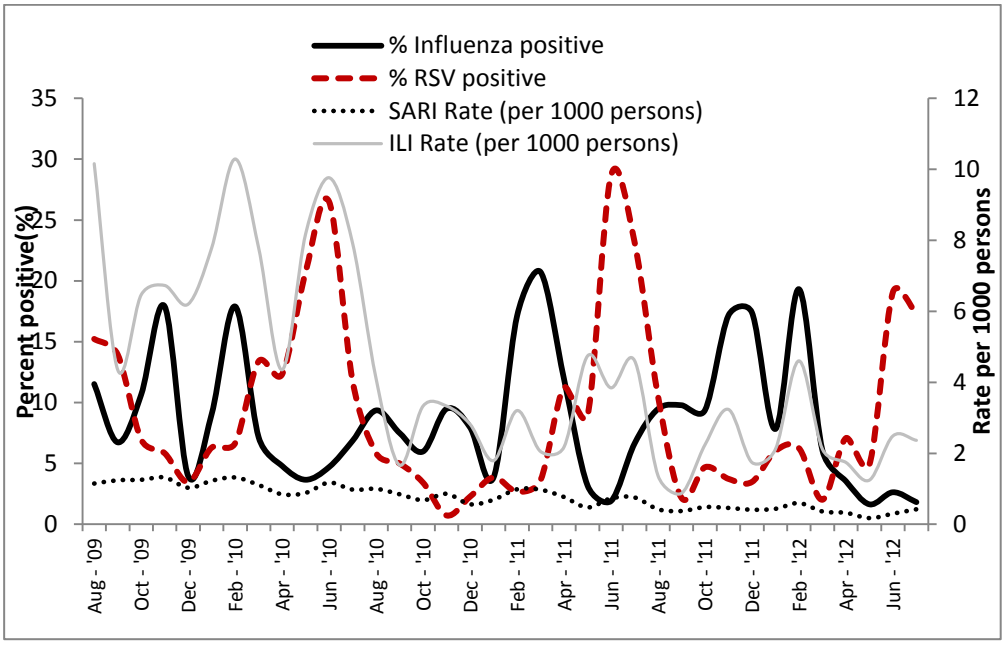

Figure 3.2: Seasonality of Influenza and RSV in Western Kenya, Aug 2009 - Jul 2012

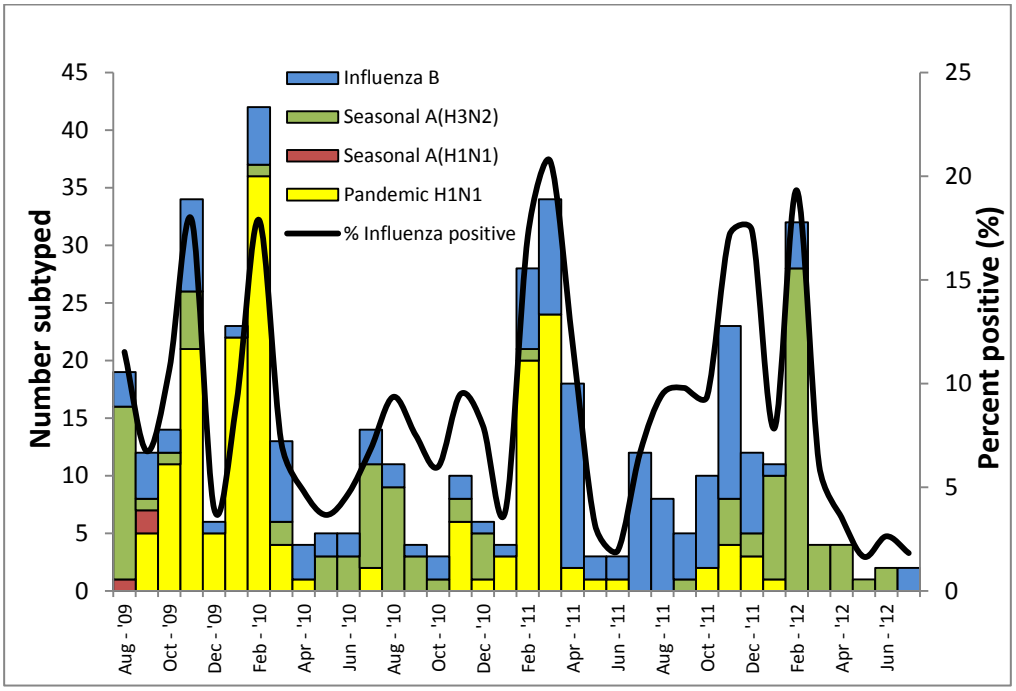

Figure 3.3: Seasonality of influenza and circulating subtypes in Western Kenya, Aug 2009 - Jul 2012

Incidence rates of RSV-associated hospitalized SARI were 0.9 (95% CI 0.7-1.2) and were higher in children aged <5 years [5.2 (95% CI 4.0-6.8)] than in persons aged ≥5 years [0.1 (95% CI 0.0-0.2)] (Table 3.3). RSV-associated hospitalizations were highest in children <2 years old [13.4(95% CI 7.5-23.8) in children <6 months; 14.0(95% CI 8.1-24.1) in children aged 6-11 months; and 8.1(95% CI 5.0-13.1) in children aged 12-23 months]. As was the case with influenza, incidence of RSV-

associated SARI was not significantly different in residents of Karemo living within 5 KM of SDH [0.9 (95% CI 0.6-1.3)] compared with those living within 10 KM of SDH [0.9 (95% CI 0.7-1.2)] and compared to those with 20 KM of SDH [0.9 (95% CI 0.7-1.2)] (Figure 3.4). More detailed age-specific incidence rates of hospitalizations associated with influenza and RSV are presented in Table 3.3. Incidence rates of hospitalizations associated with influenza or RSV were higher in the first year (August 2009 – July 2010) compared to the other two years included in this analysis (Table 3.4).

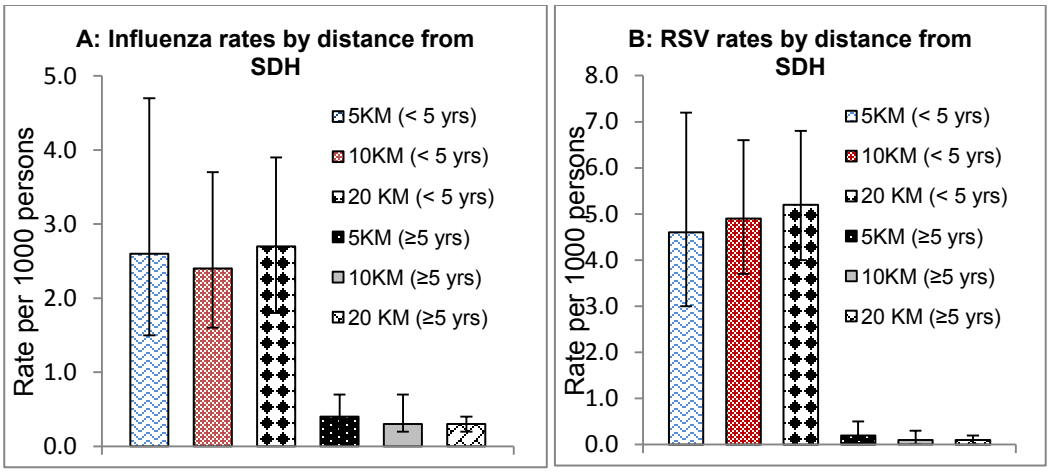

Figure 3.4: Rates of influenza and RSV associated SARI by distance from SDH, Aug 2009 –Jul 2012.

3.4.3 Incidence of medically-attended outpatient ILI and influenza and RSV-associated ILI

The estimated incidence of medically-attended outpatient visits associated with ILI among children <5 years of age was 214.9(95% CI 207.1-223.1), and 16.1(95% CI 15.1-17.1) among persons aged ≥5 years cases per 1000 persons (Table 3.2). The average annual adjusted incidence of medically-attended ILI associated with influenza was 7.2 (95% CI 5.5-9.4) and was significantly higher in children aged <5 years [21.8(95% CI 15.1-31.6)] compared to those aged ≥5 years [4.3(95% CI2.8-6.4)]. The average annual incidence of medically-attended ILI associated with RSV was 4.7 (95% CI 3.3-6.6) and was significantly higher among children <5 years [22.3(95% CI15.5-32.2)] compared to persons aged ≥5 years [0.9(95% CI 0.4-2.2)] (Table 3.2). The age-specific incidence rates of outpatient visits associated with influenza and RSV are presented on Table 3.3.

3.4.4 Non-medically attended incidence rates of influenza and RSV SARI and ILI

The incidence of non-hospitalized SARI attributable to influenza was 1.2 (95% CI 0.9-1.4) [2.9 (95% CI 2.1-4.0) in persons <5 years; and 0.5 (95% CI 0.4-0.7) in persons ≥5 years]. The incidence of non-hospitalized SARI attributable to RSV was 1.6 (95% CI 1.4-2.0) [5.6 (95% CI 4.5-7.1) in persons <5 years; and 0.2 (95% CI 0.1-0.3) in persons ≥5 years] after adjusting for persons who reported cases of pneumonia but did not go to hospital.

The overall incidence of non-medically attended ILI attributable to influenza was 9.1 (95% CI 8.5-9.8); 30.1(95% CI27.3-33.3) in persons <5 years; and 5.4(95% CI4.9-6.0) in persons ≥5 years.

The incidence of non-medically attended ILI associated with RSV was 6.0 (95% CI 5.4-6.5) [30.8(95% CI27.9-34.0) in persons <5 years; and 1.1(95% CI0.9-1.4) in persons ≥5 years] after adjusting for persons who reported ARI in the 2005 health utilization survey but did not go to any facility (Table 3.3).

3.5 Discussion

These findings suggest an important burden of both influenza and RSV among persons with hospitalized SARI and outpatient ILI in western Kenya, particularly among children aged <5 years. There is also likely an important burden of illness associated with these viral pathogens in persons with SARI and ILI who do not seek medical care.

The burden of severe respiratory disease associated with both influenza and RSV was highest in children less than 23 months of age, suggesting young children are an important potential target group for current or future vaccines and other interventions in Kenya. While pregnant women are a high risk group for influenza-associated complications in their own right (25), our additional finding that the burden of influenza associated SARI was highest in those under six months of age further suggests the potential value of vaccination of pregnant women as a way of protecting (via maternal antibody transfer) those very young children for whom no influenza vaccine is currently licensed (26). These data therefore support the 2012 recommendations by the WHO Strategic Advisory Group of Experts on Immunization that suggest pregnant women to be a high priority group for influenza vaccination (27).

The rates of influenza-associated hospitalizations presented here are comparable to the incidence reported in Kenya during the period August 2010 to July 2011 (11). These rates of hospitalized influenza are also comparable to rates published for other locations in Kenya (11), and to those reported in Bangladesh and Thailand (28, 29). However these estimates of influenza-associated hospitalizations in children <5 years are nearly two times higher than rates in the pre-pandemic period before 2009 in the same region (13). Importantly, they are also 3-7 times higher than those reported recently in the United States (30, 31).

Our adjusted incidence of hospitalizations associated with RSV among children <5 years [i.e. 5.2 (95% CI 4.0-6.8)] is nearly 2-fold higher than the incidence reported in Kilifi, in the Coastal part of Kenya (14), but is lower than rates published in a five-year cohort study in South Africa. Even without adjustment, our observed incidence rates of RSV in children under 24 months of age also appear to be nearly twice those reported in the United States (32). We also observe that the incidence of RSV-associated hospitalizations was higher than the incidence of influenza hospitalizations in younger ages, but lower in older ages, which is consistent with findings from other studies (31, 33).

Our observed incidence of outpatient ILI-associated influenza was only one-tenth of the rate reported in Bangladesh (28) but over 2-fold higher than rates reported in England and Netherlands among children <5 years (34). As was the case with influenza, our estimated incidence of ILI-associated RSV in children <5 years was over 5-times higher than the incidence published in Europe (34).

Using adjustments for health seeking behaviors, our estimates of the incidence of non-medically-attended SARI and ILI associated with influenza and RSV were higher than comparable rates of medically-attended illness in this community. This highlights the need to consider burden of disease beyond the health care facility to best inform public health policy in this setting. Indeed, the 2005 survey indicated that only 48% of children <5 years and 34% of persons ≥5 years who reported having pneumonia sought care at a hospital. Similarly, only 42% of children <5 years and 44% of persons ≥5 years who reported having ARI in the two weeks preceding the health utilization survey sought healthcare at any health facility (21). These direct estimates therefore support international indirect modeling efforts that have suggested influenza and RSV-associated severe disease rates are substantially higher in Africa and other lower resourced countries than elsewhere (2, 3, 5).

Our study was subject to several limitations. The SARI case definition did not include wheezing, nasal flaring, tachypnea, shortness of breath, and lethargy which have been associated with RSV elsewhere, and may have resulted in an under estimation of incidence of RSV, especially in very young children (3, 16, 35). This might explain why our RSV rates were similar between infants aged <6 months and 6-11 months, which is inconsistent with other studies that report much higher rates in younger infants (32). Conversely, the SARI case definition that we used is broader than the new case definition recommended by WHO which requires a history of fever or measured fever (24). There were an additional 30% SARI cases identified using this case definition compared to what would have been identified using the new WHO case definition. This may have served to improve sensitivity and thus helped to better estimate disease burden, in the very young children (<6 months) and older persons who may be less likely to present with fever as a component of influenza virus infections. Similarly, the ILI case definition – requiring a measured temperature of ≥ 38°C - was used to estimate the burden of RSV among outpatients. This also may have possibly led to an under estimation of the burden of RSV in outpatients, which may be less likely than influenza to result in presentation with fever (36, 37). The case definitions for ARI and pneumonia in this survey were also both narrower in scope than the ILI and SARI case definitions used in facility-based surveillance, respectively. This could have led to an underestimation of the incidence of illness in the community.

Another limitation was that to estimate the burden of non-hospitalized and non-medically-attended illness we used adjustment factors from a health utilization survey that was conducted in 2005 - four years earlier than the study period. Health seeking behaviors could have changed over that period of time. Additionally, the survey was powered to estimate health utilization among for both children <5 years and persons ≥5 years (21). In this respect, the health utilization adjustments may not have been as robust as ideal for the finer age-specific rate adjustments that we undertook. For example, we applied the same adjustment factor reported for health utilization among under-fives for all age categories in children <5 years (<6 months, 6-11 months, 12-23 months, 2-4 years). If the utilization rates differ across these age groups, then this could bias our estimates. Conducting health utilizations surveys with sufficient power in narrower age groups would serve to improve future estimates.

There was also minimal testing for HIV especially among younger persons and thus our study was not able to effectively estimate incidence specifically in HIV positive and negative populations. Lastly, we did not conduct a record review at hospitals in the area other than SDH to determine the proportion of residents of Karemo who went to other hospitals. Instead, we assumed that every

resident of Karemo who required hospitalization would go to SDH. We felt this was a reasonable approach given that the next nearest hospital was located 17 KM away. To support this there were also no observed differences between calculated incidence for persons who lived within 5KM, 10KM, and 20 KM of SDH. The assumption behind this validation approach was that people within very close proximity would seek care at SDH rather than elsewhere and so we would have expected the incidence to decline significantly with an increase in distance.

In conclusion, influenza and RSV both exact an important disease burden in rural western Kenya, particularly in children <5 years old. These data suggest that a future RSV vaccine could have important implications for child health in Kenya. The immunization of children and pregnant women with currently licensed influenza vaccines also has important potential to reduce a significant cause of respiratory morbidity and mortality in Kenya.

Acknowledgements: We thank the Kenya Ministry of Health and the medical staff, study surveillance officers, and study participants at Siaya District Hospital and Ting'wang'i Health Centre.

Table 3.1: Characteristics of patients who were admitted at SDH with SARI and those who presented to THC with ILI and were tested for respiratory pathogens, August 2009 - July 2012

	In-patients (SARI patients)		Out-patients (ILI patients)	
	Total Number (N=5,507)	Enrolled in Karemo HDSS (N=2,136)	Total Number (N=1,632)	Enrolled in Karemo HDSS (N=1,186)
	n (%)	n (%)	n (%)	n (%)
Sex				
Male	2,800(50.8)	1,097(51.4)	779(47.7)	567(47.8)
Female	2,707(49.2)	1,039(48.6)	853(52.3)	619(52.2)
Age Group				
<6 months	918(16.7)	351(16.4)	134(8.2)	85(7.2)
6-11 months	1,040(18.9)	414(19.4)	207(12.7)	140(11.8)
12-23 months	1,134(20.6)	495(23.2)	339(20.8)	248(20.9)
2-4 years	1,018(18.5)	411(19.2)	570(34.9)	431(36.3)
5-17 years	417(7.6)	174(8.2)	311(19.1)	236(19.9)
18-34 years	493(9.0)	133(6.2)	53(3.3)	35(3.0)
35-49 years	223(4.1)	74(3.5)	11(0.7)	7(0.6)
≥50 years	264(4.8)	84(3.9)	7(0.4)	4(0.3)
Median age years (Range)	1.6(0.01-90.0)	1.6(0.01-90.0)	2.4(0.1-0 63.4)	2.4(0.02-63.4)
Died in the hospital	390(7.1)	103(4.8)	-	-
HIV status				
Negative	2,917(53.0)	1,190(55.7)	482(29.5)	337(28.4)
Positive[¥]	654(11.9)	230(10.8)	28(1.7)	12(1.0)
Unknown	1,936(35.2)	716(33.5)	1,122(68.8)	837(70.6)
Sampled and tested for influenza and RSV	4,387(79.7)	1730(81.0)	1,508(92.4)	1,092(92.1)
Respiratory pathogen isolated				
Influenza A or B*	348(7.9)	124(7.2)	206(13.7)	155(14.2)
Influenza A*	253(5.8)	93(5.4)	159(10.5)	119(10.9)
*Seasonal A (H1N1)**	*2(0.8)*	*0(0.0)*	*1(0.6)*	*1(0.8)*
*Seasonal A (H3N2)**	*63(24.9)*	*16(17.2)*	*52(32.7)*	*42(35.3)*
*Pandemic H1N1**	*93(36.8)*	*39(41.9)*	*82(51.6)*	*59(49.6)*
*Unsubtypable**	*10(4.0)*	*3(3.2)*	*3(1.9)*	*3(2.5)*
*Not subtyped**	*81(32.0)*	*32(34.4)*	*18(11.3)*	*14(11.8)*
Influenza B*	97(2.2)	32(1.9)	51(3.4)	38(3.5)
Influenza A and B*	2(0.1)	1(0.1)	4(0.3)	2(0.2)
Respiratory syncytial virus (RSV)*	437(10.0)	176(10.2)	138(9.7)	101(9.7)
Influenza-RSV co-infection*	18(0.4)	7(0.4)	14(0.9)	11(1.0)

[¥]18% of those with known HIV status were HIV infected; *Denominator is the number of those who tested for Influenza and RSV; **Denominator in the number of influenza A cases.

Table 3.2: Age-specific average annual rates of SARI hospitalizations and ILI outpatient visits (per 1,000 persons) in Western Kenya, August 2009 - July 2012

	Karemo Population[a]	Proportion of hospitalizations[b] with SARI n(%)	Average annual SARI hospitalization rates (95% CI)	Proportion of outpatients[c] with ILI n(%)	Average annual medically-attended ILI rates[d] (95% CI)
Age Group					
<6 months	1,102	351/821(42.8)	106.2(88.6-127.3)	85/896(9.5)	233.7(206.9-264.1)
6-11 months	1,148	414/1,050(39.4)	120.2(101.7-142.0)	140/858(16.3)	369.5(336.0-406.4)
12-23 months	2,440	495/1,287(38.5)	67.6(58.1-78.8)	249/1,436(17.3)	309.2(287.9-332.1)
2-4 years	8,097	411/1,267(32.4)	16.9(14.3-20.0)	433/2,435(17.8)	162.1(153.5-171.1)
5-17 years	28,326	174/708(24.6)	2.0(1.6-2.6)	237/2,456(9.6)	31.0(29.0-33.1)
18-34 years	18,270	133/1,452(9.2)	2.4(1.8-3.3)	35/1,152(3.0)	7.1(6.0-8.4)
35-49 years	8,272	74/758(9.8)	3.0(2.0-4.4)	7/461(1.5)	3.1(2.1-4.6)
≥50 years	10,397	84/944(8.9)	2.7(1.9-3.9)	4/749(0.5)	1.4(0.9-2.4)
<5 years	12,787	1,671/4,425(37.8)	43.6(40.1-47.3)	907/5,625(16.1)	214.9(207.1-223.1)
≥5 years	65,265	465/3,862(12.0)	2.4(2.0-2.8)	283/4,818(5.9)	16.1(15.1-17.1)
All ages	78,052	1,978/8,287(23.9)	8.4(7.8-9.1)	1,179/10,443(11.3)	50.4(48.8-52.0)

[a]Mid-study-period population for Karemo (Aug 2009 – Jul 2012); [b]Total hospitalizations among residents of Keremo over three years (Aug 2009 - Jul 2012); [c]Total outpatient visits to Ting'wang'i by residents of Karemo over three years (Aug 2009 - Jul 2012); [d]Adjusted for outpatient visits to other health facilities in Karemo other than Ting'wang'i.

Table 3.3: Age-specific average annual rates for hospitalizations and outpatient visits attributable to influenza and RSV (per 1,000 persons) in Western Kenya, August 2009 - July 2012

	SARI				ILI			
	Proportion positive[a] n(%)	Unadjusted hospitalized rates (95% CI)	Adjusted Hospitalized rates[b] (95% CI)	Non-hospitalized rates[c] (95% CI)	Proportion positive[a] n(%)	Unadjusted medically-attended rates (95% CI)	Adjusted Medically-attended rates[b] (95% CI)	Non-medically attended rates[d] (95% CI)
Influenza A or B								
<6 months	15/279(5.4)	4.5(1.9-10.9)	5.7(2.4-13.8)	6.2(2.9-13.2)	5/72(6.9)	1.5(0.3-6.9)	16.2(3.5-73.8)	22.3(15.0-33.2)
6-11 months	13/337(3.9)	3.8(1.5-9.7)	4.7(1.8-11.9)	5.0(2.2-11.4)	13/128(10.2)	3.8(1.5-9.7)	37.7(14.7-96.7)	52.1(40.4-67.1)
12-23 months	27/409(6.6)	3.7(1.9-7.1)	4.4(2.3-8.5)	4.8(2.7-8.5)	23/223(10.3)	3.1(1.5-6.4)	31.7(15.6-64.4)	43.8(36.3-53.0)
2-4 years	27/319(8.5)	1.1(0.6-2.1)	1.4(0.7-2.7)	1.5(0.9-2.7)	43/402(10.7)	1.8(1.1-3.0)	17.3(10.3-29.0)	23.9(20.8-27.5)
5-17 years	13/126(10.3)	0.2(0.1-0.4)	0.2(0.1-0.5)	0.4(0.2-0.7)	54/221(24.4)	0.6(0.4-1.0)	6.1(3.9-9.8)	7.8(6.9-8.9)
18-34 years	15/117(12.8)	0.3(0.1-0.7)	0.3(0.1-0.7)	0.6(0.3-1.1)	12/35(34.3)	0.2(0.1-0.6)	2.0(0.7-5.3)	2.5(1.9-3.4)
35-49 years	8/67(11.9)	0.3(0.1-1.1)	0.4(0.1-1.2)	0.7(0.3-1.6)	*	*	*	*
≥50 years	6/76(7.9)	0.2(0.0-0.8)	0.2(0.1-0.9)	0.4(0.2-1.1)	*	*	*	*
<5 years	82/1344(6.1)	2.1(1.5-3.1)	2.7(1.8-3.9)	2.9(2.1-4.0)	84/825(10.2)	2.2(1.5-3.2)	21.8(15.1-31.6)	30.1(27.3-33.3)
≥5 years	42/386(10.9)	0.2(0.1-0.4)	0.3(0.2-0.4)	0.5(0.4-0.7)	71/267(26.6)	0.4(0.2-0.5)	4.3(2.8-6.4)	5.4(4.9-6.0)
All ages	124/1730(7.2)	0.5(0.4-0.7)	0.7(0.5-0.9)	1.2(0.9-1.4)	155/1092(14.2)	0.7(0.5-0.9)	7.2(5.5-9.4)	9.1(8.5-9.8)
RSV								
<6 months	35/279(12.5)	10.6(6.0-18.8)	13.4(7.5-23.8)	14.5(8.9-23.7)	2/72(2.8)	0.6(0.1-6.7)	6.5(0.6-71.4)	8.9(4.8-16.7)
6-11 months	39/337(11.6)	11.3(6.6-19.5)	14.0(8.1-24.1)	15.1(9.5-24.2)	14/128(10.9)	4.1(1.6-10.1)	40.6(16.4-100.6)	56.1(43.9-71.6)
12-23 months	49/409(12.0)	6.7(4.1-10.9)	8.1(5.0-13.1)	8.7(5.7-13.4)	21/223(9.4)	2.9(1.4-6.0)	29.0(13.8-60.8)	40.0(32.8-48.8)
2-4 years	37/319(11.6)	1.5(0.9-2.7)	2.0(1.1-3.4)	2.1(1.3-3.4)	49/402(12.2)	2.0(1.2-3.3)	19.7(12.1-32.0)	27.2(23.9-31.1)
5-17 years	7/126(5.6)	0.1(0.0-0.3)	0.1(0.0-0.4)	0.2(0.1-0.5)	13/221(5.9)	0.2(0.1-0.4)	1.5(0.6-3.8)	1.9(1.4-2.5)
18-34 years	7/117(6.0)	0.1(0.0-0.5)	0.1(0.0-0.5)	0.3(0.1-0.7)	1/35(2.9)	0.0(0.0-0.5)	0.2(0.0-4.9)	0.2(0.1-0.6)
35-49 years	1/67(1.5)	0.0(0.0-1.2)	0.0(0.0-1.3)	0.1(0.0-0.9)	*	*	*	*
≥50 years	1/76(1.3)	0.0(0.0-1.0)	0.0(0.0-1.1)	0.1(0.0-0.7)	*	*	*	*
<5 years	160/1344(11.9)	4.2(3.2-5.5)	5.2(4.0-6.8)	5.6(4.5-7.1)	86/825(10.4)	2.2(1.6-3.2)	22.3(15.5-32.2)	30.8(27.9-34.0)
≥5 years	16/386(4.1)	0.1(0.0-0.2)	0.1(0.0-0.2)	0.2(0.1-0.3)	15/267(5.6)	0.1(0.0-0.2)	0.9(0.4-2.2)	1.1(0.9-1.4)
All ages	176/1730(10.2)	0.8(0.6-1.0)	0.9(0.7-1.2)	1.6(1.4-2.0)	101/1092(9.2)	0.4(0.3-0.6)	4.7(3.3-6.6)	6.0(5.4-6.5)

[a]Includes only data for residents of the HDSS area of Keremo Division (2009-2012); [b]Adjusted for those that met the case definition for SARI/ILI without laboratory test results; [c]Adjusted for persons with pneumonia who did not seek care, using the results of a 2005 HUS; 48% (95% CI 35-62) of children <5 years and 34% (95% CI 23-48) of persons ≥5 years sought care for pneumonia at a hospital (Burton et al, 2005); [d]Adjusted for persons with ILI who did not seek care, using the results of a 2005 HUS; 42%(95% CI 33-51) of children <5 years and 44%(95% CI 40-53) of persons ≥5 years sought care at any facility for ARI (Burton et al, 2005). * Estimates not calculated because there were fewer than 30 specimens tested in this age-specific stratum..

Table 3.4: Annual rates[a] for hospitalizations and outpatient visits attributable to influenza and RSV by year (per 1,000 persons) in Western Kenya, Aug 2009 - Jul 2012

	SARI				ILI			
	Year 1[b]	Year 2[c]	Year 3[d]	Average annual rates	Year 1[b]	Year 2[c]	Year 3[d]	Average annual rates
Influenza A or B								
<5 years	3.8(2.8-5.1)	3.2(2.2-4.5)	1.1(0.6-2.0)	2.7(1.8-3.9)	32.9(24.4-44.4)	15.3(9.9-23.7)	17.6(11.5-26.9)	21.8(15.1-31.6)
≥5 years	0.3(0.2-0.5)	0.2(0.1-0.4)	0.3(0.2-0.4)	0.3(0.2-0.4)	8.5(6.4-11.4)	3.1(1.9-5.0)	1.5(0.8-2.9)	4.3(2.8-6.4)
All ages	0.9(0.7-1.1)	0.7(0.5-1.0)	0.4(0.3-0.6)	0.7(0.5-0.9)	12.7(10.3-15.6)	5.0(3.6-6.9)	4.1(2.9-5.9)	7.2(5.5-9.4)
RSV								
<5 years	8.8(7.2-10.8)	4.8(3.6-6.4)	1.8(1.1-2.9)	5.2(4.0-6.8)	42.9(33.0-55.7)	13.8(8.7-21.9)	10.0(5.7-17.7)	22.3(15.5-32.2)
≥5 years	0.2(0.1-0.4)	0.1(0.0-0.2)	0.1(0.0-0.2)	0.1(0.0-0.2)	2.4(1.4-4.1)	0.2(0.0-1.4)	0.2(0.0-1.2)	0.9(0.4-2.2)
All ages	1.7(1.4-2.0)	0.8(0.6-1.1)	0.3(0.2-0.5)	0.9(0.7-1.2)	9.8(7.8-12.5)	2.6(1.7-4.1)	1.8(1.0-3.1)	4.7(3.3-6.6)

[a]Adjusted for those that met the case definition for SARI/ILI without laboratory test results; [b]August 2009 - July 2010; [c]August 2010 - July 2011; [d]August 2011 - July 2012.

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Chapter 4: Estimating influenza and RSV-associated mortality in Western Kenya using data from a health demographic surveillance system, 2007-2013

Submitted for publication

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Abstract

Background: Influenza viruses and respiratory syncytial virus (RSV) associated mortality has not been well-established in tropical Africa.

Methods: We used the negative binomial regression method and the rate-difference method (i.e., deaths during low and high influenza/RSV activity months), to estimate excess mortality attributable to influenza and RSV using verbal autopsy data collected through a health and demographic surveillance system in Western Kenya, 2007-2013. Excess mortality rates were calculated for a) all-cause mortality, b) all-respiratory deaths (including pneumonia), c) HIV-related deaths, and d) pulmonary tuberculosis (PTB) related deaths.

Results: Using the negative binomial regression method, the mean annual all-cause excess mortality rate associated with influenza and RSV was 14.1 (95% confidence interval [CI] 0.0-93.3) and 17.1 (95% CI 0.0-111.5) per 100,000 person-years (PY) respectively; and 10.5 (95% CI 0.0-28.5) and 7.3 (95% CI 0.0-27.3) per 100,000 PY for all-respiratory deaths, respectively. Highest mortality rates associated with influenza were among ≥50 years, particularly among persons with PTB (41.6 [95% CI 0.0-122.7]); and with RSV were among <5 years. Using the rate-difference method, the excess mortality rate for influenza and RSV was 44.8 (95% CI 36.8-54.4) and 19.7 (95% CI 14.7-26.5) per 100,000 PY, respectively, for all-cause deaths; and 9.6 (95% CI 6.3-14.7) and 6.6 (95% CI 3.9-11.0) per 100,000 PY, respectively, for all-respiratory deaths.

Conclusions: Our study shows an important role of influenza and RSV on excess mortality in Western Kenya, especially among children <5 years and older persons, supporting recommendations for influenza vaccination and efforts to develop RSV vaccines.

4.1 Introduction

Influenza viruses and respiratory syncytial virus (RSV) cause substantial morbidity globally (1-5). Disease severity associated with influenza and RSV has been well described in temperate countries as pronounced among young children (3, 6, 7), older persons (3, 7, 8), and among persons with chronic medical conditions (4-6, 9). In Kenya, influenza virus and RSV circulate year round and although limited morbidity data exist (10-15), associated mortality has not been established. Influenza and RSV associated mortality can inform policy makers in low and middle income countries to prioritize segments of the population that are most in need of the potentially limited vaccination and treatment resources.

Conceptually, excess mortality can be estimated as the difference between observed mortality (during the periods of influenza or RSV circulation) and expected mortality (if the pathogens are not circulating) (16-20). In Kenya, as in most sub-Saharan African countries, there is an absence of systematically collected and robust vital statistics data. Furthermore, hospital-based data could under-represent the number of those who die from respiratory illness as care-seeking is low, particularly among adults who are often underrepresented in health-facility based surveillance systems (21, 22).

Here, we used verbal autopsy (VA) data collected through a health and demographic surveillance system (HDSS) in Western Kenya (23-25) to estimate the overall and age-specific excess mortality rates associated with influenza virus and RSV during the period 2007 to 2013. We also explore and discuss the merits and challenges of using two different estimation methods: (i) the negative binomial regression method which has been used in temperate countries to estimate excess mortality associated with influenza and RSV (16-19), and (ii) the rate-difference method which has previously been recommended as the method of choice when estimating excess mortality for countries without a clear disease seasonality pattern (16, 20).

4.2 Methods

4.2.1 Study site and population

The Western Kenya HDSS has been in existence since 2001 and currently comprises three geographical sites in Nyanza Province: Asembo, Gem and Karemo, (23, 25). These three areas cover an estimated area of 700 km^2 with a culturally homogenous rural population of approximately 220,000 (Figure 4.1) (23). Nyanza Province also has a high burden of malaria, pulmonary tuberculosis (PTB) (26) and human immunodeficiency virus (HIV) which has prevalence of 15% compared to 6% overall in Kenya (27).

4.2.2 Mortality and population data sources

Our study-participants included HDSS residents, i.e., lived in the site for at least four consecutive months, and their infants (23). Participants live in compounds (or households) that are geo-spatially mapped, and each person receives a unique identification number allowing record linkage. A household census is conducted throughout the study area every four months to capture births, pregnancies, deaths, in- and out- migration, and economic data (23, 28). If a death is reported, at least one month after the death trained interviewers use a standardized World Health Organization (WHO) questionnaire

(29) endorsed by International Network for the Demographic Evaluation of Populations and Their Health (INDEPTH) to collect information on the decedent's illness and care seeking behavior (30). The cause of death is assigned using the InterVA-4 method with corresponding ICD-10 codes (Appendix 4.1).

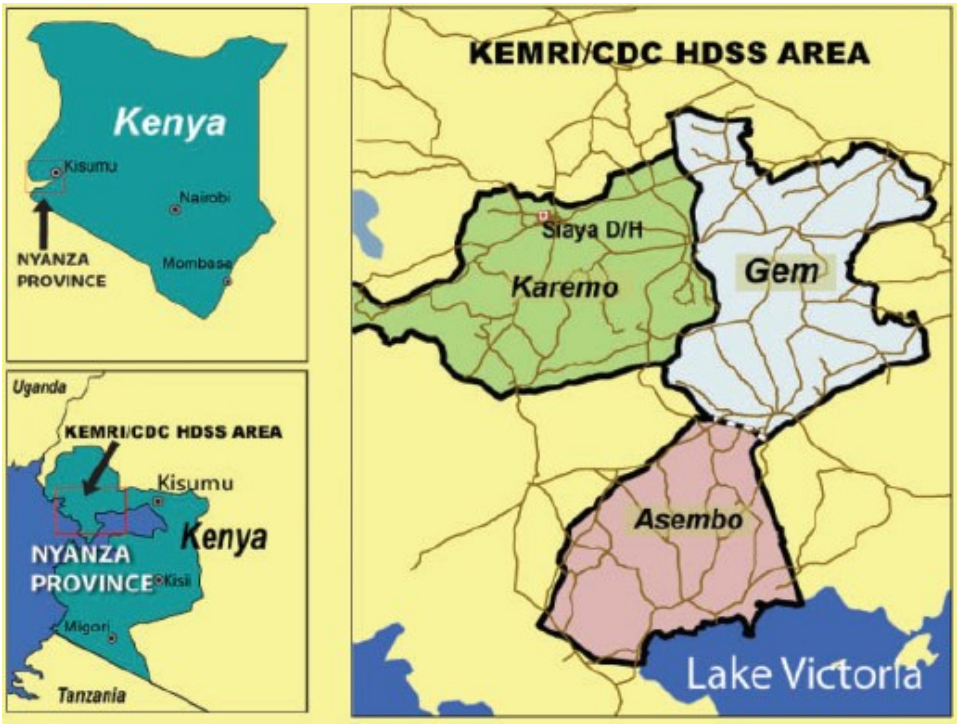

Figure 4.1: Map showing the location of the Health and Demographic Surveillance System (HDSS) in Western Kenya (Source: Odhiambo et al [23])

4.2.3 Influenza, RSV and malaria activity and data sources

Indices of influenza, RSV and malaria activity were defined using the monthly positive proportion of tested samples from our hospital-based active surveillance sites. Malaria was considered *a priori* as a potential confounder because it is endemic in the study region and has demonstrated seasonal mortality that sometimes overlaps with influenza and RSV activity. Malaria test result, as well as influenza and RSV virological data, were collected from three HDSS surveillance sites [Siaya County Referral Hospital (SCRH), Lwak Mission Hospital (Lwak), and Ting'wang'i Health Center (THC)] (Figure 4.1). Patients at these facilities were screened for malaria using methods previously described (31). Nasopharyngeal (NP) and oropharyngeal (OP) swabs were collected from patients (of all ages) with influenza-like illness (ILI) who presented as outpatients at Lwak or at THC, or patients hospitalized with severe acute respiratory illness (SARI) at Lwak or SCRH. (See Appendix 4.1 for case definitions). Laboratory testing for influenza A and B viruses and RSV was performed by real-time reverse transcription polymerase chain reaction (rRT-PCR) using CDC protocols (32, 33).

4.2.4 Data analyses

Estimates of deaths associated with influenza and RSV were calculated for four mortality outcomes: (i) all-cause deaths, (ii) all-respiratory deaths, including pneumonia, (iii) HIV-related deaths, and (iv) PTB-related deaths. All-respiratory, HIV-, and PTB-related cause of death was considered for each individual

if it was listed as a cause of death. We did not estimate excess mortality for circulatory deaths associated with influenza and RSV because of the relatively low number of deaths recorded.

4.2.4.1 Descriptive analyses and handling of missing VA data

The demographic characteristics of those who died were described using medians and ranges. Wilcoxon rank-sum and Chi-square tests were used to assess if there were differences between the age and sex distributions of cases with VA-coded underlying cause of death and those without. Influenza and RSV circulation patterns were described using monthly percentages of positive results. We adjusted for missing VA data (age groups: <5, 5-49, ≥50 years, all ages), by dividing the monthly number of outcome-specific (all-causes, all-respiratory, HIV-, and PTB-related) deaths by the monthly proportion of deaths with VA done.

4.2.4.2 Estimating excess deaths using the negative binomial regression method

Negative-binomial regression models which incorporated monthly influenza and RSV circulation data and adjusted for malaria activity were used to estimate the age-specific and pathogen-associated deaths. For each age group and mortality outcome, we explored a range of models with varying combinations of time polynomial terms (up to the 6th order) and seasonal cyclical terms (starting with a full model that incorporated time polynomials, the quarterly, semiannual and annual seasonal cyclical terms). The general model equation was of the form:

$$E(Y_t) = \beta_0 + \beta_1(t) + \beta_2(t^2) + \ldots + \beta_6(t^6) + \beta_7[\sin(2t\pi/12)] + \beta_8[\cos(2t\pi/12)] + \beta_9[\sin(2t\pi/6)] + \beta_{10}[\cos(2t\pi/6)] + \beta_{11}[\sin(2t\pi/3)] + \beta_{12}[\cos(2t\pi/3)] + \beta_{13}[Influenza] + \beta_{14}[RSV] + \beta_{15}[Malaria] + \varepsilon_t$$

Where $E(Y_t)$ is the age-specific number of deaths; t is the running time variable; β_0 is the model constant; β_1 to β_6 are the coefficients for the linear and polynomial time trends; β_7 to β_{12} are the coefficients corresponding to the cyclical terms for the annual, semiannual and quarterly background seasonal variations; β_{13}, β_{14} and β_{15} are the coefficients representing the contribution of influenza, RSV and malaria respectively, and ε_t is the error term. The final model that was selected was the one for which the Akaike Information Criterion (AIC) values were minimized.

We explored using the natural cubic spline smoothing functions of time to model the background mortality as opposed to using the polynomial time trends and sinusoidal curves but the estimates were not significantly different. However, as our time series data were monthly and only analyzed over a period of seven years, we were concerned about overfitting the models when we used the spline method. The mortality estimates that we report here are based on models that incorporated sinusoidal curves to model the background mortality.

To estimate the excess mortality associated with a specific pathogen (influenza or RSV), we first calculated the predicted monthly deaths from the model that included a term for the detection of the pathogen (full model) and then subtracted the predicted deaths from the baseline model (where the

term for the detection of the pathogen was set to zero) (6, 16, 19, 34). Only positive differences between the full and the baseline model were considered. We then calculated the age-specific excess mortality rates per 100,000 person-years (PY) by dividing the average annual number of excess deaths by the population at risk. The 95% confidence intervals (CI) were estimated using bootstrap sampling (with replacement) on blocks of calendar years over 1,000 replications (34).

4.2.4.3 Estimating excess deaths using the baseline rate-difference method

In this approach, we calculated the excess deaths attributable to influenza and RSV by taking the positive difference between age-specific deaths occurring each month when there was high pathogen circulation and the monthly average of deaths that occurred during the months of low pathogen circulation (baseline months) (16, 20). Months when the percentage of influenza and RSV cases were less than 15% and 12%, respectively, were considered as the baseline months (Figure 4.2). These baselines were defined based on the upper limit of the 95% CI on the mean pathogen detection rate over the study period (Appendix 4.1).

To avoid double counting deaths for months where both influenza and RSV activity exceed these thresholds, we apportioned excess deaths for each pathogen proportionate to how the pathogen activity deviated from the stated thresholds (15% and 12%) (Appendix 4.1). Excess mortality rates were calculated as the mean annual number of excess deaths divided by the age-specific population at risk. The Poisson approximation method was used to calculate the 95% CI around point estimates (35). In this analysis, malaria and diarrheal deaths were excluded from the all-cause death estimates as they tended to follow a seasonal pattern similar to the RSV activity pattern (Appendix Figure 4.1).

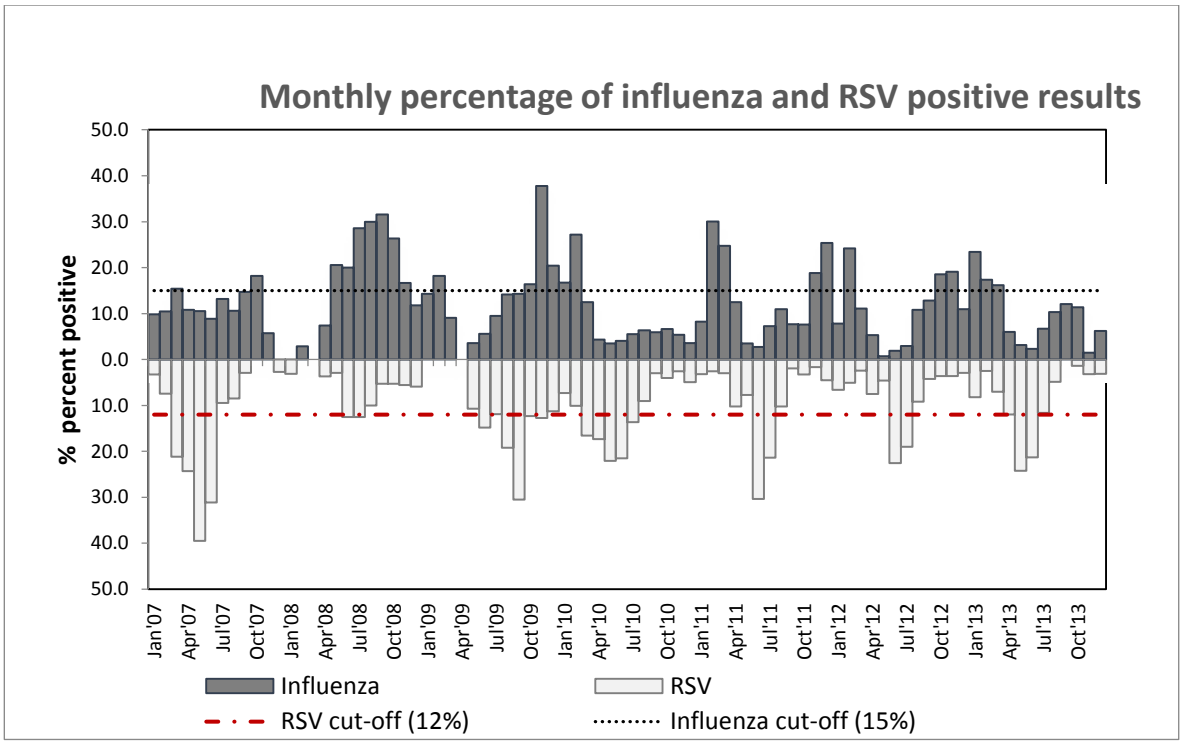

Figure 4.2: Monthly percentage of influenza and respiratory syncytial virus (RSV) positive results with cut-offs for the rate-difference method.

4.3 Ethical considerations

The HDSS protocol and consent procedures, were approved by the Ethical Review Committee of the Kenya Medical Research Institute (KEMRI SSC-1801) and the Institutional Review Board of CDC-Atlanta (CDC IRB #3308).

4.4 Results

4.4.1 Descriptive analyses

From January 2007 through December 2013, the Western Kenya HDSS population increased by 14% from 218,985 to 249,470. Over this period, there were a total of 22,899 deaths reported. Of these, 19,991 (87%) had VA conducted and a cause of death assigned. The median age of death was 32 years [interquartile range (IQR) 2-63 years]. There were no differences between those with a VA-coded cause of death and those without by sex (χ=0.8692, p=0.351). However, those without a VA-coded cause of death were younger [median age 27 years (IQR=2-46) vs. 33 years (IQR=2-65); p<0.001]. The proportion of deaths without VA data also varied by year and was highest in 2007 (17%) and lowest in 2012 (8%).

A total of 13,677 and 10,001 samples were collected and tested for influenza and RSV, respectively, over the study period. Of these, 1,620 (12%) tested positive for influenza viruses and 1,022 (10%) tested positive for RSV. The average monthly percentage of tested patients who were positive for influenza was 12% (95% CI 10-14) and for RSV was 9% (95% CI 7-11) (Figure 4.2, and Appendix Figure 4.1). Malaria parasites were detected in 43% of all patients evaluated over the entire study period.

4.4.2 Overall mortality rates and trends

Over the study period, the mean annual all-causes mortality rate was 1,446 (95% CI 1,397-1,497)/100,000 PY. Among children <5 years the annual all-causes mortality rate ranged from 1,827 to 5,059 deaths per 100,000 PY (lowest in 2012 and highest in the 2008), for a mean of 2,965 (95% CI 2,791-3,150)/100,000 (Table 4.1 and Figure 4.3). Among persons aged ≥5 years, the annual all-causes mortality rate ranged from 953 to 1,456 per 100,000 PY for a mean of 1,163 (95% CI 1,115-1,212)/100,000 PY. The mean annual all-respiratory mortality rate was 148 (95% CI 133-164)/100,000 PY, and among children <5 years was 513 (95% CI 443-593)/100,000 PY]. The mean annual mortality rates for HIV- and PTB-related deaths were 275 (95% CI 254-298) and 186 (95% CI 169-204) per 100,000 PY, respectively.

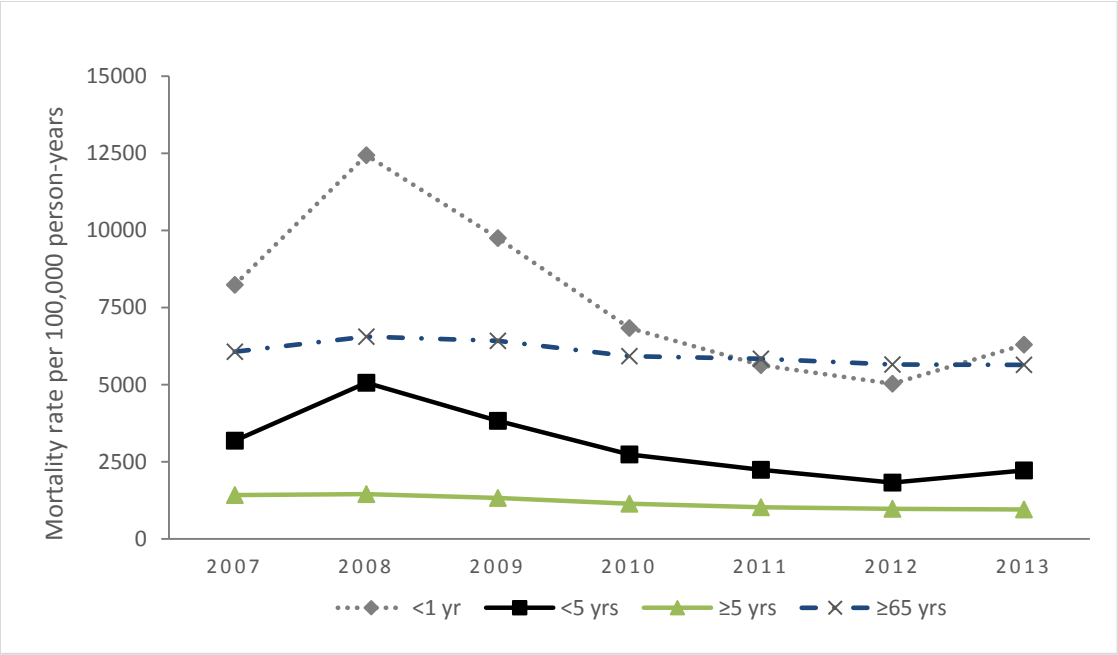

Figure 4.3: Age-specific trends in all-causes mortality rates in Western Kenya, 2007-2013

4.4.3 Influenza- and RSV-associated deaths using the negative binomial regression method

Using the negative binomial regression method, the mean annual excess all-causes mortality rate associated with influenza activity was 14.1 (95% CI 0.0-93.3)/100,000 PY; and was highest among persons aged ≥50 years (74.0 [95% CI 0.0-310.4]/100,000 PY) (Table 4.2 and Figure 4.4). Similarly, the mean annual excess mortality rate for all-respiratory deaths was highest among persons aged ≥50 years (34.6 [95% CI 0.0-81.0]/100,000 PY). Among children aged <5 years, the mean annual excess mortality rate of all-respiratory deaths associated with influenza was 16.7 (95% CI 0.0-78.2)/100,000 PY. The mean annual excess PTB related mortality rate was highest among persons aged ≥50 years (41.6 [95%CI 0.0-122.7]/100,000 PY).

The mean annual excess all-causes mortality rate associated with RSV was 17.1 (95% CI 0.0-111.5)/100,000 PY. In contrast to influenza, the mean annual excess RSV mortality rate for all-respiratory deaths was highest among children aged <5 years (38.5 [95% CI 0.0-109.9]/100,000 PY) (Table 4.3 and Figure 4.5).

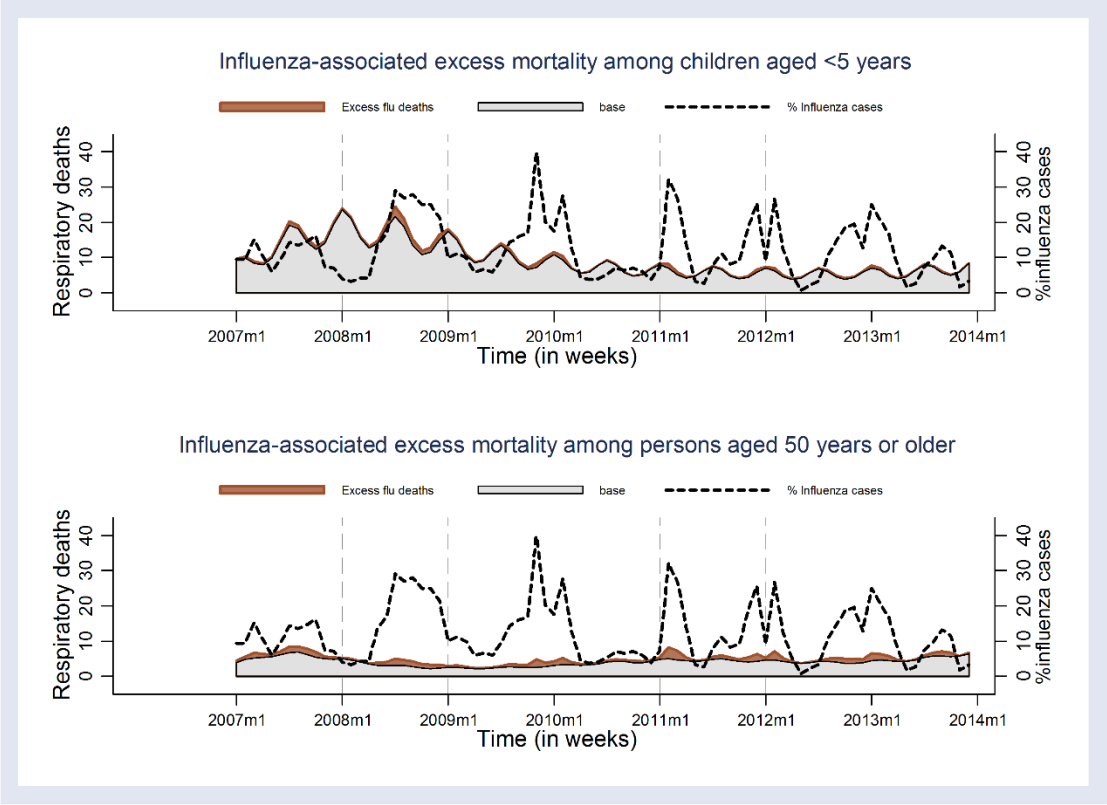

Figure 4.4: Excess deaths estimated using the negative binomial regression model that were associated with influenza among children aged <5 years and persons aged ≥50 years, 2007-2013

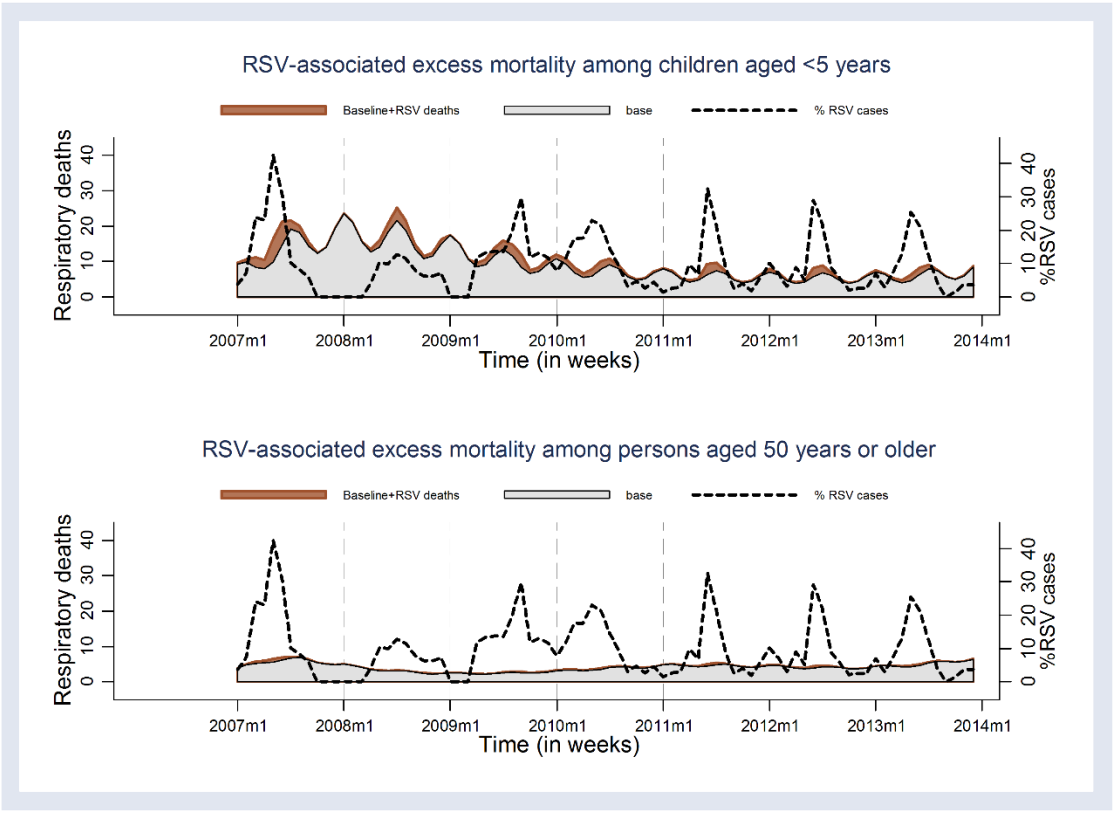

Figure 4.5: Excess deaths estimated using the negative binomial regression model that were associated with RSV among children aged <5 years and persons aged ≥50 years, 2007-2013

4.4.4 Excess deaths using the rate-difference method

The mean annual excess all-causes mortality rate using the rate difference method was 44.8 (95% CI 36.8-54.4)/100,000 PY. All-respiratory influenza-associated mortality among <5 years was 62.7 (95% CI 41.3-95.1) compared to 17.7 (95% CI 7.6-41.1)/100,000 PY among ≥50 year olds. Of HIV-related deaths, the mean annual excess influenza-associated mortality rate was highest among <5 years (40.9 [95% CI 24.4-68.6] /100,000 PY), whereas PTB related mortality rate associated with influenza was highest among persons aged ≥50 years (41.8 [95% CI24.1-72.3] /100,000 PY) (Table 4.2).

The mean annual excess all-causes mortality rate associated with RSV was highest among <5 years (90.3 [95% CI 63.8-127.8]/100,000 PY) (Table 4.3). Rate estimates of all-respiratory deaths associated with RSV was highest among children <5 years (38.1 [95% CI 22.3-65.0]/ 100,000 PY), whereas among persons aged ≥50 years was 4.7 (95% CI 0.9-24.1) /100,000 PY).

4.5 Discussion

Using two different methods (negative binomial regression and the rate-difference), our study showed that both influenza and RSV are associated with mortality among children <5 years, and adults ≥50 years. The two estimation methods were consistent, for most of the mortality outcomes and age groups considered, in showing the segments of the population with high mortality burden.

The rate-difference estimation approach has been suggested for estimating excess deaths where there are multiple peaks with no clear seasonality patterns, or where there is only a limited time series of data available (less than five years of data) (16). However, its major drawback is its inability to account for the effect of other pathogens that co-circulate with the pathogen investigated. In a region like Western Kenya where malaria is endemic and RSV sometimes overlaps with influenza activity (13), the rate-difference method could potentially overestimate influenza-associated excess deaths. Unlike the case with the rate-difference method, the negative binomial regression models were adjusted for the effect of RSV/influenza and malaria. This could partially explain the consistently lower estimates using this method when compared to estimates obtained using the rate-difference method.

Our estimates of all-causes excess mortality associated with influenza are comparable to estimates from Singapore (36), Hong Kong (37-39), and New Zealand (40) among persons of all ages. Estimates of all-respiratory excess deaths associated with influenza among children <5 years were comparable to the estimates reported in South Africa (6), but over ten-fold higher than rates reported in the United States (7, 41). The PTB related excess mortality that was associated with influenza was higher among persons ≥50 years compared to children, consistent with other studies (34), highlighting the risk for influenza-associated complications among PTB patients and the potential impact of influenza vaccination in areas of high prevalence of PTB. Because of the relatively low number of deaths, we were not able to estimate the excess HIV-related deaths that were associated with influenza for various age groups using the negative binomial regression method. However, estimates from the rate-difference method suggest an important HIV-related mortality associated with influenza among children aged <5 years. Further analysis may be warranted when more data become available as studies conducted in South Africa have

suggested a higher mortality rate associated with influenza among persons with HIV compared to those without (6, 8).

Although the confidence intervals suggest comparable all-respiratory mortality rates associated with influenza and RSV among children aged <5 years, using the negative binomial regression method, our study found relatively higher point estimates for mortality rates in this age group associated with RSV compared to influenza, which is consistent with findings from studies conducted elsewhere (7, 41). The estimates of excess mortality associated with RSV were higher than rates reported in South Africa (6), and in the United States (7, 41). We also noted a high all-cause mortality associated with RSV among persons aged ≥50 years, which was similar to that associated with influenza and consistent with other studies that have suggested RSV as an important cause of morbidity and mortality among older adults (41, 42).

It is not clear which death outcome category is more appropriate to characterize excess mortality associated with influenza or RSV in countries where these diseases have no marked seasonality and where there are competing causes of deaths such as malaria, PTB, and HIV. As in other studies (8, 17, 39, 43), our estimates for all-causes excess mortality were higher than estimates for all-respiratory excess mortality for both influenza and RSV due to its low specificity. In appreciation of this challenge, most of studies try to make estimates available using several death outcomes including pneumonia and influenza and cardiovascular disease (7, 8, 17); however, the underlying characteristics of the population in sub-Saharan Africa may differ from that in temperate countries which may limit the utility of this approach.

Our study was subject to several limitations. First, our study was underpowered to estimate mortality using regression methods for finer age groups, and due to few data points (particularly for RSV), estimates had wide confidence intervals, particularly when using negative-binomial of which all overlapped with zero. This could also be the reason why we did not observe statistically significant excess mortality estimates associated with influenza and RSV using regression methods and supports a need for more robust datasets for estimation using negative binomial regression models. Second, we used VA data and not clinician certified cause-of-death data and thus estimates may vary as a function of the true cause of death composition in the population. Indeed, a study conducted elsewhere estimated the cause-specific mortality fraction accuracy at 0.625 and 0.629 for adults and children respectively, using verbal autopsy with the cause of death assigned using the InterVA-4 method (44). Lastly, we could not evaluate the impact of different virus subtypes on excess mortality due to limited data available.

In conclusion, our study suggests a role of influenza and RSV on excess mortality in Western Kenya, especially among children <5 years and persons ≥50 years. These data suggest that future RSV vaccines (45, 46), and vaccination of children, older adults and persons with chronic medical conditions against seasonal influenza has the potential to reduce mortality rates in Western Kenya.

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Table 4.1: Age-specific mean annual mortality rates in Western Kenya, January 2007 - December 2013

Age group	Person-years	All-cause mortality* (95% CI)	Respiratory mortality (including pneumonia)* (95% CI)	HIV-related mortality* (95% CI)	Pulmonary TB (PTB) related mortality* (95% CI)
0-11 months	6,956	7,690 (7,065-8,370)	1,896 (1,598-2,249)	704 (532-932)	0 (-)
12-23 months	7,059	3,908 (3,473-4,397)	403 (279-582)	1,139 (916-1,418)	18 (3-103)
24-59 months	21,271	1,107 (975-1,258)	97 (63-150)	203 (151-274)	6 (1-34)
<5 years	35,286	2,965 (2,791-3,150)	513 (443-593)	489 (422-568)	7 (2-25)
5-14 years	65,209	213 (181-252)	21 (13-36)	39 (26-57)	8 (3-19)
15-49 years	93,149	1,025 (962-1,092)	54 (41-71)	340 (304-379)	254 (223-288)
50-64 years	17,847	1,923 (1,730-2,137)	138 (93-204)	395 (313-499)	364 (286-464)
≥65 years	12,737	5,964 (5,554-6,403)	482 (376-619)	253 (180-358)	840 (695-1,015)
≥50 years	30,584	3,606 (3,399-3,825)	281 (228-347)	336 (277-408)	562 (484-653)
≥5 years	188,943	1,163 (1,115-1,212)	79 (68-93)	235 (214-258)	219 (199-241)
Total	224,228	1,446 (1,397-1,497)	148 (133-164)	275 (254-298)	186 (169-204)

*Deaths per 100,000 person-years; CI-Confidence intervals; HIV-Human immunodeficiency virus

Table 4.2: Age-specific mean annual excess mortality rate associated with influenza in Western Kenya, 2007 - 2013

Cause of death by age	Negative-binomial regression method		Rate-difference method (High[a] activity vs. baseline[b])	
	Estimated deaths	Mortality Rate* (95% CI)	Estimated deaths	Mortality Rate* (95% CI)
All causes				
<5 years	8	22.2 (0.0-145.2)	44	125.5 (93.4-168.4)
5-49 years	1	0.8 (0.0-40.0)	37	23.6 (17.1-32.5)
≥50 years	23	74.0 (0.0-310.4)	29	95.1 (66.1-136.7)
All ages	32	14.1 (0.0-93.3)	100	44.8 (36.8-54.4)
All respiratory, including pneumonia				
<5 years	6	16.7 (0.0-78.2)	22	62.7 (41.3-95.1)
5-49 years	7	4.5 (0.0-7.2)	4	2.2 (0.8-6.3)
≥50 years	11	34.6 (0.0-81.0)	5	17.7 (7.6-41.1)
All ages	24	10.5 (0.0-28.5)	22	9.6 (6.3-14.7)
HIV/AIDS				
<5 years	1	3.6 (0.0-27.3)	14	40.9 (24.4-68.6)
5-49 years	NE	NE	9	6.3 (3.4-11.7)
≥50 years	NE	NE	4	13.4 (5.1-35.2)
All ages	NE	NE	25	11.3 (7.7-16.7)
Pulmonary Tuberculosis (PTB)				
<5 years	1	2.2 (0.0-8.2)	1	2.8 (0.4-20.1)
5-49 years	10	6.5 (0.0-31.6)	27	17.4 (11.9-25.2)
≥50 years	13	41.6 (0.0-122.7)	13	41.8 (24.1-72.3)
All ages	24	10.6 (0.0-40.2)	39	17.5 (12.8-23.9)

[a]Monthly percentage of influenza positive cases ≥15%; [b]Monthly percentage of influenza cases <15%; NE-Not estimated

*Deaths per 100,000 person-years.

Table 4.3: Age-specific mean annual excess mortality rate associated with respiratory syncytial virus (RSV) in Western Kenya, 2007 - 2013

Cause of death by age	Negative-binomial regression method		Rate-difference method (High[a] activity vs. baseline[b])	
	Estimated deaths	Mortality Rate* (95% CI)	Estimated deaths	Mortality Rate* (95% CI)
All causes				
<5 years	12	32.6 (0.0-397.1)	32	90.3 (63.8-127.8)
5-49 years	6	3.7 (0.0-28.7)	9	5.5 (2.8-10.6)
≥50 years	21	68.7 (0.0-208.0)	15	48.2 (28.9-80.3)
All ages	39	17.1 (0.0-111.5)	44	19.7 (14.7-26.5)
All respiratory, including pneumonia				
<5 years	14	38.5 (0.0-109.9)	13	38.1 (22.3-65.0)
5-49 years	1	0.6 (0.0-8.4)	2	1.0 (0.2-4.8)
≥50 years	2	5.9 (0.0-29.0)	1	4.7 (0.9-24.1)
All ages	17	7.3 (0.0-27.3)	15	6.6 (3.9-11.0)
HIV/AIDS				
<5 years	1	3.7 (0.0-87.0)	19	53.7 (34.2-84.2)
5-49 years	NE	NE	11	6.7 (3.6-12.2)
≥50 years	NE	NE	3	10.9 (3.7-31.9)
All ages	NE	NE	29	13.1 (9.1-18.8)
Pulmonary Tuberculosis (PTB)				
<5 years	1	1.8 (0.0-160.3)	1	2.1 (0.2-20.5)
5-49 years	2	1.4 (0.0-31.4)	7	4.3 (2.0-9.1)
≥50 years	11	35.1 (0.0-73.4)	9	28.3 (14.5-55.1)
All ages	14	6.0 (0.057.6)	12	5.2 (2.9-9.2)

[a]Monthly percentage of RSV positive cases ≥12%; [b]Monthly percentage of RSV cases <12%; NE-Not estimated

*Deaths per 100,000 person-years.

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Appendix 4.1: Supplementary Methods

Case definitions

Influenza-Like Illness

For patients of all ages, influenza-like illness was defined as an axillary temperature ≥38^{o}C and cough or sore throat in an outpatient (1, 2).

Severe Acute Respiratory Illness (SARI)

SARI was defined differently for children under five years and for persons aged ≥5 years. Among children aged <5 years, SARI was defined using a modified version of the World Health Organization's Integrated Management of Childhood Illness (IMCI) definition for pneumonia. This was defined as hospitalization with cough OR difficulty breathing, AND at least one of (maternal report of lower-chest wall in-drawing, stridor in a calm child, unable to drink or breast feed, vomiting, convulsions, lethargic or unconscious, oxygen saturation <90%). Among persons aged 5 years, SARI was defined as hospitalization with cough OR difficulty breathing OR shortness of breath AND a documented fever (≥38^{o}C) (1, 2). At Lwak Mission hospital, a modified "SARI" case definition that did not require hospitalization was used. Among children <5 years, SARI was defined as defined as cough OR difficulty breathing, AND at least one of (inability to drink or breastfeed, vomiting everything, convulsions, lethargy or unconscious, lower-chest wall in-drawing, stridor, oxygen saturation <90%). For persons aged ≥5 years, SARI was defined as cough OR difficulty breathing OR chest pain, AND a documented axillary temperature of ≥38.0°C OR and oxygen saturation level of ≤90% (1).

Verbal autopsy data

The InterVA-4 model software which was introduced in the year 2009 was used to assign the possible cause of death. To maintain uniformity, data that were collected prior to its introduction were re-assigned a cause of death using the InterVA-4 software. It is important to mention that data from this HDSS area were included in a multi-country study that compared the physician–coded verbal autopsy (PCVA) cause of death to the cause of death as determined by the InterVA-4 model (3). Results from this analysis showed a very strong correlation 0.83 (95% CI 0.75 to 0.91) among the five participating countries. Specifically for the Western Kenya HDSS data (with 21,236 deaths), the correlation was 0.85 (95% CI 0.79 - 0.92) (3). Table 1 below shows the cause-of-death list for the mortality outcomes that we considered with the corresponding ICD-10 codes (4).

Appendix Table 4.1: Cause-of-death list for verbal autopsy with corresponding broad ICD-10 codes

Verbal autopsy title	ICD code	ICD title
Tuberculosis	A159	Respiratory tuberculosis, unspecified, confirmed bacteriologically and histologically
	A169	Respiratory tuberculosis, unspecified, without mention of bacteriological or histological confirmation
	A179	Tuberculosis of nervous system, unspecified
	A192	Acute miliary tuberculosis, unspecified
	A199	Miliary tuberculosis, unspecified
HIV/AIDS	B209	HIV disease resulting in unspecified infectious or parasitic disease
	B219	HIV disease resulting in unspecified malignant neoplasm
	B227	Human immunodeficiency virus [HIV] disease resulting in multiple diseases classified elsewhere
	B238	Human immunodeficiency virus [HIV] disease resulting in other specified conditions
	B24	Unspecified human immunodeficiency virus [HIV] disease
Acute lower respiratory infections (including pneumonia and acute bronchitis)	J129	Viral pneumonia, unspecified
	J159	Bacterial pneumonia, unspecified
	J180	Bronchopneumonia, unspecified
	J181	Lobar pneumonia, unspecified
	J182	Hypostatic pneumonia, unspecified
	J189	Pneumonia, unspecified

Defining influenza and RSV 'baseline' and 'activity months'

Contrary to temperate countries which are characterized by distinct seasons (5, 6), influenza and RSV are detected in Kenya almost throughout the year (1, 2, 7) without distinct periods of activity, which is particularly true for influenza. We therefore used a cut-off defined using the average monthly percentage of cases detected to define the 'baseline' and 'increased activity' months for influenza and RSV that were used for the estimation of excess mortality using the rate-difference method. From the distribution of the monthly percentage of influenza positive cases over the entire study period, we determined that the average was 12% (95% CI 10-14). Months where ≥15% (higher than the upper confidence limit on the average percentage) cases of influenza were detected were classified as increased influenza activity months. Similarly, the average monthly percentage of RSV cases was 9% (95% CI 7-11) and months where ≥12% cases of RSV were detected were classified as increased RSV activity months.

Dealing with potential double counting of deaths in the rate-difference method

The following steps were applied in calculating excess deaths associated with influenza and RSV for months when the activity index of both pathogens exceeded the stated thresholds (15% and 12% for influenza and RSV respectively):

1. We standardized the activity index variables (based on the monthly percentage of influenza and RSV cases)
2. The excess deaths were then calculated as the positive difference between the monthly number of deaths and the average monthly number of deaths that occurred when the pathogen circulation was low (<15% and <12% for influenza and RSV respectively).
3. Excess deaths were then apportioned on the basis of pathogen activity, as indicated by the standardized pathogen index as shown below:

$$Excessdeaths_{flu} = \left(Excessdeaths \times \frac{Z_{flu}}{Z_{flu} + Z_{rsv}} \right)$$

Where:
$Excessdeaths_{flu}$ = Excess deaths associated with influenza activity for a specific month
$Excessdeaths$ = Excess deaths for a specific month over the average monthly number of deaths that occurred during the months of low influenza activity
Z_{flu} = Standardized index for influenza activity for a specific month
Z_{rsv} = Standardized index for RSV activity for a specific month

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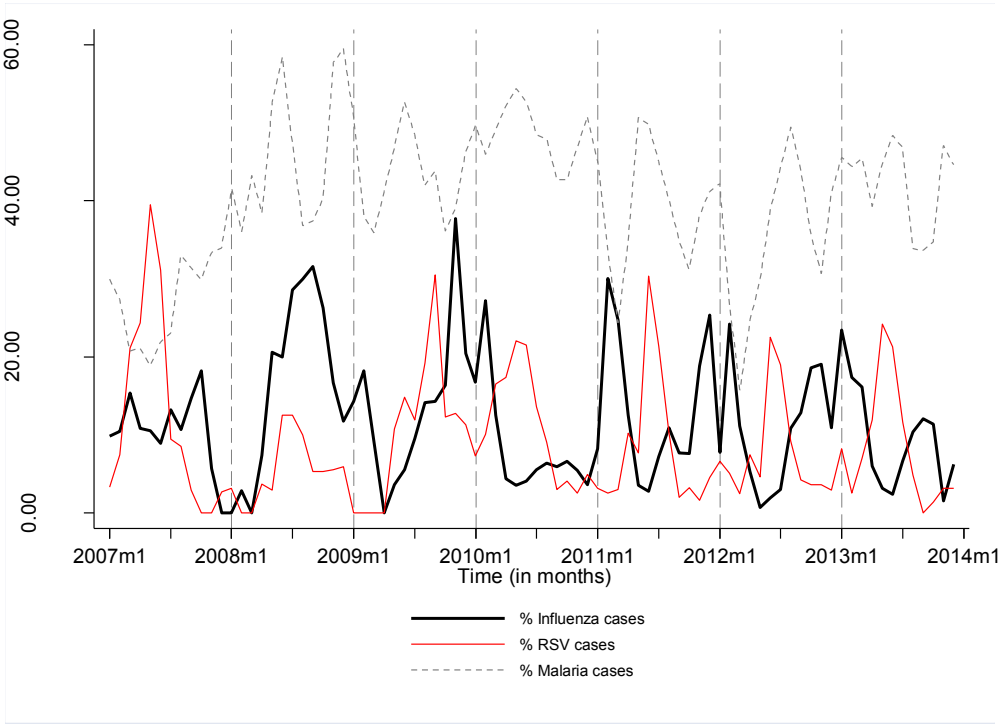
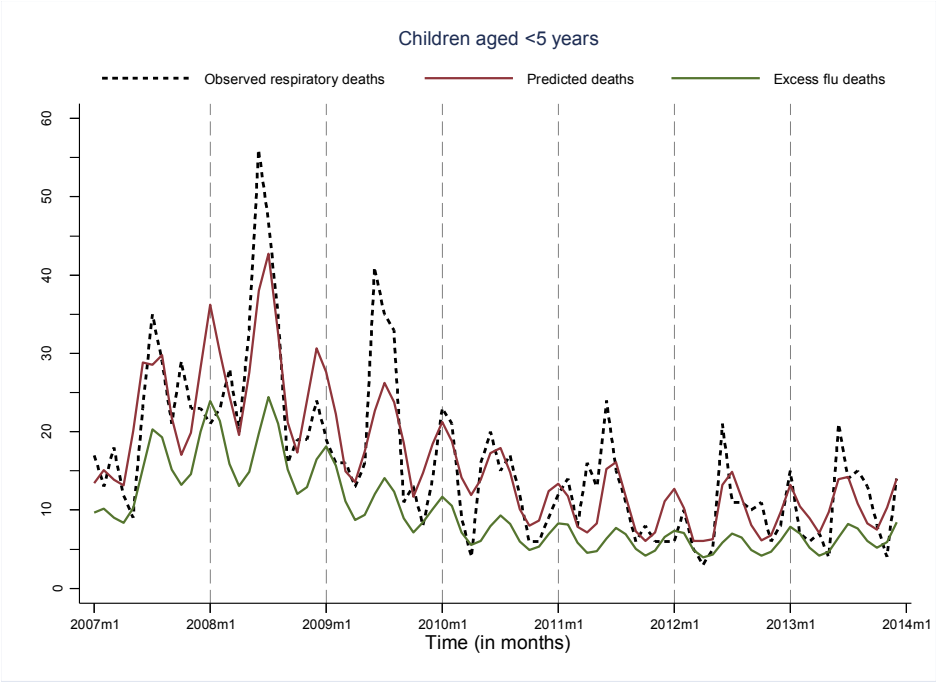
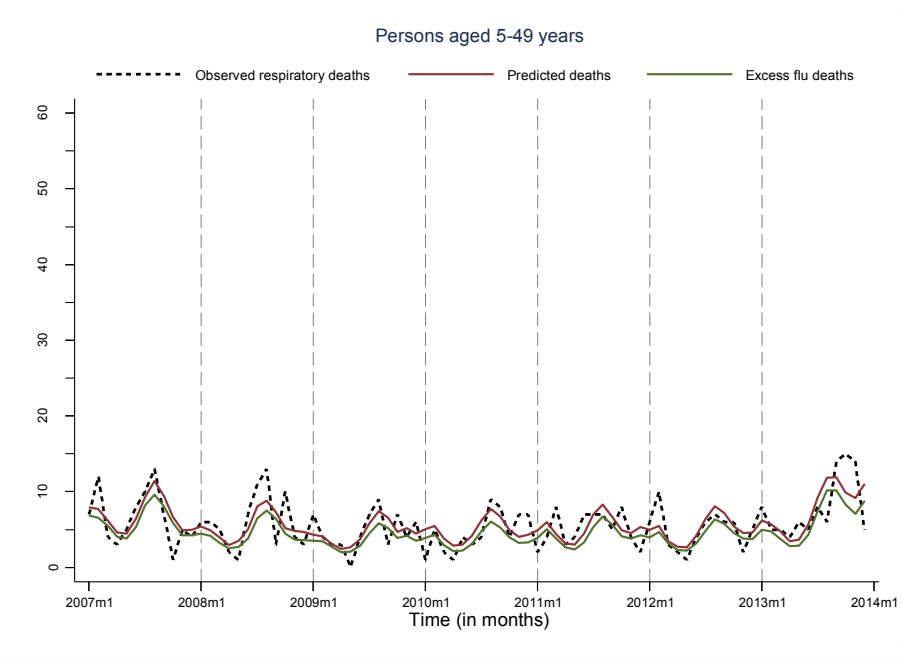


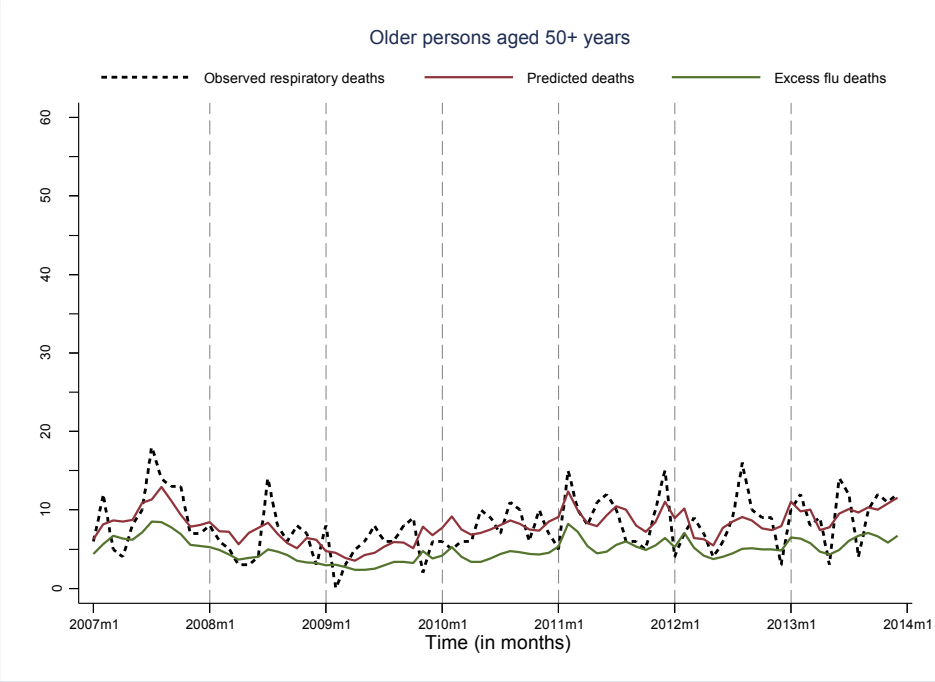
Appendix Figure 4.1: Influenza, RSV and malaria activity patterns in Western Kenya, 2007-2013



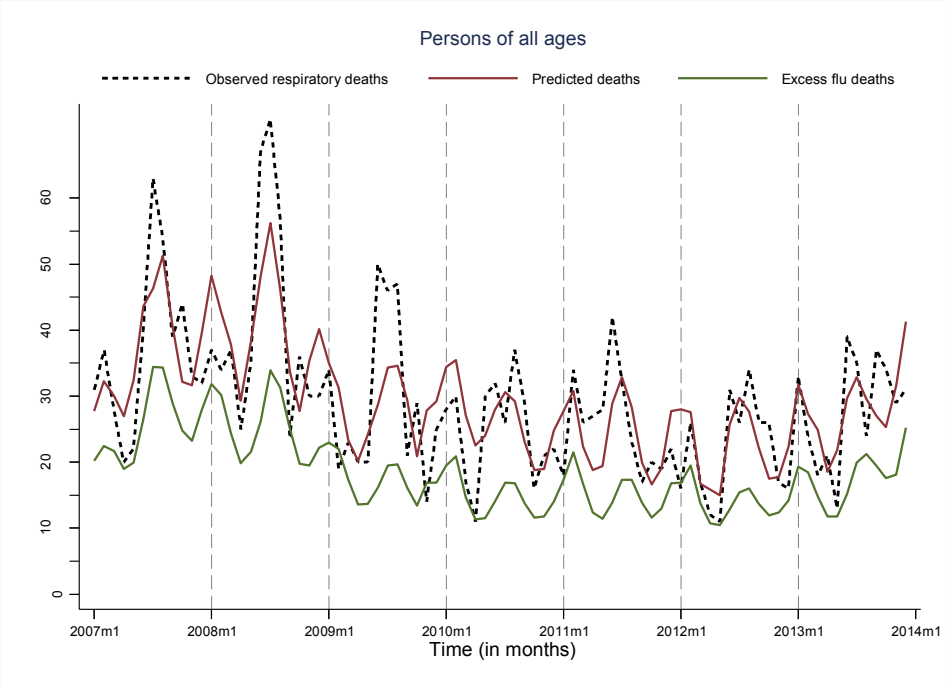
Appendix Figure 4.2: Graph showing the observed all-respiratory deaths, predicted deaths, and baseline for children aged <5 years, 2007–2013



Appendix Figure 4.3: Graph showing the observed all-respiratory deaths, predicted deaths, and baseline for persons aged 5-49 years, 2007-2013



Appendix Figure 4.4: Graph showing the observed all-respiratory deaths, predicted deaths, and baseline for persons aged ≥50 years, 2007-2013



Appendix Figure 4.5: Graph showing the observed all-respiratory deaths, predicted deaths, and baseline for persons of all ages, 2007-2013

Chapter 5: The role of HIV in the household introduction and transmission of influenza in an urban slum, Nairobi, Kenya, 2008-2011

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Abstract

Background: Little is known about how HIV infection affects influenza transmission within homes in sub-Saharan Africa.

Methods: We used respiratory illness surveillance and HIV testing data gathered in Kibera, an urban slum in Nairobi, Kenya to examine the impact of HIV status on i) introducing influenza to the home and ii) transmission to household contacts.

Results: While HIV status did not affect the likelihood of being an influenza index case, household contacts of HIV-infected influenza index cases had twice the risk of developing secondary ILI than contacts of HIV-negative index cases.

Conclusions: HIV-infected influenza index cases may facilitate transmission of influenza within the home.

5.1 Introduction

Studies of household influenza transmission dynamics have mostly taken place outside of densely-populated, urban settings in sub-Saharan Africa (1-3). However, this region may have distinct influenza transmission patterns due to the high prevalence of HIV infection (4).

We conducted a retrospective cohort study of 176 households in an urban slum in Nairobi, Kenya using household and clinic data gathered during 2008 -2011 to examine i) the association between the HIV status of household members and their risk of introducing influenza to the home, and ii) whether the HIV status of index cases of influenza impacts risk of developing secondary influenza-like illness (ILI) among their household contacts.

5.2 Methods

5.2.1 Study site

We analyzed respiratory illness data and HIV testing data from a Kenya Medical Research Institute (KEMRI) and Centers for Disease Control and Prevention-Kenya (CDC) active population-based infectious disease surveillance (PBIDS) site in the urban slum of Kibera, Nairobi, Kenya (5).

5.2.2 Household and clinic data collection

Approximately 28,000 PBIDS enrollees with a median (IQR) follow-up time of 2.5 (1.0-3.8) person-years in 6,000 households are being followed prospectively. Trained community interviewers regularly visit and interview all participating households for persons reporting symptoms of diarrhea, fever, jaundice, and respiratory illness occurring within the past two weeks. These interviewers encourage participants who report illnesses to go to the Tabitha Clinic, a local medical facility owned by Carolina for Kibera Inc. (Chapel Hill, NC) and supported by KEMRI and CDC. (5).

In 2008, all adult PBIDS enrollees (≥18 years) were offered the option to consent and participate in a home-based HIV testing and counseling (HBTC) program (6), while more restricted enrollment was offered to enrollees <18 years of age. Among 10,673 individuals who were offered HBTC, 83% accepted. Participants not accepting HBTC at PBIDS enrollment and those enrolled after 2008 had access to voluntary clinic-based testing at the free medical facility (6).

5.2.3 Case Definitions Used for Influenza Testing at Tabitha Clinic

All persons with severe acute respiratory infection (SARI) and the first five daily cases of influenza-like illness (ILI) reporting to Tabitha clinic were tested for influenza. ILI was defined as an acute onset (<14 days) with a recorded temperature ≥ 38.0°C or home-reported "hotness of body" and cough or sore throat in a patient of any age. For children <5 years, SARI was defined as acute onset (<14 days) of cough or difficulty breathing and ≥1 of the following danger signs: chest in-drawing; stridor in a calm child; oxygen saturation <90%; unable to breastfeed or drink; vomits everything; convulsions; lethargy; unconsciousness; admitted with respiratory illness. For persons ≥5 years of age, SARI was defined as cough or difficulty breathing or chest pain with acute onset (<14 days) and either temperature ≥38.0°C or oxygen saturation <90%.

5.2.4 Clinic-based testing for influenza

Consenting patients provided verbal responses to a standardized questionnaire and had nasopharyngeal and oropharyngeal (NP/OP) specimens collected by trained medical personnel at the study clinic. Specimens were tested at the KEMRI-CDC laboratory in Nairobi by real time reverse transcription polymerase chain reaction (PCR) for influenza A and B with additional influenza A subtyping (7).

5.2.5 Influenza index cases and secondary cases in the household

Laboratory-confirmed influenza cases were linked to their households by study identification numbers. Household index cases of influenza were then identified as the first study participants with laboratory-confirmed influenza in a household of known HIV status where no other member had reported or been diagnosed with ILI or SARI within the past two weeks. Only households with influenza index cases and known household HIV status were included in the study.

After the influenza index cases were identified, we defined a secondary ILI case as any household contact of the index case that developed ILI within two weeks. Over 95% of cases were home reported. All secondary ILI cases were also secondary SARI cases. We selected a two-week follow-up period to account for approximately two influenza infectious periods (8). The overall secondary attack rate (SAR) for ILI was defined as the proportion of household contacts developing ILI within 14 days after index case identification.

5.2.6 Individual and household-level HIV status

Individual HIV status was defined as the most recent result of an HIV test conducted up to 18 months after household influenza index case identification. Persons whose HIV status was not determined by the HBTC in 2008 or by voluntary testing at the study clinic during the study period were regarded as having unknown HIV status. Among study participants with known HIV status, 24% had their most recent test via HBTC. An HIV-positive household was defined as one in which ≥1 member was found to be HIV-infected by a test conducted up to 18 months after influenza index case identification. An HIV-negative

household was defined as a household that had ≥3 members who tested HIV-negative, or a household where ≥ 50% of the household tested negative for HIV, and no one was HIV-infected.

5.2.7 Bivariate analysis

We used bivariate log-binomial generalized estimating equation (GEE) models accounting for household clustering to assess crude relative risks between independent variables and i) the influenza index case status of household members, as well as ii) development of ILI among household contacts of influenza index cases (9). Independent variables included individual HIV status of the index cases and household contacts, age group of each household member at time of index case identification, household size, and gender.

5.2.8 Multivariate analysis

The variables included in the two multivariate log-binomial GEE models, also accounting for household clustering, demonstrated a significant association with the respective outcomes in bivariate analyses and substantially changed the regression parameter of the primary exposure variable (by ≥10%) after being added to the model. The first multivariate model compared 176 influenza index cases to their 874 household contacts in 176 households; predictors of influenza index case status included individual HIV status, age group of household members, and their respective household sizes. The second model compared 72 household contacts with ILI to the 802 household contacts without ILI; predictors of secondary ILI development included age groups of all household contacts and HIV status of their respective household index cases. Statistical analysis was performed using SAS 9.3 for Windows (SAS Institute, Cary, NC) and Stata 12 for Mac OS 10.7.5 (StataCorp, College Station, TX).

5.3 Ethical considerations

The protocol for data collection and written consent forms were reviewed and approved by the ethical review committees of the Centers for Disease Control and Prevention (Atlanta, GA; protocol number 4566) and the Kenya Medical Research Institute (Nairobi, Kenya; protocol number 932).

5.4 Results

5.4.1 Description of the Study Population

After exclusions, our sample (n=1,050) consisted of 176 households, each with an influenza index case and a known household HIV status (Appendix Table 5.1). In addition to the 176 laboratory-confirmed influenza index cases, there were 874 household contacts in these households. Of the influenza index cases, 10 (6%) were HIV-infected, 57 (32%) HIV-negative, and 109 (62%) were HIV status unknown. Of the 874 household contacts, 55 (6%) were HIV-infected, 398 (46%) HIV-negative, and 421 (48%) were HIV status unknown. Among the 874 household contacts, there were 72 (8%) secondary ILI cases (5 HIV-infected, 31 HIV-negative, and 36 HIV unknown) and 802 household contacts with no ILI (50 HIV-infected, 367 HIV-negative, and 385 HIV unknown) (Appendix Figure 5.1).

Influenza types and subtypes for the household index cases are summarized in Appendix Table 5.2. The median (range) age of index cases was 8.3 (0.2 – 48.1) years; 49% were male. Among those with known HIV status, HIV seroprevalence (95% CI) was 15% (7 – 26).

The median (range) age among secondary ILI cases was 6.3 (0.3 – 52.4) years; 46% were male. Among those with known HIV status, HIV seroprevalence (95% CI) was 14% (2 – 26). Household contacts with no secondary ILI had a median (range) age of 19.2 (0.1 – 66.1) years and 47% were male. Among those with known HIV status, HIV seroprevalence (95% CI) was 12% (9 – 15).

The average (95% CI) household secondary attack rates (SARs) due to influenza by year during 2008, 2009, 2010, and 2011 were 9% (1-17), 6% (4-9), 10% (4-15), and 6% (2-11), respectively. The unadjusted SAR was significantly higher in the 8 homes with an HIV-infected index case and no HIV-positive household contacts (26%) than in the 45 homes with an HIV-negative index case and no HIV-positive household contacts (8%) (7/27 vs. 18/239, p=0.002).

5.4.2 Risk factors for influenza introduction to the household

In the multivariate model, being HIV infected was not significantly associated with household influenza index case status (as compared to having known HIV-negative status from testing) when controlling for age of each household member and household size. However, younger age and smaller household size remained significantly associated with index case status (Table 5.1).

5.4.3 Risk factors for secondary transmission within the household

In the multivariate model, the risk of being a secondary ILI case when the household influenza index case was HIV-infected was about two times the risk of being a secondary ILI case when the household index case was HIV-negative, adjusting for age group of the household contacts (aRR: 2.36, 95% CI: 1.19, 4.66). Being an HIV-infected household contact of the index case was not significantly associated with the development of secondary ILI, compared to being an HIV-negative household contact (Table 5.2).

5.5 Discussion

To our knowledge, this is the first study to investigate the effects of HIV infection on household influenza transmission dynamics in a densely-populated, urban setting in sub-Saharan Africa. After age-adjustment, household contacts of HIV-infected influenza index cases were about twice as likely to develop ILI as household contacts of HIV-negative influenza index cases—a finding that may be explained by prior observations that HIV-infected individuals shed infectious pathogens in general (10) and influenza viruses in particular in higher titers and for longer periods of time than HIV-negative individuals (11, 12).

Children were more likely to be index cases than adults. While our findings may simply reflect an increased burden of influenza in younger children in general, these results are consistent with studies that suggest young and school-aged children are most likely to become infected with influenza due to increased socially-mediated exposure and biologic susceptibility (1), and that they often introduce influenza into their homes (13).

Using a relatively conservative window of two weeks, we observed an unadjusted SAR for ILI of 8% in exclusively HIV-negative homes in Kibera. Overall influenza-associated SARs during each year of our study were not substantially different than the recent comparative observational study conducted in Hong Kong that found average (95% CI) SARs of 8% (3-14) and 9% (5-15) from pandemic and seasonal influenza viruses, respectively (2).

There were multiple limitations to this study. We lacked the influenza virus shedding data for our index cases to quantitatively support prior observations of high titer and prolonged pathogen shedding. Another limitation was sub-optimal coverage of HIV testing and counseling, especially among younger individuals, which led to significant numbers of study participants with unknown HIV status. However, a relatively low overall estimated HIV seroprevalence of 3% for persons <18 years (14) would somewhat limit the number of missed HIV-positive children. Limited testing and refusal of testing likely reduced our power to evaluate the impact of HIV on influenza transmission, and perhaps also limited the representativeness of our study population. Finally, data on median CD4 counts and on highly active anti-retroviral treatment (HAART) among HIV-infected individuals were not available. Therefore, we assumed HIV-infected individuals had all progressed to a state of meaningful immunosuppression.

Despite these limitations, this study suggests that an ancillary benefit of HIV control prevention and programs may be to reduce the spread of influenza in homes. Furthermore, coupled with the knowledge that HIV-infected individuals are at an elevated risk for severe clinical symptoms and mortality (15, 16), our findings highlight the potential value of thoughtful delivery of effective influenza vaccines to HIV-infected individuals.

Acknowledgements: We thank all study participants and their families. We also thank the Kibera community interviewers and data team, Warren Dalal, Becky Bunnel, Danny Feikin, Heather Burke, Andrea Kim, Kevin DeCock, and Philip Brachman.

Table 5.1: Risk Factors for Introducing Influenza to the Household as an Index Case Among 1050 Household Members, Kibera, Kenya, 2008–2011

Risk Factor	All Household members	Index cases[a]	Index case status, RR (95% CI)[b]	
	n(%)	n(%)	Unadjusted	Adjusted
Individual HIV status				
Positive	65 (6)	10 (15)	3.30 (2.00–5.46)	1.23 (.55–2.75)
Unknown	530 (51)	109 (21)	1.21 (.65–2.24)	1.05 (.74–1.48)
Negative	455 (43)	57 (13)	1.00	1.00
Age (years)				
<2	66 (6)	26 (39)	17.66 (10.19–30.62	5.69 (3.67–8.82)
2–4	109 (10)	30 (28)	7.88 (3.87–16.05)	3.83 (2.40–6.11)
5–17	380 (36)	74 (19)	4.10 (1.84–9.12)	3.08 (2.02–4.71)
≥18	495 (47)	46 (9)	1.00	1.00
Persons/household (number)				
≤6	412 (39)	102 (25)	3.44 (3.18–3.72)	3.14 (2.73–3.61)
>6	638 (61)	74 (12)	1.00	1.00
Sex				
Male	496 (47)	87 (17)	1.15 (.64–2.06)	-
Female	554 (53)	89 (16)	1.00	

Abbreviation: HIV, human immunodeficiency virus.

[a]Index cases are defined as study participants who had laboratory-confirmed influenza in a household with a known HIV status where no other member had reported or received a diagnosis of influenza-like illness or severe acute respiratory infection within the past 2 weeks. In households with >1 laboratory-confirmed influenza case within a 2-week period, the first with a nasopharyngeal or oropharyngeal swab specimen testing positive for influenza virus by reverse transcription–polymerase chain reaction analysis was designated as the index case.

[b]Unadjusted relative risks (RRs) and 95% confidence intervals (CIs) were computed using a generalized estimating equations (GEE) log-binomial bivariate model, and adjusted RRs and 95% CIs were computed using a GEE log-binomial multivariate model.

Table 5.2: Risk Factors for Secondary Influenza-Like Illness (ILI) Among 874 Household Contacts of Influenza Virus–Positive Index Cases, Kibera, Kenya, 2008–2011

Risk Factor	All household contacts	Secondary ILI cases[a]	Secondary ILI status, RR(95% CI)[b]	
	n(%)	n(%)	Unadjusted	Adjusted
HIV status of household index case				
Positive	33 (4)	8 (24)	3.40 (1.52–7.63)	2.36 (1.19–4.66)
Unknown	538 (62)	43 (8)	1.14 (.65–2.00)	1.27 (.72–2.21)
Negative	303 (35)	21 (7)	1.00	1.00
HIV status of household contact				
Positive	55 (6)	5 (9)	1.22 (.54–2.76)	-
Unknown	421 (48)	36 (9)	1.12 (.71–1.77)	-
Negative	398 (46)	31 (8)	1.00	
Age of household contact (years)				
<2	40 (5)	16 (40)	6.73 (3.99–11.35)	6.56 (3.96–10.85)
2–4	79 (9)	14 (18)	3.20 (1.87–5.50)	3.02 (1.73–5.27)
5–17	306 (35)	17 (6)	1.00 (.61–1.64)	1.01 (.61–1.66)
≥18	449 (51)	25 (6)	1.00	1.00
Age of household index case (years)				
<18	661 (76)	48 (7)	0.64 (.38–1.08)	-
≥18	213 (24)	24 (11)	1.00	
Persons/household (number)				
≤6	310 (35)	31 (10)	1.39 (.81–2.36)	-
>6	564 (65)	41 (7)	1.00	
Sex				
Male	409 (47)	33 (8)	0.89 (.60–1.32)	-
Female	465 (53)	39 (8)	1.00	

Abbreviation: HIV, human immunodeficiency virus.

[a]Secondary ILI cases are defined as any member of the same household as the index case who had home reported or clinically diagnosed ILI within 2 weeks of index case identification.

[b]Unadjusted relative risks (RRs) and 95% confidence intervals (CIs) were computed using a generalized estimating equations (GEE) log-binomial bivariate model, and adjusted RRs and 95% CIs were computed using a GEE log-binomial multivariate model.

Appendix Table 5.1: Characteristics of 176 Households Meeting Study Inclusion Criteria, Kibera, Kenya, 2008-2011

Household characteristics	
Median (range) size, persons	6 (2-15)
Mean (95% CI) household age, years	19.4 (18.6-20.2)
HIV-positive households (n)	32
With 1 HIV-infected person	26
With 2 HIV-infected persons	6
Median (range) persons tested for HIV	3 (1-7)

Appendix Table 5.2: Influenza types and subtypes cultured from household index cases of influenza, Kibera, Kenya, 2008-2011

Type, Subtype	n (%)
Influenza A	
Pandemic H1N1	59 (33)
H3N2	47 (26)
H1N1	21 (12)
Subtype Inconclusive	14 (8)
Influenza B	38 (21)

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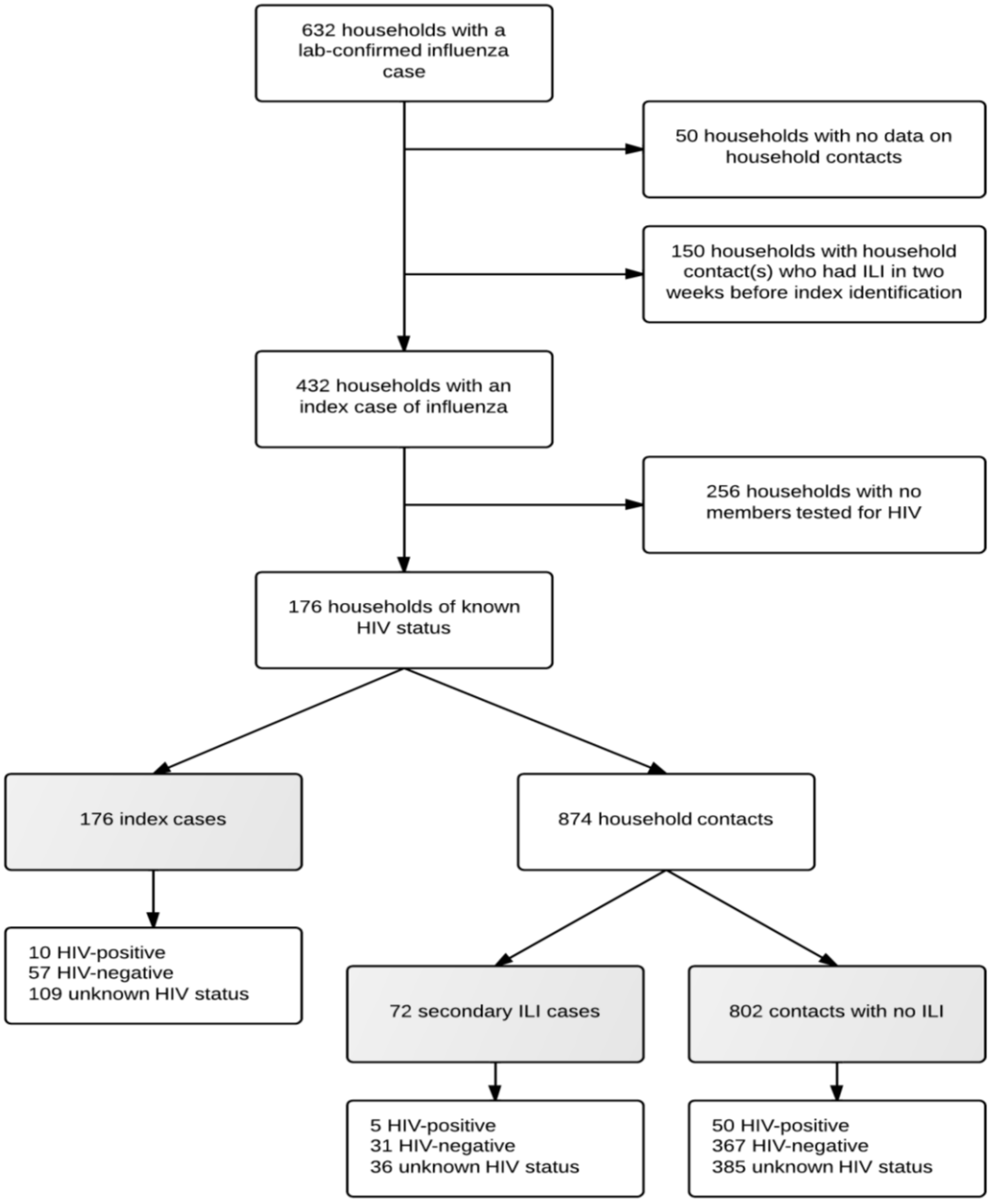
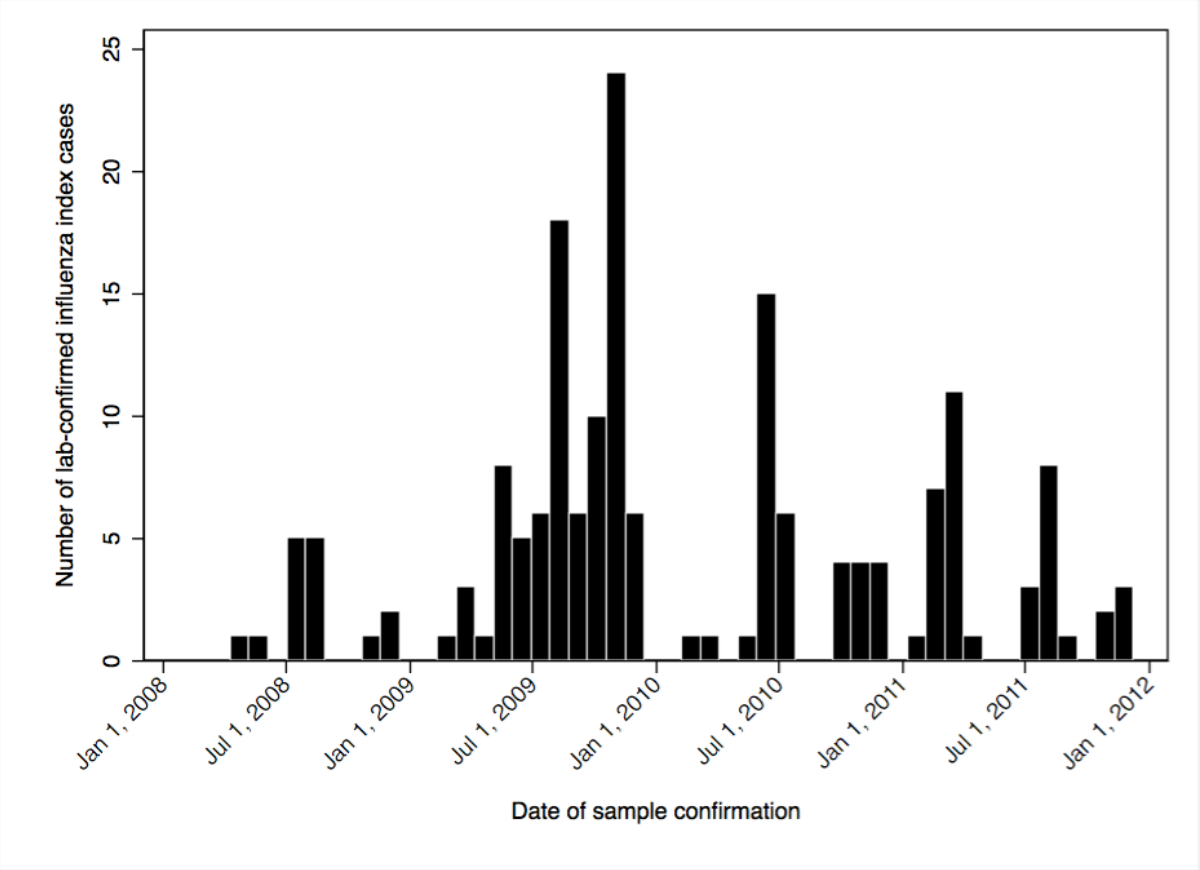
Appendix 5.1: Supplemenary Figures



Appendix Figure 5.1: Number of Surveillance Participants and Exclusions from Study Analysis – Kibera, Kenya, 2008-2011. Individuals in gray boxes were subject of analyses.



Appendix Figure 5.2: Number of Laboratory-confirmed Influenza Index Cases by Sample Confirmation Date – Kibera, Kenya, 2008-2011.

Chapter 6: Influenza activity in Kenya, 2007-2013: timing, association with climatic factors, and implications for vaccination campaigns

Influenza Other Respir Viruses. Apr 2016; DOI:10.1111/irv.12393

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Abstract

Background: Information on the timing of influenza circulation remains scarce in Tropical regions of Africa.

Objectives: We assessed the relationship between influenza activity and several meteorological factors (temperature, specific humidity, precipitation), and characterized the timing of influenza circulation, and its implications to vaccination strategies in Kenya.

Methods: We analyzed virologically-confirmed influenza data for outpatient influenza-like illness (ILI), hospitalized for severe acute respiratory infections (SARI), and cases of severe pneumonia over the period 2007-2013. Using logistic and negative binomial regression methods, we assessed the independent association between climatic variables (lagged up to 4 weeks) and influenza activity.

Results: There were multiple influenza epidemics occurring each year and lasting a median duration of 2-4 months. On average, there were two epidemics occurring each year in most of the regions in Kenya, with the first epidemic occurring between the months of February and March and the second one between July and November. Specific humidity was independently and negatively associated with influenza activity. Combinations of low temperature (<18^{o}C) and low specific humidity (<11g/Kg) were significantly associated with increased influenza activity.

Conclusions: Our study broadens understanding of the relationships between seasonal influenza activity and meteorological factors in the Kenyan context. While rainfall is frequently thought to be associated with influenza circulation in the tropics, the present findings suggest low humidity is more important in Kenya. If annual vaccination were a component of a vaccination strategy in Kenya, the months of April to June are proposed as optimal for associated campaigns.

6.1 Introduction

Influenza exerts a significant health burden on human populations across temperate, sub-tropical and tropical regions (1, 2). In temperate regions, influenza epidemics exhibit clear seasonality with peaks during winter months (3, 4) suggestive of an association with climatic factors. In these regions lower temperature, and lower specific humidity have been shown to be significantly associated with increased influenza activity (5, 6). In contrast, influenza seasonal characteristics are less predictable in tropical and sub-tropical regions which are characterized by semi-annual epidemics or year-round influenza activity (5, 7-10). A meteorological factor that is frequently reported to be associated with high influenza incidences in the tropical areas is rainfall (8, 9, 11).

In temperate countries a well-defined seasonality allows for a precise timing of influenza vaccination campaigns to precede periods of peak circulation. However in tropical African countries more data are needed on influenza seasonality and its determinants. In Kenya, where there is currently no influenza vaccination strategy in place, these data may help to inform vaccine implementation strategy decisions. Kenya experiences long rains that occur from March to May and short rains occurring in October and November. Temperatures are highest during the months of January to March (12). However there is considerable climate variability within Kenya such that influenza surveillance has been set up in different locations, including the coastal tropical regions characterized by hot and humid weather year round; semi-arid and desert-like conditions in the Northern and North Eastern part of Kenya; and cooler highland locations in Central and parts of Western of Kenya. Data collected from influenza sentinel surveillance sites across the country have suggested increased influenza activity during rainy seasons (11, 13) but the full extent of how meteorological factors influence influenza activity is yet to be elucidated.

We assessed the relationship between the onset week of influenza activity as well as the weekly number of influenza cases with temperature, rainfall, and specific humidity during the years 2007-2013. We also described the patterns of periods of increased influenza circulation in different regions in Kenya and suggested possible implications for future vaccination programs.

6.2 Methods

6.2.1 Study sites and population

We analyzed data collected between January 2007 and December 2013 from patients of all ages at all the twelve sites that conduct surveillance for influenza in Kenya. Included in our analysis were four sites from the Western Kenya region; four sites from the Central Kenya region; two sites from the Northern/North Eastern Kenya region; and two sites from the Coastal Kenya region (Figure 6.1 and Table 6.1). These surveillance sites are representative of four climatic regions (Western, Central, Northern/North Eastern and Coastal) in Kenya.

The Western region receives more rainfall (1250 –1700 mm annually) with average monthly temperatures ranging from 18°C to 26°C. The Central region has a relatively higher altitude compared to the other regions, and experiences some of the lowest temperatures in the country (as low as 7°C

during the July-August cold season). The Northern/North Eastern regions have semi-arid and desert-like conditions and experience sunny and dry weather most of the year. The Coastal region experiences hot and humid weather conditions year-round with average monthly temperatures ranging between 25°C and 29°C and an average annual rainfall of over 1,000 mm (14, 15).

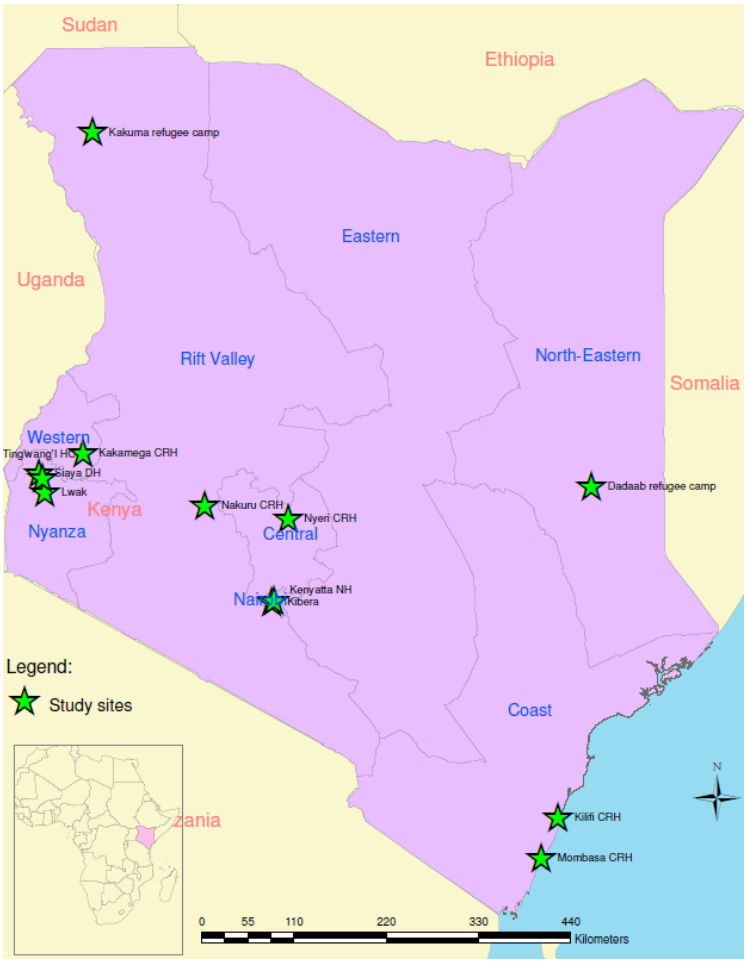

Figure 6.1: Map of Kenya showing the influenza surveillance sites

6.2.2 Laboratory confirmation of influenza

Samples were collected from influenza-like illness (ILI) outpatient case-patients; and hospitalized severe acute respiratory infection (SARI) case-patients (Table 6.1) (13). At Kilifi County Hospital (KCH), samples were collected from children <5 years who were hospitalized with severe or very severe pneumonia. The case definitions used are provided in Appendix 6.1. Samples collected were tested by real-time reverse transcription polymerase chain reaction (rRT-PCR) for influenza A and B viruses. Influenza A-positive specimens were subtyped for A(H1N1), A(H3N2), and A(H1N1)pdm09.

6.2.3 Influenza activity patterns

To assess influenza circulation over time, we calculated the average monthly proportion of influenza positive cases among those tested across the study period. Data from the pandemic period (August

2009 to July 2010) were excluded because (i) these were likely to influence the pattern of results, and (ii) we were interested in seasonal influenza. We also calculated the proportion of specimens that tested positive for influenza in the first half of the year within which the first epidemic typically occurs (January to June), and in the second half of the year within which the second epidemic occurs (July to December). Data from all the twelve surveillance sites were included in this analysis.

6.2.4 Defining "influenza circulation periods"

"Influenza circulation periods" were defined as a period of ≥2 successive weeks where ≥10% of the total weekly cases tested were positive for influenza (9, 16). The 10% threshold was close to the average proportion (12%) of cases that tested positive for influenza over the entire study period. In situations where there were <25 cases tested in a week, we considered the proportions as unstable and used the five-point moving average method to estimate the number of influenza cases and the percentage positive for influenza (17). Influenza circulation periods separated by ≥5 successive weeks where there was low influenza activity (<10%) were considered as two distinct periods. The first week of influenza circulation period is herein referred also as the start-week or onset week (Appendix 6.2).

6.2.5 Meteorological Data

The environmental data used in this analysis were satellite-derived measurements and were collected over the same period of time as the influenza data. These variables were, average surface temperature (^{0}C), and near surface specific humidity (g/Kg) obtained from the Global Land Data Assimilation System (GLDAS) (18); and accumulated rainfall (mm) obtained from the Tropical Rainfall Measuring Mission (TRMM) (19) (Appendix 6.1).

6.2.6 Data Analyses

6.2.6.1 Descriptive analyses for influenza and meteorological factors

Influenza circulation was described using proportions of influenza A and/or B positive cases. The age distribution, and the influenza activity patterns were described using medians and ranges. The meteorological factors were described using means and standard deviations (SD).

6.2.6.2 Bivariate and multivariate analyses of influenza activity

Data from nine out of the twelve sites were used when assessing the associations between influenza activity and meteorological variables. Three surveillance sites (Kenyatta National Hospital, Mombasa County Referral Hospital, and Ting'wang'i Health Center) were excluded from these analyses because of multiple missing data points in the time series (Appendix 6.1).

We applied two analytical approaches to determine the association between influenza activity and meteorological variables: (i) logistic regression to determine the association between the onset of influenza activity and meteorological variables, and (ii) negative binomial regression to determine the association between the weekly number of influenza cases and meteorological variables. In the first approach, the binary outcome variable "start-week" was coded as "1" if the week considered was the onset week of influenza activity or otherwise coded as "0". In the second approach, the outcome

variable was the weekly count of influenza positive cases identified at each site. Negative binomial regression was chosen over the over Poisson regression to account for over-dispersion in the data. The variables that were considered as covariates in the models were, site, year and week of the year (week= 1, 2, 3,…, 52). With the exception of the site and year variables which were analyzed as a categorical variables, all the other variables were entered into the respective models as continuous variables.

We investigated associations of up to 4 lagged weeks on all meteorological variables to assess a possible delayed weather effect on influenza activity (Appendix 6.1) (7, 18). We additionally assessed if "cold-dry" and "humid-rainy" conditions - as suggested in a recent global seasonality study - were associated with influenza activity (5). We used combinations of temperature and specific humidity at thresholds of $<18^0$C and <11g/kg respectively to define "cold-dry" conditions; and combinations of specific humidity and rainfall at thresholds of >14g/kg and >150mm respectively to define "humid-rainy" conditions. In addition to investigating the effect of the "cold-dry" and "humid-rainy "conditions on influenza activity, we also assessed the effect of the two-way product interaction (included as continuous variables) between temperature and specific humidity, and between specific humidity and rainfall. The interactions were evaluated in the model alongside the main effects of temperature, specific humidity and rainfall.

The multiple variable models for the logistic and negative binomial regression analyses were fitted by including the site variable as well as all the variables that were associated with influenza in the bivariate analysis at overall p-value<0.2. Statistical significance was considered if the p-value was <0.05. All data analyses were performed using Stata version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

6.3 Ethical considerations

The study protocols were approved by both the institutional review board (IRB) of the U.S. CDC (CDC-3308, CDC-4566), and the ethical review committee of the Kenya Medical Research Institute (KEMRI) (SSC-1801, SSC-932, SSC- 1161, SSC-1055, 1526, 1858). At Nakuru, Kakamega and Nyeri County Referral Hospitals, the Kenya Ministry of Health (KMoH) issued a letter stating that sentinel surveillance for influenza, should be considered part of routine public health surveillance, and therefore did not require formal ethical review. Verbal consent at these sites was obtained from all patients before questionnaires were administered and specimens were collected. For children, verbal consent was obtained from guardians.

6.4 Results

6.4.1 Descriptive analyses

A total of 55,192 patients were tested for influenza at the twelve surveillance sites over the period 2007 to 2013 of which 6,721(12%) tested positive for influenza. The proportion of patients who tested positive for influenza ranged from 4% in Kilifi to 19% among patients who were seen at Dadaab refugee

camp. The median age of the patients who were tested for influenza was 1.7 years [interquartile range (IQR)=0.8-4.2 years] (Table 6.1).

The mean average weekly temperature was lowest in Nakuru (18.2^{0}C), and highest at Dadaab refugee camp (30.7^{0}C) (Table 6.2). The mean average weekly specific humidity ranged from 11.1 g/Kg to 15.1 g/Kg with Nyeri recording the lowest measurements, while Kilifi recorded the highest. The "cold-dry" conditions defined earlier were observed in only at two sites in the Central Kenya region (Nakuru and Kibera). However, the "humid-rainy" conditions were only experienced at the coastal site (KCH) and at only four different time-points (weeks) over the course of the study period.

6.4.2 Influenza activity patterns

A total of 48 periods of increased influenza circulation were identified across the nine study sites. Nineteen of these episodes occurred within the first quarter of the year [median onset month was February]; 16 episodes occurred in the second quarter [median onset month was July]; and the remaining 13 occurred in the last quarter [median onset month was October]. On average, most of the study sites experienced two episodes of increased influenza circulation annually which lasted for a median duration of 2-4 months.

When we analyzed the monthly seasonal cycle of influenza activity, there was a pattern showing periods of increased influenza circulation occurring between February and March; and between July and November. There were more influenza positive cases identified in the last half of the years included in the analysis - within which the second epidemic occurs - compared to the first of half of the years [3,886 (58%) influenza cases during July – December vs. 2,835 (42%) during January - June]. The month of May had the lowest influenza activity (Figure 6.2 and Appendix 6.2).

6.4.3 Bivariate and multivariable analyses

In the bivariate models for onset of influenza activity, specific humidity was significantly and negatively associated with the onset of influenza activity (p<0.05). In the negative binomial regression models, influenza activity was found to be negatively associated with both temperature and specific humidity (p<0.05). The presence of the "cold-dry" conditions, defined earlier, were also found to be significantly associated with influenza activity (p<0.05). No statistically significant associations were observed between influenza activity and rainfall (Table 6.3).

In the multivariable logistic regression model, specific humidity was independently and negatively associated with the onset of influenza activity at lag-weeks one [odds ratio (OR)=0.79 (95% CI 0.66-0.94)] and two [OR=0.82 (95% CI 0.69-0.98)] in the models that adjusted for the site variable. Similarly, specific humidity was significantly associated with influenza activity in the negative binomial regression models for the weekly count of influenza cases at the current week [incidence rate ratio (IRR)=0.94 (95% CI 0.90-0.98)], and at all the four lag weeks investigated (p<0.001). The presence of "cold-dry" conditions was also found to be positively associated with influenza activity when we adjusted for the site variable at current week [IRR=1.90 (95% CI 1.20-3.01)], and at lag weeks one [IRR=2.07 (95% CI 1.21-3.55)] and three [IRR=1.95 (95% CI 1.11-3.44)]. However, temperature was not significantly associated with influenza activity when we adjusted for the site variable. All the other variables assessed including

rainfall and the two-way interactions between specific humidity and temperature, and between specific humidity and rainfall were not significantly associated with influenza activity when we adjusted for the site variable (Table 6.4). An exploratory analysis to assess the relationship between the onset week of influenza activity and meteorological variables showed similar results to the ≥10% activity threshold when we used the median proportion (7% threshold) to define the onset of influenza activity (results not shown).

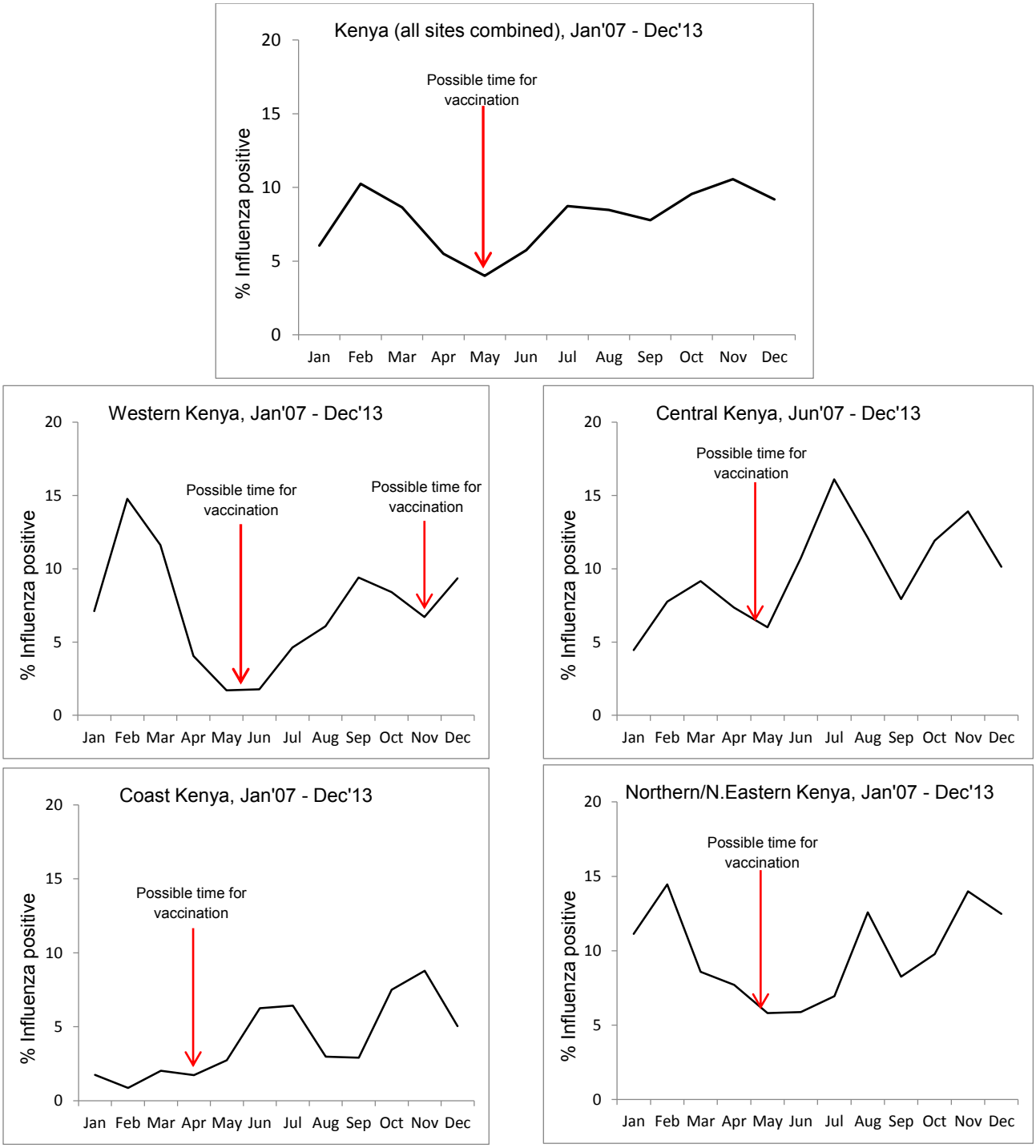

Figure 6.2: Monthly seasonal cycle of influenza activity in Kenya by region

6.5 Discussion

In this study, we found that there were multiple periods of increased influenza activity annually in Kenya. On average, there were two epidemics occurring each year in most of the regions in Kenya and these epidemics lasted a median duration of 2-4 months. The first epidemic occurred between February and March, and the second between July and November. The period between April and May had the least influenza activity. We also identified that lower specific humidity was significantly, associated with influenza activity in Kenya. As has been noted in other continents (5), we found that influenza was more likely to circulate when both temperature and specific humidity were below 18^{o}C and 11g/Kg respectively, independent of the study site. Contrary to what has been hypothesized previously (5), we found no significant association between influenza activity and rainfall.

Unlike temperate climates, the presence of multiple influenza epidemics each year in most of the regions in Kenya presents a challenge to the selection of the appropriate influenza vaccine formulation to use. Recent investigations have found that the Southern Hemisphere (SH) vaccine formulation was well-matched [80% (95% CI 77-84) over a nine-month period] to circulating strains over the period 2007 to 2013 [Waiboci *et al;* accepted for publication in Vaccine]. The Northern Hemisphere (NH) vaccine formulation was also well matched [82% (95% CI 78-85) over a nine-month period]. These findings suggest that for the primary period of increased influenza circulation in Kenya (July-November), the SH vaccine formulation (available in April) could offer good protection. While this vaccine could also provide protection during the subsequent February and March peaks as well, the NH formulation (available in November) could also be considered for that period.

Our finding of a negative association between influenza activity and specific humidity is consistent with findings from other studies that were conducted in temperate (5, 20), and sub-tropical regions. This is also consistent with experimental results which have linked low humidity to prolonged influenza virus survival (IVS) as well as efficient aerosol transmission (21, 22). These findings also suggest a site-specific association between temperature and influenza activity as temperature was negatively and significantly associated with influenza activity in the bivariate analysis but not when we adjusted for the site variable. Whereas rainfall has previously been suggested to be correlated with influenza activity in tropical and sub-tropical regions (5, 7), our study did not find a significant association. A recent global study found that “humid-rainy” (high specific humidity and rainy) conditions were associated with influenza circulation (5). However, our analysis did not support this finding. The lack of association between the “humid-rainy” conditions with influenza activity in our study context may in part be explained by the fact that we do not experience necessary thresholds of high specific humidity (>14g/Kg) and high rainfall (>150 mm) measurements as previously suggested (5). Indeed, these conditions were only experienced at four different time-points over the course of the study period at the coastal site (KCH).

The relative merits of annual influenza vaccination vs. the integration of influenza vaccination into routine immunization schedules remain to be evaluated in Kenya, and are beyond the scope of this discussion. However if annual mass vaccination campaigns are being considered, the period between April and June would perhaps be the optimal time for several reasons. First, this would potentially offer better protection considering the fact that the period of influenza activity between July and December account for most of the annual influenza cases (58%). Considering the possibility of waning immunity

over time (23, 24), it would probably be preferable to vaccinate during the month of June. However, a wider period may need to be considered in the context of the possible logistical challenges of vaccine delivery and accessing the target populations. Second, according to the Kenyan education calendar, schools are closed for holidays during the months of April, August and December. April would therefore be a more convenient time for school-going children to be immunized in non-school settings. Lastly, caretakers of young children may take advantage of the presence of older children during these holidays in order to take care of household chores as they attend to other health-related matters such as taking the smaller children for immunization.

Our study was subject to some other important limitations. First, we were not able to account for the effect of other factors such as social-economic conditions, population susceptibility, and human migration dynamics on the association between influenza activity and meteorological variables because these data were not collected. Second, we only relied on satellite derived meteorological measurements for our analysis. Even though we had a reasonable temporal resolution in the meteorological data, using actual ground data could possibly have provided more accurate results. Third, although we tried to adjust for the effect of the site differences in our models, we could not sufficiently explore the regional variation of meteorological factors in Kenya and how they correlate with influenza activity because of limited influenza testing data available. Lastly, we could not explore if the association between influenza activity and meteorological factors varied by age as older persons were underrepresented in the hospital-based surveillance because of low healthcare seeking behavior (25).

In conclusion, our study broadens our understanding of the relationships between seasonal influenza activity and meteorological factors in tropical regions, and more specifically in the Kenyan context. We additionally highlight the influenza activity patterns in Kenya with regard to the onset-months of periods of increased influenza circulation. These could help to inform the timing of future influenza vaccination campaigns in Kenya, and highlight periods when added diagnostic measures, treatment efforts or infection control strategies may be put in place.

Acknowledgments: We thank the Kenya Ministry of Health, the surveillance officers, the laboratory, and data management staff for their role in influenza surveillance in Kenya. We also offer sincere thanks to the KEMRI/Wellcome Trust Research Programme in Kilifi, the parents and children who participated in the PERCH study, and the PERCH staff and the PERCH Study Group. The work was funded in part by The Wellcome Trust, UK (Grant No. 084633).

Table 6.1: Descriptive statistics for influenza testing, January 2007 - December 2013

Hospital/clinic	Period of data included in analysis	Number tested	Tested positive for influenza n(%)	Hospitalized SARI cases tested	SARI cases tested positive for influenza n(%)	Outpatient ILI/ALRI[c] cases tested	ILI/ALRI cases tested positive for influenza n(%)	Male n(%)	Median age in years (IQR)
St. Elizabeth Hospital (Lwak)[a]	2007-2013	7,493	1,107(14.8)	1,162	105(9.0)	6,331	1002(15.8)	3,655(48.8)	5.0(2.1-12.8)
Siaya County Referral Hospital (CRH)	2010-2013	4,769	325(6.8)	4,769	325(6.8)	N/A	N/A	2,373(49.8)	1.8(0.8-7.6)
Kakamega CRH	2008-2013	5,801	630(10.9)	3,970	331(8.3)	1,831	299(16.3)	3,226(55.6)	1.7(0.8-3.5)
Ting'wang'i Health Center	2010-2013	1,453	191(13.1)	N/A	N/A	1,453	191(13.1)	690(47.5)	2.2(1.1-4.2)
Western Kenya region	2007-2013	19,516	2,253(11.5)	9,901	761(7.7)	9,615	1,492(15.5)	9,944(51.0)	2.7(1.0-7.0)
Kenyatta National Hospital	2008-2013	3,576	268(7.5)	2,288	124(5.4)	1,288	144(11.2)	2,019(56.5)	0.8(0.5-1.5)
Tabitha Clinic (Kibera)[a]	2008-2013	6,964	1,263(18.1)	N/A	N/A	6,964	1,263(18.1)	3,306(47.5)	5.2(1.9-15.3)
Nyeri CRH	2008-2013	4,927	653(13.3)	3,159	351(11.1)	1,768	302(17.1)	2,741(55.6)	1.3(0.8-3.0)
Nakuru CRH	2008-2013	4,138	561(13.6)	2,288	250(10.9)	1,850	311(16.8)	2,258(54.6)	1.0(0.7-2.2)
Central Kenya region	2008-2013	19,605	2,745(14.0)	7,735	725(9.4)	11,870	2,020(17.0)	10,324(52.7)	1.6(0.8-4.4)
Dadaab refugee camp	2008-2013	3,064	571(18.6)	2,165	384(17.7)	899	187(20.8)	1,713(55.9)	1.4(0.8-4.0)
Kakuma refugee camp	2007-2013	4,942	649(13.1)	3,584	441(12.3)	1,358	208(15.3)	2,701(54.7)	1.0(0.7-3.0)
Northern/North Eastern region	2007-2013	8,006	1,220(15.2)	5,749	825(14.4)	2,257	395(17.5)	4,414(55.1)	1.0(0.7-3.0)
Mombasa CRH	2008-2013	2,907	278(9.6)	2,097	171(8.2)	810	107(13.2)	1,669(57.4)	1.0(0.5-2.0)
Kilifi CH[b]	2007-2013	5,158	225(4.4)	5,158	225(4.4)	N/A	N/A	2,995(58.1)	0.7(0.2-1.5)
Coastal Kenya region	2007-2013	8,065	503(6.2)	7,255	396(5.5)	810	107(13.2)	4,664(57.8)	0.8(0.3-1.7)
All sites	2007-2013	55,192	6,721(12.2)	30,640	2,707(8.8)	24,552	4,014(16.3)	29,346(53.2)	1.7(0.8-4.2)

[a]Population-based disease surveillance sites; [b]At Kilifi CH, samples were collected from children <5 years who were hospitalized with severe or very severe pneumonia; [c]Acute Lower Respiratory Illness; N/A; Not applicable.

Table 6.2: Descriptive statistics for the meteorological variables used in the analysis, January 2007 - December 2013

Hospital/clinic	Period of data included in analysis	Yearly number of influenza circulation periods	Temperature (ºC)		Specific humidity (g/Kg)		Accumulated rainfall (mm)	
			Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	Median (IQR)
St. Elizabeth Hospital (Lwak)	2007-2013	2	21.4(1.5)	21.2(20.3-22.3)	13.0(1.3)	13.3(12.4-13.9)	32.8(27.7)	26.2(10.5-46.2)
Siaya CRH	2010-2013	2	21.2(1.4)	20.9(20.3-21.9)	13.0(1.2)	13.1(12.5-13.7)	34.1(28.4)	26.4(10.6-49.0)
Kakamega CRH	2008-2011	1	21.4(1.6)	21.2(20.3-22.5)	13.2(1.3)	13.4(12.5-14.0)	32.9(28.6)	25.1(11.4-43.4)
Ting'wang'i Health Center[a]	N/A	-	N/A		N/A		N/A	
Western Kenya region	2007-2013	2	21.4(1.5)	21.2(20.3-22.3)	13.0(1.2)	13.3(12.4-13.9)	32.8(27.7)	26.2(10.5-46.2)
Kenyatta National Hospital[a]	N/A	-	N/A		N/A		N/A	
Tabitha Clinic (Kibera)	2009-2013	2	19.8(1.3)	19.7(18.8-20.7)	11.5(1.3)	11.6(10.7-12.6)	15.0(24.1)	4.5(1.1-19.3)
Nyeri CRH	2009-2012	2	19.8(1.1)	19.6(19.0-20.6)	11.1(1.4)	11.3(10.3-12.1)	21.2(28.0)	9.5(3.0-31.1)
Nakuru CRH	2009-2013	2	18.2(1.2)	17.9(17.3-18.8)	11.1(1.5)	11.6(10.4-12.3)	23.9(21.5)	17.5(7.6-33.8)
Central Kenya region	2009-2013	2	19.2(1.2)	19.0(18.4-20.0)	11.3(1.3)	11.5(10.6-12.1)	20.0(22.1)	11.9(5.2-28.5)
Dadaab refugee camp	2008-2009	2	30.7(1.8)	30.9(29.4-32.1)	13.4(1.6)	13.1(12.2-14.5)	5.8(14.5)	0.0(0.0-2.0)
Kakuma refugee camp	2007-2012	2	30.1(1.7)	30.1(29.1-31.1)	11.7(2.1)	11.8(10.2-13.3)	6.4(11.7)	0.0(0.0-7.2)
Northern/North Eastern region	2007-2012	2	30.0(1.8)	30.1(29.1-31.2)	12.1(2.0)	12.2(10.9-13.5)	6.6(11.8)	0.4(0.0-8.4)
Mombasa CRH[a]	N/A	-	N/A		N/A		N/A	
Kilifi CH	2007-2013	1	27.6(1.5)	27.5(26.4-28.7)	15.1(1.5)	15.3(13.7-16.3)	12.5(29.0)	4.3(1.2-12.4)
Coastal Kenya region	2007-2013	1	27.6(1.5)	27.5(26.4-28.7)	15.1(1.5)	15.3(13.7-16.3)	12.5(29.0)	4.3(1.2-12.4)
All sites	2007-2013	2	24.77(4.5)	25.5(20.5-28.9)	13.0(2.1)	13.1(11.6-14.3)	18.3(26.1)	8.1(1.8-25.5)

[a]Data from these sites were excluded from the analysis of association of influenza activity and meteorological variables because of multiple missing data points in the time series; N/A; Not applicable.

Table 6.3: Bivariate analysis of the meteorological factors associated with influenza activity in Kenya, January 2007 - December 2013

	Association with the onset of influenza activity		Absolute association with influenza activity	
	Odds Ratio (95% CI)	p-value	Incidence Rate Ratio (95% CI)	p-value
Year		0.233*		<0.001*
2007	0.70(0.23-2.15)	0.538	0.45(0.37-0.55)	<0.001
2008	0.74(0.30-1.84)	0.516	0.78(0.64-0.94)	0.010
2009	0.34(0.10-1.18)	0.089	0.79(0.62-1.00)	0.048
2010	0.31(0.07-1.36)	0.120	0.96(0.79-1.16)	0.649
2011	Ref		Ref	
2012	0.99(0.46-2.11)	0.979	0.60(0.49-0.74)	<0.001
2013	0.42(0.14-1.27)	0.125	0.69(0.56-0.85)	<0.001
Week	0.98(0.97-1.00)	0.123	1.00(0.99-1.00)	0.285
Site		0.813*		<0.001*
St. Elizabeth Hospital	Ref		Ref	
Tabitha Clinic (Kibera)	1.52(0.56-4.12)	0.410	1.70(1.36-2.11)	<0.001
Nyeri CRH	0.75(0.19-2.85)	0.667	0.83(0.64-1.08)	0.169
Kakamega CRH	1.00(0.30-3.37)	1.000	1.07(0.83-1.36)	0.609
Nakuru CRH	1.13(0.39-3.30)	0.825	0.77(0.61-0.97)	0.025
Siaya CRH	1.10(0.35-3.41)	0.871	0.67(0.53-0.85)	0.001
Dadaab refugee camp	1.44(0.37-5.57)	0.594	0.94(0.73-1.22)	0.649
Kakuma refugee camp	1.05(0.38-2.94)	0.924	0.88(0.71-1.09)	0.238
Kilifi County Referral Hospital	0.49(0.15-1.66)	0.253	0.25(0.19-0.33)	<0.001
Temperature (^{0}C)				
No lag	0.99(0.93-1.05)	0.682	0.97(0.95-0.98)	<0.001
Lag 1 week	0.98(0.92-1.04)	0.484	0.96(0.95-0.98)	<0.001
Lag 2 weeks	0.97(0.91-1.04)	0.350	0.96(0.95-0.98)	<0.001
Lag 3 weeks	0.97(0.91-1.04)	0.346	0.96(0.95-0.98)	<0.001
Lag 4 weeks	0.97(0.91-1.04)	0.394	0.96(0.95-0.98)	<0.001
Specific humidity (g/kg)				
No lag	0.86(0.75-0.98)	0.031	0.86(0.84-0.89)	<0.001
Lag 1 week	0.82(0.71-0.94)	0.004	0.85(0.83-0.88)	<0.001
Lag 2 weeks	0.84(0.73-0.96)	0.013	0.85(0.82-0.87)	<0.001
Lag 3 weeks	0.89(0.78-1.02)	0.108	0.84(0.82-0.87)	<0.001
Lag 4 weeks	0.86(0.75-0.99)	0.035	0.84(0.82-0.86)	<0.001
Accumulated rainfall (mm)				
No lag	1.00(0.99-1.01)	0.807	1.00(1.00-1.00)	0.360
Lag 1 week	0.99(0.98-1.00)	0.115	1.00(1.00-1.00)	0.268
Lag 2 weeks	1.00(1.00-1.01)	0.409	1.00(1.00-1.00)	0.074
Lag 3 weeks	1.00(0.99-1.01)	0.677	1.00(1.00-1.00)	0.138
Lag 4 weeks	1.00(0.99-1.01)	0.811	1.00(1.00-1.00)	0.106
Presence of cold-dry conditions[§]				
No lag	8.17e-06(0--)	0.295	1.65(1.09-2.50)	0.019
Lag 1 week	8.17e-06(0--)	0.295	2.05(1.10-3.83)	0.024
Lag 2 weeks	8.17e-06(0--)	0.295	1.58(0.98-2.53)	0.059
Lag 3 weeks	8.17e-06(0--)	0.295	2.12(1.13-4.01)	0.020
Lag 4 weeks	8.18e-06(0--)	0.319	1.25(0.74-2.11)	0.401

[§]-Cold-dry periods were defined as weeks when the average temperature was <18^{o}C and specific humidity was <11g/Kg; *Overall p-value

Table 6.4: Multivariable analysis of the meteorological factors associated with influenza activity in Kenya, January 2007 - December 2013

	Association with the onset of influenza activity		Absolute association with influenza activity	
	Odds Ratio (95% CI)	p-value	Incidence Rate Ratio (95% CI)	p-value
Temperature (^{0}C)				
No lag	1.06(0.87-1.28)	0.573	1.03(1.00-1.08)	0.086
Lag 1 week	0.97(0.80-1.18)	0.752	1.01(0.97-1.05)	0.720
Lag 2 weeks	0.90(0.74-1.10)	0.308	1.01(0.97-1.05)	0.750
Lag 3 weeks	0.90(0.74-1.10)	0.299	0.99(0.95-1.02)	0.464
Lag 4 weeks	0.93(0.76-1.13)	0.443	0.98(0.94-1.01)	0.219
Specific humidity (g/kg)				
No lag	0.85(0.71-1.02)	0.078	0.94(0.90-0.98)	0.005
Lag 1 week	0.79(0.66-0.94)	0.007	0.91(0.87-0.95)	<0.001
Lag 2 weeks	0.82(0.69-0.98)	0.027	0.90(0.86-0.94)	<0.001
Lag 3 weeks	0.91(0.76-1.09)	0.307	0.88(0.85-0.92)	<0.001
Lag 4 weeks	0.86(0.71-1.02)	0.088	0.88(0.85-0.91)	<0.001
Accumulated rainfall (mm)				
No lag	1.00(0.99-1.01)	0.761	1.00(1.00-1.00)	0.955
Lag 1 week	0.99(0.97-1.00)	0.099	1.00(1.00-1.00)	0.671
Lag 2 weeks	1.00(0.99-1.01)	0.348	1.00(1.00-1.00)	0.798
Lag 3 weeks	1.00(0.98-1.01)	0.623	1.00(1.00-1.00)	0.778
Lag 4 weeks	1.00(0.99-1.01)	0.763	1.00(1.00-1.00)	0.841
Presence of cold-dry conditions[§]				
No lag	NE	-	1.90(1.20-3.01)	0.006
Lag 1 week	NE	-	2.07(1.21-3.55)	0.008
Lag 2 weeks	NE	-	1.64(0.97-2.78)	0.062
Lag 3 weeks	NE	-	1.95(1.11-3.44)	0.021
Lag 4 weeks	NE	-	1.15(0.59-2.24)	0.675

[§]-Cold-dry periods were defined as weeks when the average temperature was <18^{o}C and specific humidity was <11g/Kg; NE-Not estimated

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Appendix 6.1: Supplementary Methods

Case definitions

Influenza-Like Illness: was defined as an axillary temperature ≥38^{o}C and cough or sore throat in an outpatient of any age (1, 2).

Severe Acute Respiratory Illness (SARI): was defined differently for children under five years and for persons ≥5 years. Among children aged <5 years, SARI was defined using a modified version of the World Health Organization's Integrated Management of Childhood Illness (IMCI) definition for pneumonia. This was defined as hospitalization with cough OR difficulty breathing, AND at least one of (maternal report of lower-chest wall in-drawing, stridor in a calm child, unable to drink or breast feed, vomiting, convulsions, lethargic or unconscious, oxygen saturation <90%). Among persons aged 5 years, SARI was defined as hospitalization with cough OR difficulty breathing OR shortness of breath AND a documented fever (≥38^{o}C) (1, 2).

At the Kilifi site, severe pneumonia was defined as cough OR difficult breathing AND lower chest wall in-drawing and no signs of very severe pneumonia. Very severe pneumonia was defined as cough OR difficult breathing AND at least one of (hypoxia (oxygen saturation <90%), cyanosis, prostration (inability to drink or breast feed, inability to sit), or coma at admission) (3).

Missing data

We applied several procedures to handle missing data at each site. First, we excluded data for the whole year if there were five or more successive weeks with no influenza testing conducted. Second, if no data were collected in a specific week but data were collected in the previous and succeeding weeks, we substituted the missing data point by the average of two immediate weeks (one from each side). This applied to 2% of the weeks in the entire dataset. Lastly, for cases where data were missing for 2-4 successive weeks, we substituted the missing observation with data from the last week when influenza testing was conducted. This applied to 3% of the weekly data points in the dataset. Overall, we obtained 1,872 weeks of influenza surveillance data for further analyses of which 5% were imputed.

Meteorological Data

All the environmental data used in this analysis were satellite-derived measurements obtained from The National Aeronautics and Space Administration (NASA), and were collected over the same period as the influenza data. The environmental variables included in the analysis were, average surface temperature (^{0}C), and near surface specific humidity (g/Kg) obtained from the Global Land Data Assimilation System (GLDAS) (4); and accumulated Rainfall (mm) obtained from the Tropical Rainfall Measuring Mission (TRMM) (5). The temperature and specific humidity measurements were all three-hourly temporal datasets with a spatial resolution of 1.0^{0} x 1.0^{0} latitude/longitude. The rainfall data were daily temporal datasets and had a finer resolution of 0.25^{0} x 0.25^{0} latitude/longitude. These data were downloaded through NASA's Goddard Earth Sciences and Data Information Service Center (GES-DISC) Interactive Online Visualization and Analysis Infrastructure (GIOVANNI). All the meteorological

measurements (3-hourly and daily) were then averaged over each week to obtain the weekly measurements which were used in the final analysis.

To determine if influenza was associated with earlier measurements of the meteorological variables, we investigated associations of up to 4 lagged weeks on all meteorological variables. We selected this lag period because the exploratory analyses indicated no association when we considered lag periods beyond four weeks. Also given that the influenza incubation period ranges from 1-4 days after exposure and that the infected persons could continue to be infectious for another 5-7 days after the onset of symptoms (6) in normal circumstances, we believed that 4 weeks was an optimal period for an epidemic to start and spread into the community.

References for supplemental methods

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Appendix 6.2: Supplementary Figures

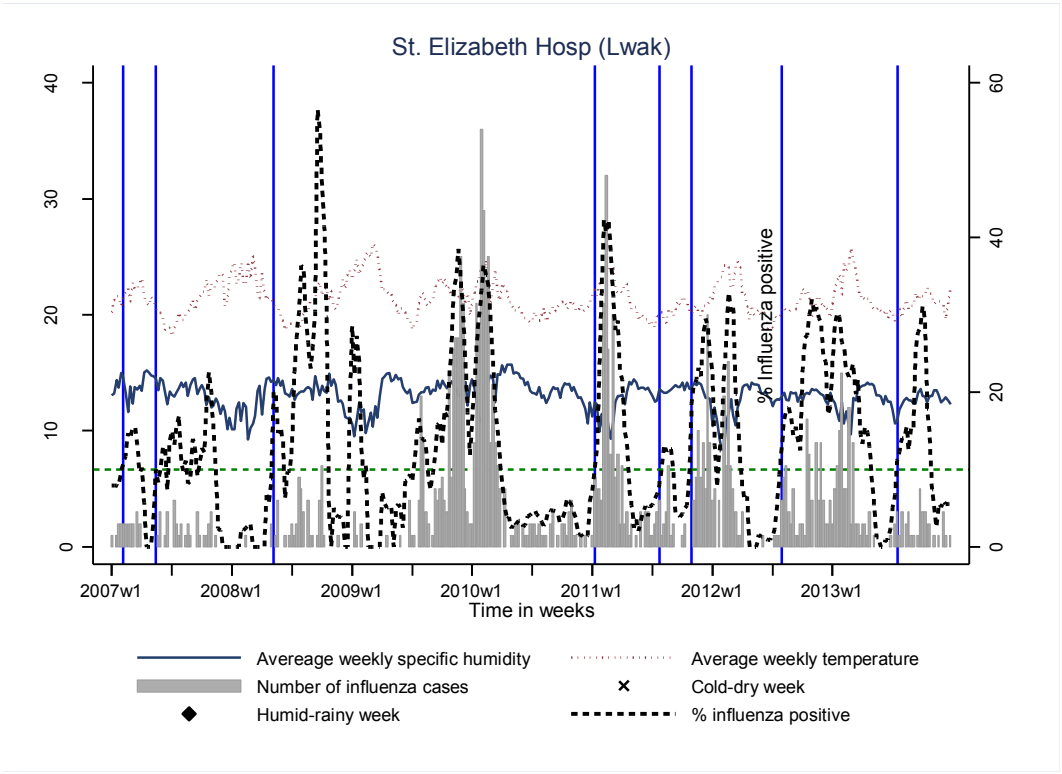
Supplemental figures showing the time series of the average weekly temperature, specific humidity and percent influenza positive cases by site, 2007 to 2013

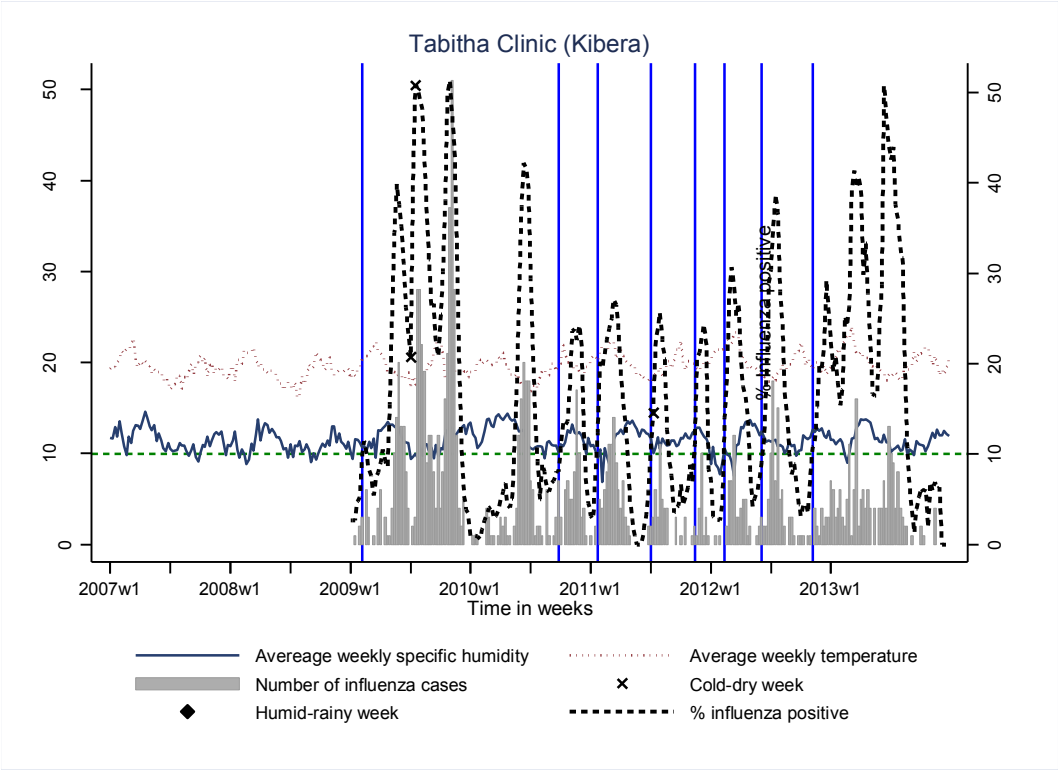
The vertical lines indicates the identified onset week and the dotted horizontal line shows the 10% infleunza positive cut-off point.

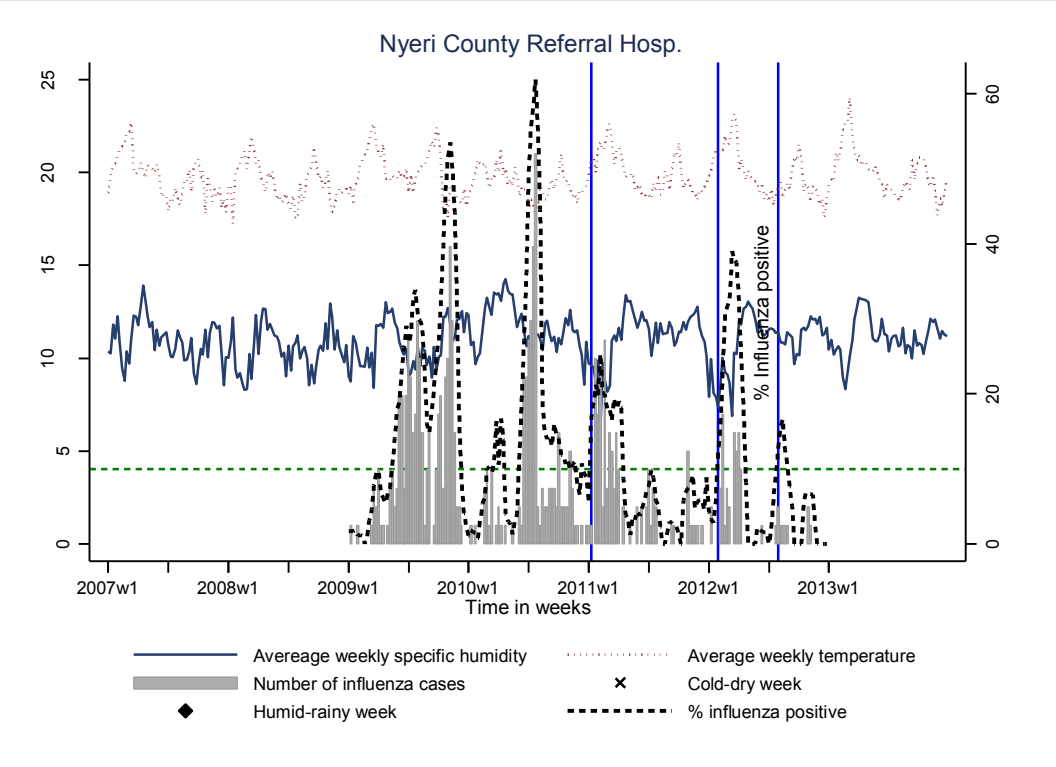
Definitions:

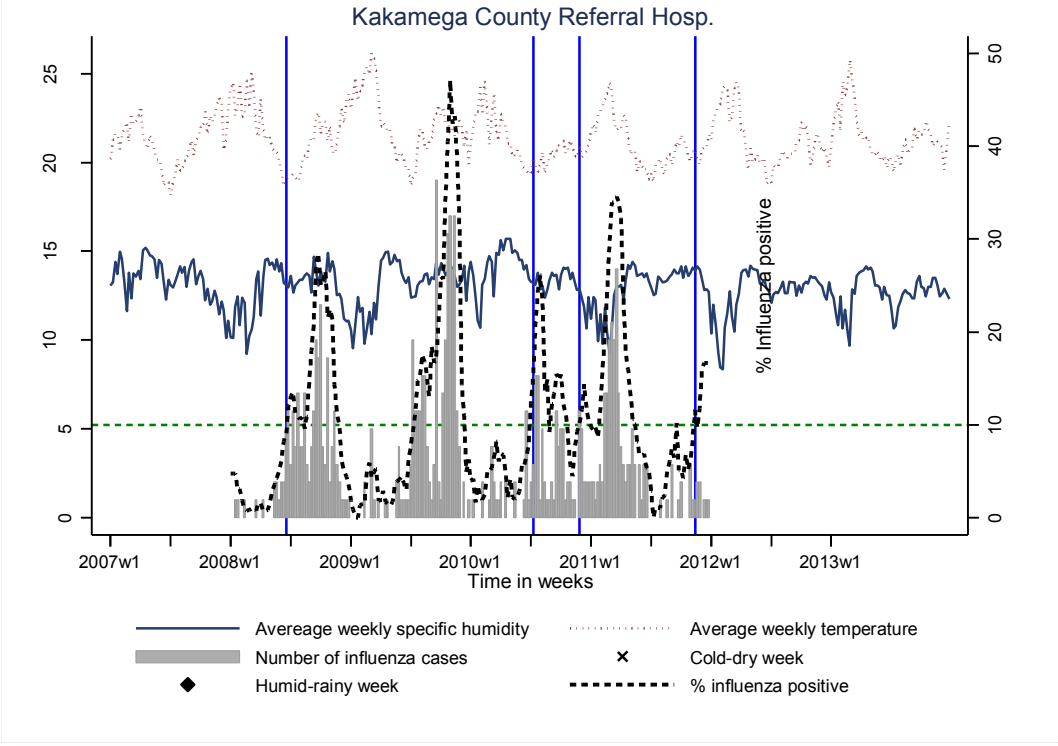
a) *Cold-dry* week was defined as the week when temperature was $<18^0$C and specific humidity was <11g/kg.

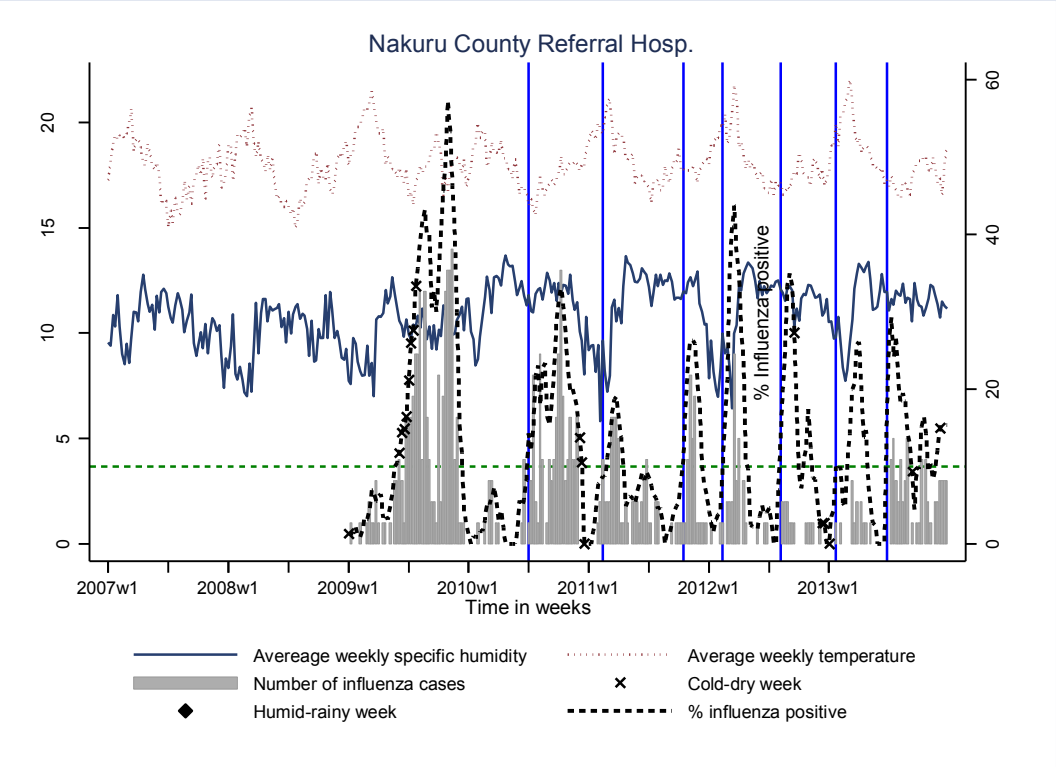
b) *Humid-rainy* week was defined as the week when specific humidity was >14g/kg and rainfall was >150mm.

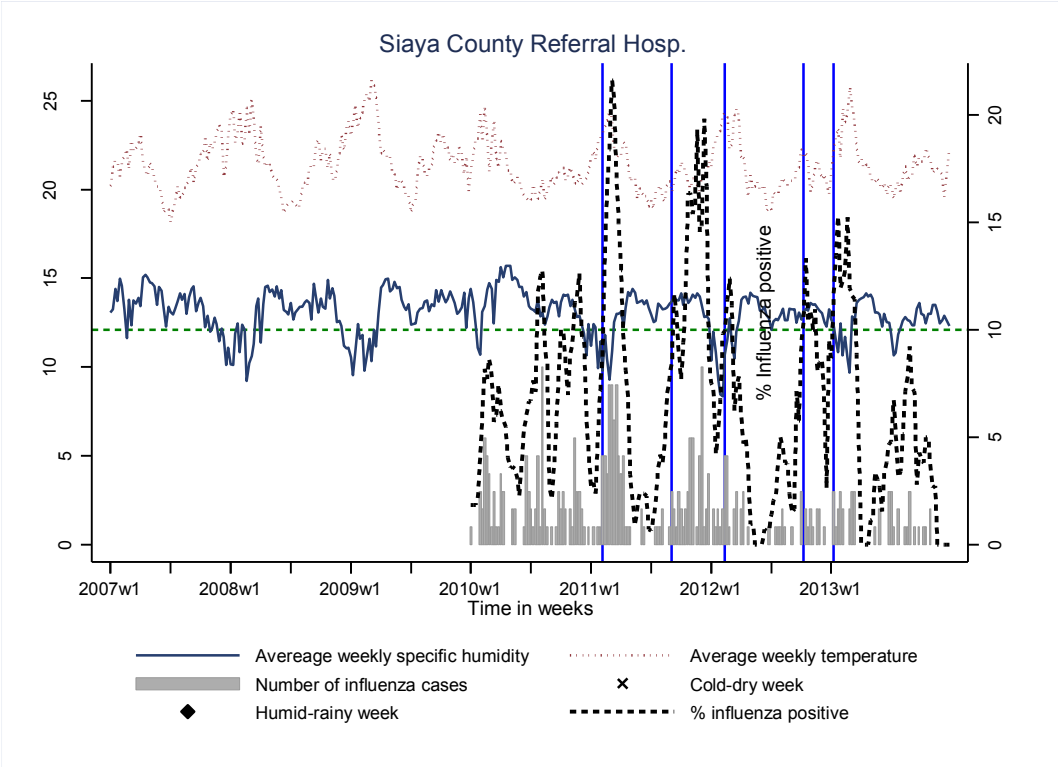

St. Elizabeth Hosp (Lwak)
% Influenza positive
Time in weeks
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Avereage weekly specific humidity
Number of influenza cases
Humid-rainy week
Average weekly temperature
Cold-dry week
% influenza positive

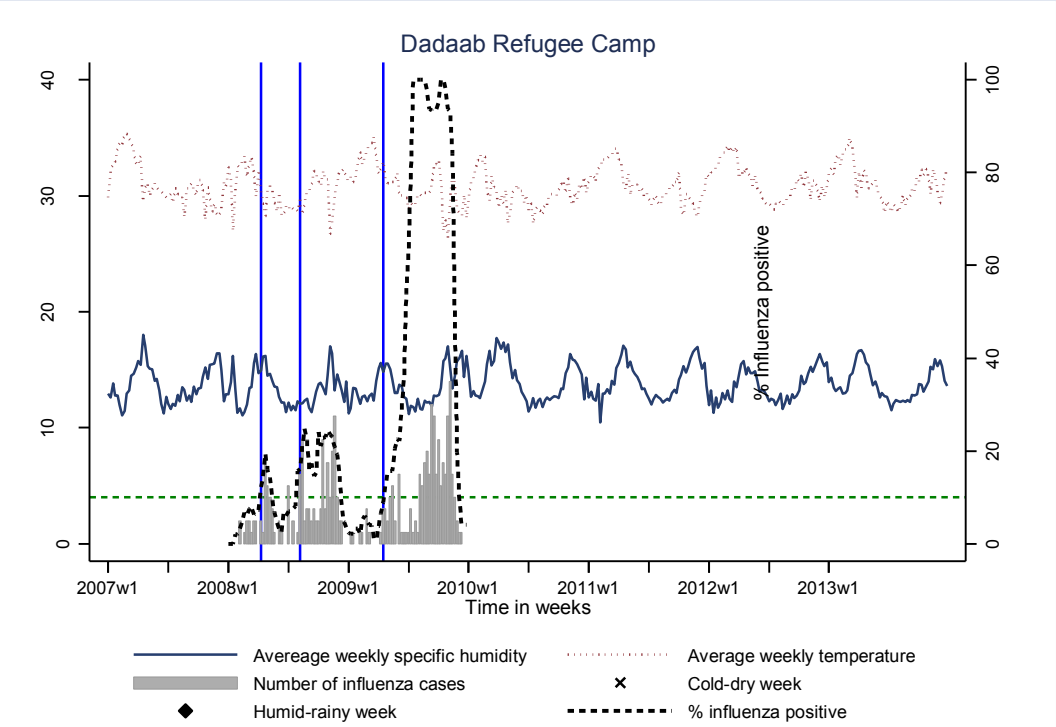

Tabitha Clinic (Kibera)
% Influenza positive
Time in weeks
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Avereage weekly specific humidity
Number of influenza cases
Humid-rainy week
Average weekly temperature
Cold-dry week
% influenza positive

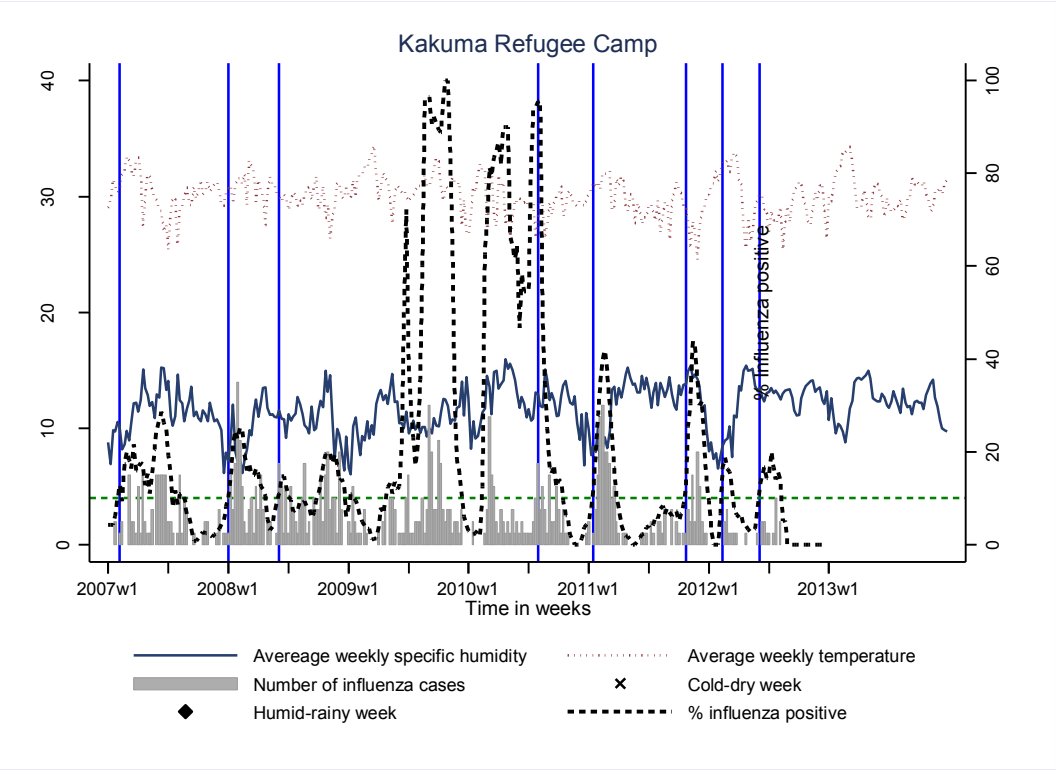

Nyeri County Referral Hosp.
% Influenza positive
Time in weeks
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Avereage weekly specific humidity
Number of influenza cases
Humid-rainy week
Average weekly temperature
Cold-dry week
% influenza positive

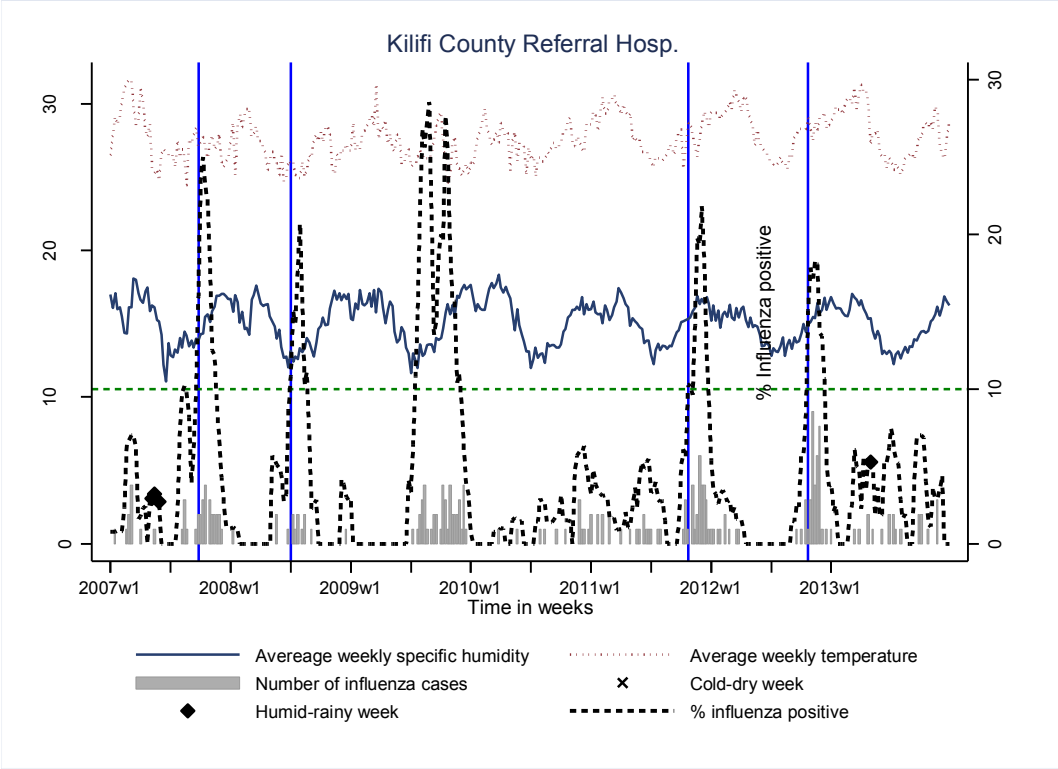

Kakamega County Referral Hosp.
% Influenza positive
Time in weeks
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Avereage weekly specific humidity
Number of influenza cases
Humid-rainy week
Average weekly temperature
Cold-dry week
% influenza positive


Nakuru County Referral Hosp.
% Influenza positive
Time in weeks
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Avereage weekly specific humidity
Average weekly temperature
Number of influenza cases
Cold-dry week
Humid-rainy week
% influenza positive


Siaya County Referral Hosp.
% Influenza positive
Time in weeks
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Avereage weekly specific humidity
Average weekly temperature
Number of influenza cases
Cold-dry week
Humid-rainy week
% influenza positive


Dadaab Refugee Camp
0
10
20
30
40
0
20
40
60
80
100
% influenza positive
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Time in weeks
Avereage weekly specific humidity
Average weekly temperature
Number of influenza cases
Cold-dry week
Humid-rainy week
% influenza positive


Kakuma Refugee Camp
0
10
20
30
40
0
20
40
60
80
100
% influenza positive
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Time in weeks
Avereage weekly specific humidity
Average weekly temperature
Number of influenza cases
Cold-dry week
Humid-rainy week
% influenza positive


Kilifi County Referral Hosp.
0
10
20
30
% Influenza positive
2007w1
2008w1
2009w1
2010w1
2011w1
2012w1
2013w1
Time in weeks
Avereage weekly specific humidity
Number of influenza cases
Humid-rainy week
Average weekly temperature
Cold-dry week
% influenza positive

Chapter 7: The cost of influenza-associated hospitalizations and outpatient visits in Kenya

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Abstract

Background: We estimated the cost-per-episode and the annual economic burden associated with influenza in Kenya.

Methods: From July 2013-August 2014, we recruited patients with severe acute respiratory illness (SARI) or influenza-like illness (ILI) associated with laboratory-confirmed influenza from 5 health facilities. A structured questionnaire was used to collect direct costs (medications, laboratory investigations, hospital bed fees, hospital management costs, transportation) and indirect costs (productivity losses) associated with an episode of influenza. We used published incidence of laboratory-confirmed influenza associated with SARI and ILI, and the national population census data from 2014, to estimate the annual number of influenza-associated hospitalizations and outpatient visits and calculated the annual economic burden by multiplying cases by the mean cost.

Results: We enrolled 275 patients (105 inpatients and 170 outpatients). The mean cost-per-episode of influenza was US$117.86 (standard deviation [SD], 88.04) among inpatients; US$114.25 (SD, 90.03) for children <5 years, and US$137.45 (SD, 76.24) for persons aged ≥5 years. Among outpatients, the mean cost-per-episode of influenza was US$19.82 (SD, 27.29); US$21.49 (SD, 31.42) for children <5 years, and US$16.79 (SD, 17.30) for persons aged ≥5 years. National annual influenza-associated cost ranged from US$2.96-5.37 million for inpatients and US$5.96-26.35 million for outpatients.

Conclusions: Our findings highlight influenza as causing substantial economic burden in Kenya, underlining the potential benefit of influenza vaccine recommendations.

7.1 Introduction

In Kenya, influenza virus circulates year-round and is an important contributor to the acute respiratory illness associated burden, disproportionately affecting children aged <5 years (1, 2). Despite the documented burden of influenza disease in Kenya, a national influenza vaccination program is yet to be implemented. Other than the health impact caused by influenza virus infection itself, influenza illness has been shown to exert a considerable economic burden, although most of the data available come from temperate and resource rich countries (3-6). Understanding the costs of influenza-associated illness in Kenya is critical to allow health authorities and policy makers to develop practical plans for vaccine recommendations.

We estimated the cost-per-episode, from a societal perspective, of laboratory-confirmed influenza-associated illness in Kenya using data collected from interviews with case-patients or their care-takers, and abstracted from medical records. Additionally, we estimated the annual economic burden of influenza-associated illness in Kenya by applying the estimated costs to the annual national morbidity burden using previously published data on burden of influenza-associated disease.

7.2 Methods

7.2.1 Study sites and population

From July 2013 through August 2014, we prospectively enrolled patients from four hospitals [Mombasa County Referral Hospital (CRH), Nakuru CRH, Nyeri CRH, and St. Elizabeth Mission Hospital in Lwak] and one outpatient facility (Tabitha clinic in Kibera) (Figure 7.1). Mombasa CRH, Nakuru CRH and Nyeri CRH are public health facilities. Kibera clinic is located in an urban informal settlement in Nairobi and is operated by Carolina for Kibera (7). St. Elizabeth Mission hospital is a rural site in western Kenya operated by the Franciscan Sisters of St. Anna (7). The study sites were purposely selected for their diversity and their representation of populations in multiple geographical locations (Figure 7.1).

Patients were enrolled if they met the case definitions for severe acute respiratory illness (SARI) or influenza-like illness (ILI) and tested positive for influenza A and/or B using the Becton Dickson (BD) Veritor™ rapid diagnostic test (RDT) in nasal swabs collected at interview (8, 9). SARI was defined as hospitalization with an acute respiratory infection within the last ten days with a history of fever or measured temperature ≥38 C°, and cough. ILI was defined as an acute respiratory infection within the last seven days with a measured temperature ≥38 C° and cough.

7.2.2 Confirmatory testing for influenza

Nasopharyngeal (NP) and oropharyngeal (OP) swabs were collected from all consenting and enrolled patients. The NP/OP swabs were combined into a single viral transport media, and tested by real-time reverse transcription polymerase chain reaction (rtRT-PCR) for influenza A and B virus at the Kenya Medical Research Institute (KEMRI) and U.S Centers for Disease Control and Prevention (CDC) laboratory

in Nairobi (10). Data from patients whose NP/OP specimens were confirmed to be positive for influenza virus by rtRT-PCR were used in the final data analysis.

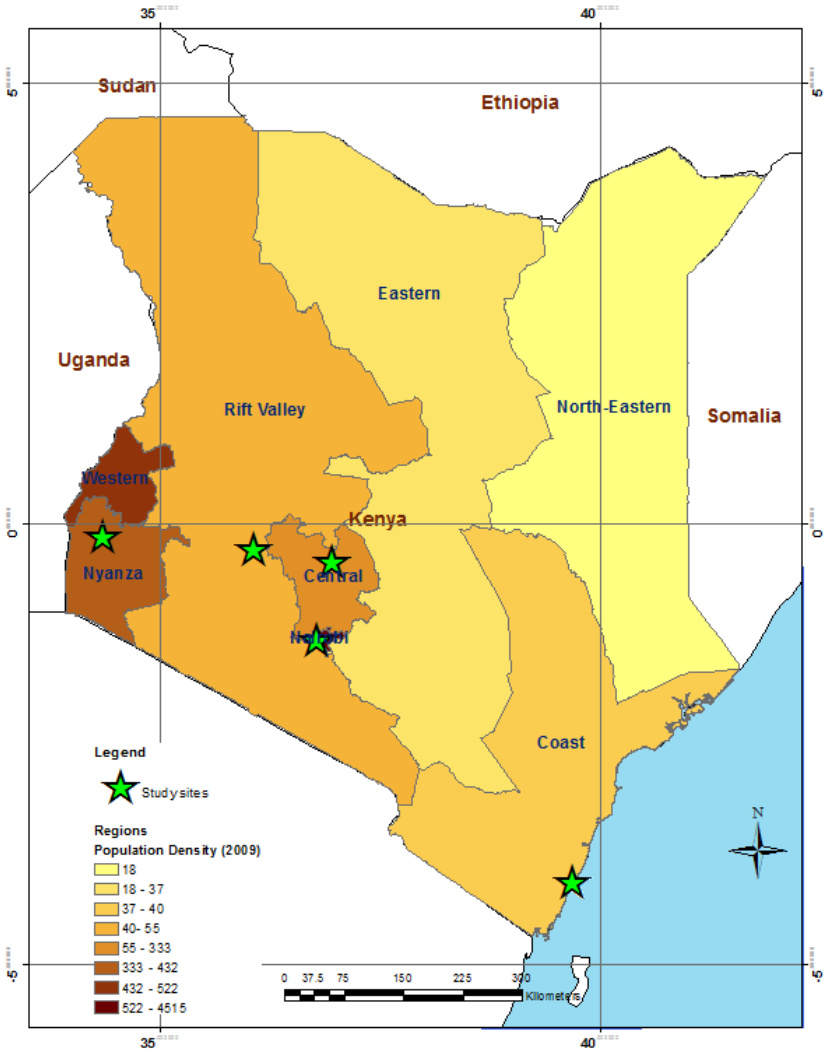

Figure 7.1: Map of Kenya showing the location of the study sites

7.2.3 Data collection

Patients who were aged ≥18 years were interviewed directly by trained surveillance officers using a structured questionnaire. For those who were aged <18 year, their care-takers were interviewed. Enrolled study participants were subsequently followed-up using telephone interviews to determine additional costs incurred over a period of 14 days from the date of testing for influenza. This period was chosen because most uncomplicated influenza infections resolve within a period of two weeks (11). To minimize the possibility of recall bias, the follow-up telephone interviews were conducted on a weekly basis. The first interview was conducted on the 8th day (to cover the preceding 7 days); and the last on the 15th day (to cover the other 7 days). Data on clinical management of the patients were abstracted from the medical records of the case-patients (i.e., patient files and charge sheets). As study participants

at the two population-based study sites receive free medical care provided by KEMRI and CDC, we used costs chargeable to non-study participants and costs of purchase provided by the study administrative staff at Lwak and Kibera, respectively.

7.2.4 Direct and indirect cost components

The direct cost components included facility-based medical-cost items (i.e. medications, laboratory investigations and other routine diagnostics, hospital bed fees, and hospital management costs) (Appendix Table 7.1), and travel costs by the case-patients and/or their household members. Facility-based medical-cost items were obtained from the hospital bill charge sheets for inpatients, price catalogue charts, and receipts issued to the outpatients (Appendix 7.1 and Appendix Table 7.1). Other direct costs included costs incurred for seeking care prior and after discharge from the hospital or outpatient visit (e.g. over the counter prescriptions). Other than children <5 years whose medical costs were paid for by the government in public health facilities, all costs (excluding consultation fees) were paid for out-of-pocket by older patients (12). The costs of testing for influenza were not included as they are not routinely ordered by clinicians independently from the ongoing surveillance.

The indirect cost component was the productivity losses (days of work lost) at the household level by the case-patients themselves, and/or any of their household members (Appendix 7.1). Data on days of work lost were only considered for those who were engaged in formal or informal income generating employment who would otherwise not be financially compensated for the lost workdays.

7.2.5 Data Analyses

5.2.5.1 Descriptive analyses and tests of associations

Data on patient characteristics were described using proportions. Tests of association were performed using chi-square tests for categorical variables. For continuous variables, data were described using means, standard deviations (SD), medians, and interquartile ranges (IQR). Comparisons of means were done using the independent t-test or one-way analysis of variance, and median and IQR were compared using Wilcoxon rank sum test or Kruskal-Wallis test as appropriate. Data analyses were performed using Stata version 13.0 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

5.2.5.2 Cost-per-episode of influenza-associated illness

The cost-per-episode of influenza-associated illness was estimated as the sum of the facility-based medical costs, household transportation costs, the costs of seeking health care prior to the current visit, and the household lost productivity cost (Appendix 7.1) (6, 13). The routine service delivery cost at the facility – which included buildings and equipment maintenance, transport, electricity, water, fuel, communication, stationery, and wages for support staff – was estimated for each patient using health facility administration data collected over the financial year 2014 (Appendix 7.1). We also explored the option of using the WHO-Choice estimates for routine healthcare service costs for hospitalized patients (cost per bed day) and outpatients (cost per outpatient visit) (14). We found minimal differences

compared to when we used actual data and subsequently opted to report costs calculated using the actual routine healthcare service cost data collected from the study sites (Appendix 7.1). Definitions and data sources of the cost components are provided in Appendix Tables 7.1.

5.2.5.3 National economic burden of influenza-associated illness

To estimate the annual economic burden of influenza-associated illness, we used the published national annual incidence (between 2007 and 2013) of influenza-associated hospitalizations and outpatient visits for children <5 years and persons ≥5 years (15). We carried out a sensitivity analysis for the best- and worst-case scenario assuming a low and high incidence of influenza-associated illness respectively (15). We applied the incidence rates to the population size in 2014, projecting an annual growth rate of 2.7% from the 2009 national census, to estimate the annual number of hospitalizations and outpatient visits associated with influenza illness (16, 17). We used bootstrap samples – with 1,000 replications of the same size as the original dataset and sampled with replacement – to estimate the mean costs which were then applied to the hospitalizations and outpatient visits to estimate overall costs. All costs reported in our analysis are in United States (U.S.) Dollars (1 US$=90 Kenya Shillings in 2014).

7.3 Ethical considerations

The KEMRI Ethical Review Committee (KEMRI SSC-2492) and Institutional Review Board of U.S CDC (CDC IRB # 6539) approved this study. Written informed consent was obtained from all participants or caretakers/guardians of all minors prior to enrolment in the study and sample collection.

7.4 Results

7.4.1 Descriptive analyses

From July 2013 through August 2014, a total of 418 patients were initially recruited in the study. After excluding patients who tested negative for influenza by rtRT-PCR and those without follow up data, a total of 275 case-patients were included in the final analysis (Figure 7.2 and Table 7.1). Among these were 105 inpatients (<5 years=88; ≥5 years=17), and 170 outpatients (<5 years=112; ≥5 years=58). The majority (73%) of the case-patients were children <5 years. Among persons ≥5 years, median age was 11 years (interquartile range [IQR], 7-30); only 7 (9%) were aged ≥40 years. Overall 135 (49%) were males (Table 7.1). The median length of hospitalization was 4 days (IQR, 3-6); 5 days (IQR, 3-7) among children <5 years compared to 4 days (IQR, 3-4) among older patients (p=0.050). The average monthly household income was US$ 225.83 (20,325 Kenya shillings).

Forty six percent of the case-patients aged <5 years were taken to care or had drugs bought for them over the counter prior to enrollment compared to 20% for persons aged ≥5 years (p<0.001). The median (IQR) number of workday opportunity losses was 2 days (0-6); 5 days (2-9) among inpatients vs. 1 day (0-3) among outpatients (p<0.001). The median (IQR) number of school-days lost in the households of the case-patients was 4 days (3-6); 3 days (1-6) among inpatients vs. 4 days (3-6) among outpatients (Table 7.1).

7.4.2 Cost of influenza-associated illness

We found differences in the distributions of the costs per-episode of influenza by site among outpatients (mean costs ranged from US$ 12.29 - 47.78; p=0.002), but no differences among inpatients (mean costs ranged from US$ 110.82 - 130.97; p=0.461). The overall mean (SD) cost per episode among hospitalized patients was US$117.86 (88.04): <5 years=US$114.25 (90.03); and ≥5 years=US$137.45 (76.24). The mean (SD) cost per episode among outpatients overall was US$19.82 (27.29): <5 years=US$21.49 (31.42); and ≥5 years=US$16.79 (17.30) (Table 7.2 and Appendix Tables 7.2 and 7.3). The health facility service delivery mean (SD) costs among inpatients were estimated at US$59.19 (59.39), and were thirteen times higher compared to outpatients (US$4.34 [1.30]). Overall, the mean fraction of the total cost-per-episode of influenza-associated illness relative to the average monthly household income was 60% (95% CI 45 – 75) among hospitalized patients. However, when the costs that were paid by the government for children <5 years were excluded, cost-per-episode related to monthly income was 40% (95% CI 34 - 46). Cost-per-episode for outpatients relative to monthly income was 12% (95% CI 10 - 14); 11% (95% CI 9 - 13) if costs paid by the government for children <5 years were excluded.

Direct mean (SD) costs associated with influenza were ten times higher for hospitalizations (US$ 75.43 [66.73]) compared to outpatient visits (US$ 7.68 [5.63]). The mean (SD) cost associated with hospitalization was US$75.42 (71.10) for children <5 years and US$75.45 (36.27) for persons ≥5 years. For outpatient visits the mean (SD) cost was US$8.62 (6.15) for children <5 years, and US$5.97 (4.07) for persons ≥5 years (Table 7.2 and Appendix Tables 7.2 and 7.3). The overall mean (SD) indirect cost-per-episode of influenza-associated illness was US$42.01 (41.54) (<5 years=US$38.94 [38.59]; and ≥5 years=US$58.61 [53.37]) among hospitalized patients compared to US$12.84 (27.17) (<5 years=US$13.87 [31.36]; and ≥5 years=US$10.88 [16.65]) among outpatients.

7.4.3 National economic burden of influenza-associated illness

Assuming the lowest (<5 years= 2.7 per 1,000 children; ≥5 years= 0.2 per 1,000 persons) and highest (<5 years=4.7 per 1,000 children; ≥5 years=0.4 per 1,000 persons) published incidence of hospitalizations associated with influenza activity in Kenya [15], we estimated total hospitalizations to range from 25,154 to 45,672 (<5 years=17,875 - 31,115; ≥5 years=7,279 - 14,557). These would result in costs ranging from US$ 2.96 to 5.37 million (<5 years= US$2.04 – 3.55 million; ≥5 years= US$1.00 – 1.99 million) (Table 7.3). Similarly, assuming lowest (<5 years= 21.8 per 1,000 children; ≥5 years= 4.3 per 1,000 persons) and highest rates (<5 years= 58.0 per 1,000 children; ≥5 years= 26.0 per 1,000 persons) [15], we estimated that outpatient visits associated with influenza would range from 300,813 to 1,330,200 [<5 years=144,322 - 383,977; ≥5 years=156,491 - 946,223]. These would translate to a total

cost ranging from US$5.96 to 26.35 million (<5 years= US$3.09 – 8.23 million; ≥5 years=US$2.64 – 15.96 million). The overall cost associated with influenza (combining in- and outpatients) could range from US$ 8.92 to 31.72 million.

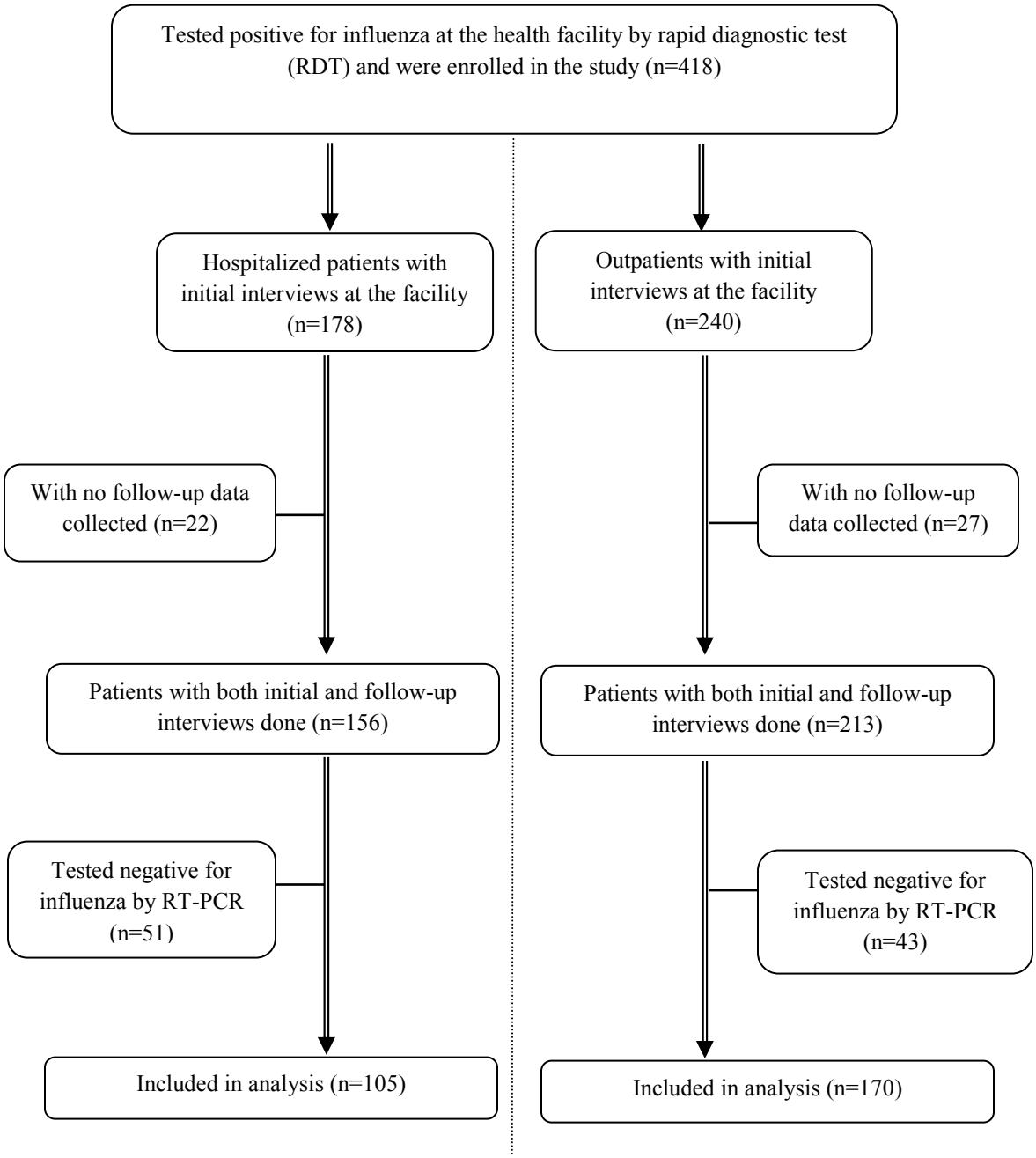

Figure 7.2: Data flow diagram

7.5 Discussion

This is the first estimate of the economic impact associated with medically-attended influenza in Kenya. We found that, depending on annual influenza virus circulation, the costs associated with influenza in Kenya could be as high as US$ 32 million. We estimated that the overall mean cost per episode was US$118 for hospitalization and US$20 for outpatient visits, a substantial burden for Kenyan families when we consider their average monthly income, the loss of self-employment wages by missed days at work, and that most of medical costs are paid out-of-pocket. Influenza vaccine is the most effective way to prevent influenza and should be considered for groups at risk of influenza-associated complications and hospitalizations in Kenya.

The overall cost-per-episode of influenza-associated hospitalizations was six times higher when compared to outpatient visits. This was driven by the facility-based medical cost component, where the hospitalization cost was thirteen-fold higher, and was similar to the results published in Bangladesh (13). Because of the higher frequency of outpatient visits, the annual economic burden for outpatient influenza-associated illness in Kenya was substantially high relative to hospitalizations, which is consistent with results reported from other studies (3, 13). However, the overall cost-per-episode of influenza in our study was lower than reported elsewhere in developed countries (5, 18). This could be explained by the relative lower cost of healthcare and the comparatively low income level in Kenya where the gross national income per capita is estimated at US$939 (19).

The duration of hospitalization was higher for children <5 years compared to older persons. This is contrary to findings reported elsewhere (6) and may be explained by the fact that in our study population only 7 persons were >40 years old. Older adults tend to stay longer in hospital due to complications associated with underlying diseases (20). We also found that the cost-per-episode when the illness involved a child <5 years old was similar to the cost among older patients aged ≥5 years. Other than the effect of underrepresentation of older patients in our study, this finding could also be explained by the fact that a higher percentage (46%) of children <5 years compared to older patients (20%) had sought healthcare or had drugs bought over the counter prior to the hospitalization or outpatient visit. The fact that an influenza-associated illness involving young children – who are at a high risk of influenza-associated complications (21, 22) – also results in high economic cost highlights the need for the development of targeted vaccination and other preventive strategies among this age group.

Besides the loss of income opportunities, influenza-associated illness also resulted in school absenteeism with a median of 4 days of missed school, which was comparable to findings from a study conducted in Hong Kong (23), and another study conducted in the US (4). Notably, we found that school absenteeism was higher among households of outpatients compared to those of hospitalized patients. This could be explained by the fact that older siblings may be asked to stay at home and take care of the younger ones as the caretakers take the sick child to a health facility. However, in a case of hospitalization - where it may not be certain when the mother/parent will return - young children may be left at the care of relatives or neighbors.

Overall, a single episode of influenza-associated hospitalization resulted in a substantial cost of approximately 60% of the household average monthly income while outpatient-associated influenza costs represented 12%. Regardless of the fact that medical costs at the hospital were covered by the government for children < 5 years (12), the overall resultant costs from an influenza-associated hospitalization – which were paid out-of-pocket (40% of the household average monthly income) –

could put a financial strain on families (24) and may also negatively impact on other competing household priorities such as food and education. Considering the possibilities of influenza-associated complications, the financial impact to the household arising from such cases could even be greater.

The mean cost-per-episode of influenza among children <5 years in our study (US$114) was similar to the coast reported in a study of malaria patients that was conducted in Kenya in 2009 which reported a mean cost of US$100 (25). However, there were some differences in the methodologies of these studies that would limit our ability to make direct comparisons. Unlike in our study, death was included in the household indirect cost where it was calculated as the net present value of future potential earnings. The resultant total indirect cost accounted for 60% of the overall mean cost per episode of malaria.

Our study had some important limitations. First, older patients were underrepresented in our patient-population as healthcare seeking is low in this group (26), and our cost estimates associated with influenza could be underestimated in this group, principally considering the high prevalence of underlying medical conditions that could lead to prolonged hospitalization. Indeed, as routinely seen in our hospital-based surveillance, only 3% of the study participants were aged ≥40 years. Second, we did not include the physician's fees in our analysis. We also did not incorporate the indirect cost of days with reduced activity among case-patients, productivity loss for non-income generating activities, and deaths in our data collection and subsequently in the analysis. This could have further served to underestimate the actual costs associated with influenza. Third, the self-reported costs on prior expenditures and post-discharge expenditures could have suffered some degree of under- or over reporting as they were not substantiated by receipts. Fourth, we were not able to stratify our cost analysis by underlying comorbidities, e.g., only 5% of the study participants had been tested for HIV. Lastly, we did not include costs incurred by persons who did not seek care because of influenza illness; costs of self-medication within the community and related loss of productivity by these persons went unmeasured.

Our findings show that medically attended, influenza-associated illness in Kenya generate substantial direct and indirect costs. The burden is driven mostly by outpatient visits. Recommendations to vaccinate young children <5 years may be warranted as this age group bears a disproportionately high influenza disease burden which results in substantial financial costs to their families and the government (27). Whereas this study highlights an important societal economic impact of influenza-associated illness, further studies should explore the cost-effectiveness of targeted influenza vaccination in Kenya and account for years lost due to death or disability.

Acknowledgments: We thank the study participants at the study sites without whom this study would not have taken place. We also thank the clinical and laboratory staff at St. Elizabeth Hospital in Lwak, Tabitha Clinic in Kibera, and the influenza surveillance officers at Mombasa, Nyeri, and Nakuru for their hard work in data and specimen collection and processing of the specimens. We acknowledge the important role played by Dr. Florence Diemo, and Dr. Victor Bandika for providing oversight of the study protocol at St. Elizabeth Lwak, and Mombasa CRH respectively. We also acknowledge the role played by the data management team in Nairobi lead by Geoffrey Arunga.

Table 7.1: General characteristics of study patients with influenza-associated illnesses in Kenya, July 2013 - August 2014

Variable	All data (n=275)	Inpatients			Outpatients		
		<5 years (n=88)	≥5 years (n=17)	Total (n=105)	<5 years (n=112)	≥5 years (n=58)	Total (n=170)
Hospital, n(%)							
Coast PGH	38 (13.8)	25 (28.4)	0 (0.0)	25 (23.8)	13 (11.6)	0 (0.0)	13 (7.7)
Nyeri PGH	35 (12.7)	28 (31.8)	5 (29.4)	33 (31.4)	2 (1.8)	0 (0.0)	2 (1.2)
Nakuru PGH	98 (35.6)	35 (39.8)	12 (70.6)	47 (44.8)	45 (40.2)	6 (10.3)	51 (30.0)
Tabitha Clinic (Kibera)	89 (32.4)	0 (0.0)	0 (0.0)	0 (0.0)	48 (42.9)	41 (70.7)	89 (52.4)
St. Elizabeth Hosp. (Lwak)	15 (5.5)	0 (0.0)	0 (0.0)	0 (0.0)	4 (3.6)	11 (19.0)	15 (8.8)
Sex of patient (Male), n(%)	135 (49.1)	50 (56.8)	7 (41.2)	57 (54.3)	58 (51.8)	20 (34.5)	78 (45.9)
Age of patient (<5 years), n(%)	200 (72.7)	88 (100.0)	N/A	88 (83.81)	112 (100.0)	N/A	112 (65.9)
Relationship of respondent to patient, n(%)							
Self	31 (11.3)	0 (0.0)	8 (47.1)	9 (8.6)	0 (0.0)	22 (37.9)	22 (12.9)
Mother	222 (80.7)	81 (92.0)	8 (47.1)	88 (83.8)	105 (93.8)	29 (50.0)	134 (78.8)
Father	13 (4.7)	4 (4.6)	0 (0.0)	4 (3.8)	6 (5.4)	3 (5.2)	9 (5.3)
Other	9 (3.3)	3 (3.4)	1 (5.9)	4 (3.8)	1 (0.9)	4 (6.9)	5 (2.9)
Sought care prior to this hospitalization/outpatient visit, n(%)	107 (38.9)	58 (65.9)	10 (58.8)	68 (64.8)	34 (30.4)	5 (8.6)	39 (22.9)
Purchased any medications prior to hospital/clinic visit, n(%)	77/107 (72.0)	42/58 (72.4)	7/10 (70.0)	49/68 (72.1)	24/34 (70.6)	4/5 (80.0)	28/39 (71.8)
Sought care after discharge from the hospital/clinic, n(%)	26 (9.5)	8 (9.1)	3 (17.7)	11 (10.5)	11 (9.8)	4 (6.9)	15 (8.8)
Household member(s) missed work due to illness, n(%)	177 (64.4)	72 (81.8)	17 (100.0)	89 (84.8)	54 (48.2)	34 (58.6)	88 (51.8)
Total number of workdays lost in a household, median(IQR)	4 (3-8)	7 (4-10)	6 (3-13)	6 (4-10)	3 (2-6)	3 (2-5)	3 (2-5)
Average number of household workdays lost due to illness, median (IQR)*	4 (2-7)	5 (3-9)	6 (3-12)	5 (3-9)	3 (2-5)	3 (2-4)	3 (2-5)
Household member(s) missed school due to illness, n(%)	90 (32.7)	17 (19.3)	6 (35.3)	23 (21.9)	35 (31.3)	32 (55.2)	67 (39.4)
Total number of school days missed, median(IQR)	4 (3-6)	2 (1-6)	5 (4-9)	3 (1-6)	3 (2-6)	4 (3-7)	4 (3-6)
Paid for child care in the course of sickness, n(%)	6 (2.2)	3 (3.4)	0 (0.0)	3 (2.9)	1 (0.9)	2 (3.5)	3 (1.8)
Paid for child care in the course of sickness, n(%)	6 (2.2)	3 (3.4)	0 (0.0)	3 (2.9)	1 (0.9)	2 (3.5)	3 (1.8)

NA – Not applicable; *Calculated as the total number of workdays lost by all household members who reported to be engaged in an income activity divided by the number of persons who reported to be engaged in an income activity.

Table 7.2: Overall costs, including direct and indirect costs, related to influenza-associated illness in Kenya, July 2013 - August 2014

Expenditure item	Costs among inpatients (US$ǂ)						Costs among outpatients (US$ǂ)					
	<5 years		≥5 years		Total		<5 years		≥5 years		Total	
	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)	n	Mean(SD)
Direct cost	76	75.42 (71.10)	14	75.45 (36.27)	90	75.43 (66.73)	100	8.62 (6.15)	55	5.97 (4.07)	155	7.68 (5.63)
Healthcare prior to hospital/clinic visit	88	7.59 (16.95)	17	6.56 (8.48)	105	7.42 (15.86)	110	2.04 (4.67)	58	0.17 (0.82)	168	1.39 (3.90)
Total facility-based medical costs	83	59.81 (63.60)	15	55.77 (27.05)	98	59.19 (59.39)	108	4.30 (1.27)	57	4.43 (1.36)	165	4.34 (1.30)
Medications	83	13.90 (52.47)	15	18.31 (17.45)	98	14.58 (48.72)	108	0.96 (1.11)	57	1.10 (1.20)	165	1.01 (1.14)
Hospital bed fees	83	22.11 (13.95)	15	15.70 (6.13)	98	21.13 (13.24)	0	N/A	0	N/A	0	N/A
Procedure fees (non-/surgical)	83	2.48 (5.03)	15	2.44 (2.19)	98	2.48 (4.70)	108	0.00 (0.00)	57	0.00 (0.00)	165	0.00 (0.00)
Diagnostic tests	83	4.59 (9.72)	15	7.84 (10.33)	98	5.09 (9.83)	108	0.11 (0.51)	57	0.11 (0.24)	165	0.11 (0.43)
Routine health facility service management cost[a]	83	16.59 (10.24)	15	11.40 (4.02)	98	15.80 (9.72)	108	3.23 (0.00)*	57	3.23 (0.00)*	165	3.23 (0.00)*
Total transportation costs	88	4.68 (8.02)	17	6.86 (9.78)	105	5.03 (8.32)	112	0.48 (0.83)	58	0.25 (0.94)	170	0.40 (0.87)
Personal car/taxi	10	10.88 (9.51)	5	23.91 (28.40)	15	15.22 (18.14)	1	0.56 (-)	0	-	1	0.56 (-)
Matatu/bus	70	9.39 (9.79)	17	6.74 (5.35)	87	8.87 (9.13)	42	3.91 (8.42)	6	8.24 (9.52)	48	4.45 (8.58)
Motorbike/bike/tuktuk	15	5.36 (5.08)	2	16.39 (12.18)	17	6.66 (6.73)	17	2.59 (1.95)	5	3.33 (1.96)	22	2.76 (1.93)
Healthcare after discharge	88	3.25 (5.95)	17	3.43 (7.53)	105	3.28 (6.19)	112	2.46 (4.77)	58	1.19 (3.48)	170	2.03 (4.40)
Child care cost	88	0.14 (0.81)	17	0.00 (0.00)	105	0.11 (0.75)	112	0.04 (0.42)	58	0.13 (0.78)	170	0.07 (0.57)
Indirect cost (Average household productivity loss[b])	81	38.94 (38.59)	15	58.61 (53.37)	96	42.01 (41.54)	106	13.87 (31.36)	56	10.88 (16.65)	162	12.84 (27.17)
Total cost per episode[c]	76	114.25 (90.03)	14	137.45 (76.24)	90	117.86 (88.04)	100	21.49 (31.42)	55	16.79 (17.30)	155	19.82 (27.29)
Total cost per episode paid out of pocket	76	76.45 (55.13)	14	137.45 (76.24)	90	85.94 (62.49)	100	19.21 (30.70)	55	16.79 (17.30)	155	18.35 (26.69)

SD–Standard Deviation; NA-Not applicable; [a]Routine healthcare facility management costs for healthcare service costs per day (equipment maintenance, electricity, water, stationary, e.t.c); [b]Estimated by multiplying the average days when the household lost income opportunities by the household average daily income; [c]Sum of direct and indirect costs.

ǂ1 US$=90 Kenya Shillings; *No variability as the same amount was used for all patients

Table 7.3: Estimated annual costs (in millions of 2014 US$) of influenza-associated illnesses in Kenya

Cost Item (per episode)	Hospitalized patients				Outpatients			
	Best-case scenario		Worst-case scenario		Best-case scenario		Worst-case scenario	
	Estimated cases	Cost (US$[†] Millions) (95% CI[c])	Estimated cases	Cost (US$[†] Millions) (95% CI[c])	Estimated cases	Cost (US$[†] Millions) (95% CI[c])	Estimated cases	Cost (US$[†] Millions) (95% CI[c])
Children <5 years[a]	17,875		31,115		144,322		383,977	
Total direct costs		1.34 (1.10-1.63)		2.34 (1.92-2.84)		1.25 (1.09-1.41)		3.33 (2.89-3.76)
Facility-based medical costs		1.08 (0.89-1.34)		1.87 (1.54-2.33)		0.62 (0.59-0.66)		1.65 (1.56-1.75)
Transportation costs		0.08 (0.06-0.12)		0.15 (0.10-0.21)		0.07 (0.05-0.09)		0.18 (0.13-0.24)
Other costs[b]		0.20 (0.13-0.27)		0.34 (0.23-0.47)		0.66 (0.48-0.85)		1.76 (1.27-2.25)
Total indirect		0.70 (0.56-0.85)		1.21 (0.97-1.48)		2.01 (1.23-2.97)		5.35 (3.28-7.91)
Total costs		2.04 (1.73-2.41)		3.55 (3.01-4.19)		3.09 (2.32-4.07)		8.23 (6.18-10.84)
Persons ≥5 years[a]	7,279		14,557		156,491		946,223	
Total direct costs		0.55 (0.41-0.69)		1.10 (0.81-1.37)		0.93 (0.78-1.11)		5.64 (4.72-6.69)
Facility-based medical costs		0.41 (0.32-0.53)		0.81 (0.63-1.07)		0.69 (0.64-0.75)		4.20 (3.89-4.55)
Transportation costs		0.05 (0.02-0.09)		0.10 (0.04-0.18)		0.04 (0.01-0.08)		0.24 (0.05-0.50)
Other costs[b]		0.07 (0.04-0.11)		0.15 (0.07-0.22)		0.23 (0.10-0.40)		1.42 (0.63-2.43)
Total indirect		0.43 (0.26-0.65)		0.86 (0.51-1.30)		1.69 (1.09-2.40)		10.24 (6.61-14.49)
Total costs		1.00 (0.71-1.30)		1.99 (1.42-2.59)		2.64 (1.99-3.38)		15.96 (12.02-20.43)
All ages	25,154		45,672		300,813		1,330,200	
Total direct costs		1.89 (1.60-2.25)		3.44 (2.90-4.09)		2.32 (2.08-2.58)		10.24 (9.18-11.40)
Total indirect		1.06 (0.86-1.28)		1.92 (1.55-2.33)		3.87 (2.71-5.24)		17.11 (11.98-23.17)
Total costs		2.96 (2.57-3.41)		5.37 (4.66-6.19)		5.96 (4.80-7.49)		26.35 (21.22-33.14)

[a]Estimated using published rates of influenza-associated disease in Kenya [hospitalization rate (<5 years=2.7-4.7 per 1,000; ≥5 years=0.2-0.4 per 1,000) and outpatient rate (<5 years=13.0-58.0 per 1,000; ≥5 years=4.3-26.0 per 1,000)]; [b]Combines costs for childcare, and healthcare seeking prior and after hospitalization or outpatient visit; [c]Mean cost and 95% confidence intervals estimated using 1,000 bootstrap samples

Best-case scenario: Assuming the lowest published incidence rate of influenza-associated illness

Worst-case scenario: Assuming the highest published incidence rate of influenza-associated illness

[†]1 US$=90 Kenya Shillings (2014).

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Appendix 7.1: Supplementary methods

Estimation of the routine service delivery cost

The routine service delivery cost – which included buildings and equipment maintenance, transport, electricity, water, fuel, communication, stationery, and wages for support staff – was estimated per day for each patient using the following steps:

1. Using a structured questionnaire, we obtained data on the actual service delivery costs covering the items mentioned above from the administrative personnel at the five study sites for the financial year 2014 (FY2014).
2. From the health records office, we obtained data on the total bed occupancy (daily sum of the patients who were hospitalized) and the outpatient visits over the same period (FY2014).
3. We then calculated the average cost per patient by dividing the total annual cost (combining data from all the five sites) by the sum total of hospitalized patients and outpatients seen each day at the five facilities over the period FY2014.
4. For hospitalized patients in our study, we then multiplied the estimate calculated in step 3 above by the number of days the patients was hospitalized. For outpatients, the estimate calculated in step 3 was used as the cost of routine health facility service delivery.

To minimize the potential for double counting costs, registration fees were not included in the analysis of the facility-based medical fees as such.

Estimation of the lost opportunity cost

To estimate the household lost opportunity cost, we used data on average monthly household income and number of people who missed work or income opportunities due to the illness of the case-patient. Studies conducted elsewhere have limited their calculation of opportunity loses to the case-patient and/or their care taker (1-3). In our context, we thought that this would potentially underestimate the cost involved as household members tend to play an important role in an illness episode which may include absenteeism from work and school (4). We used the following steps to calculate the household opportunity cost:

1. For each household of the case-patient enrolled in our study, we collected data on the average monthly household income. We also collected data for each person in the household (including the case-patient) who missed work or income opportunities as a result of the illness of the case-patient, and the total number of days when they missed such opportunities.
2. As the next step, we calculated the household average number of days of missed work opportunities by dividing the sum total of the number of days of work missed by all the household members by the number of people in the household who reported to be engaged in an income generating activity.
3. We then calculated the average daily household income by dividing the average monthly household income by 30 days.

4. The average daily household income was then multiplied by the average number of days of missed work opportunities in the household as calculated in step 2 above to estimate overall opportunity cost over the duration of the illness episode.

We also considered using data on the individual-based opportunity cost reported for each of the household members who missed work opportunities but refrained from using the data as we found that some of the numbers reported were unusually high and in contradiction to the reported monthly household income.

Comparison of cost data estimated with and without WHO-CHOICE estimates

We explored the option of using the WHO-CHOICE estimates for health facility service delivery costs [5]. However, we found minimal differences when we used actual data collected from the study sites to estimate the health facility service delivery costs compared to when we used the WHO-Choice estimates. Among inpatients the overall mean (SD) cost per episode was US$117.86 (88.04) using the actual data compared to US$112.06 (87.41) when we used the WHO-Choice estimates (p=0.658). Among outpatients the overall mean (SD) cost per episode was US$19.82 (27.29) using the actual data compared to US$19.14 (27.31) when we used the WHO-Choice estimates (p=0.8254). Similarly, no statistically significant differences were found when we compared the overall medical costs among inpatients using these two different methods [mean (SD) = US$59.35 (61.12) using actual data compared to mean (SD) = US$53.55 (60.87) using the WHO-Choice estimates]. However, the medical costs were significantly higher among outpatients when we used the actual data [mean (SD) = US$ 4.29 (1.24)] compared to [mean (SD), US$3.60 (1.23)] when we used the WHO-Choice estimates (p<0.001).

References for supplemental methods

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Appendix Table 7.1: Definition and data source of key study variables

Variable	Definition	Rationale	Data source
Facility-based medical costs	All medical costs incurred at the facility. Includes registration fees, cost of medications, hospital bed fees, medical procedure costs, diagnostics, and Healthcare service delivery cost. Costs were calculated up to a maximum of 14 days from the date when the patient was tested for influenza. Costs among children<5 years are paid for by the government while costs among persons >5 years are borne by the patient. There were no extra charges on hospital bed fees for caretakers inpatients	Component of direct costs	These data were collected at the time of discharge by referring to the patient files, hospital discharge billing sheets and outpatient receipts, catalogue of prices for medications and laboratory tests. Additional costs of medication collected during follow-up interviews for patients who sought healthcare after discharge.
Routine service delivery costs	Cost of routine management of the health facility including (buildings and equipment management, transport, electricity, water, fuel, communication, Stationery, wages for support staff). These costs are borne by the government	Component of direct costs	Health facility administrative records
Healthcare cost prior to hospital/clinic visit	Total costs (medications and transportation) associated with current illness episode for which healthcare was sought prior to hospitalization or outpatient visit. These costs are borne by the patient	Component of direct costs	Self-reported in the initial interview upon enrolment
Post-discharge healthcare cost	Total costs (medications and transportation) to the household associated with current illness episode for which healthcare was sought after the case-patient was discharged and to a maximum of 14 days from the date of testing for influenza. These costs are borne by the patient	Component of direct costs	Self-reported costs during follow-up interviews. Excludes medication costs for the days the patient was still hospitalized
Transport cost	Costs to facilitate movement to and from the medical facility or place of seeking care by the patient and household members. Includes both private and public means. These costs are borne by the patient	Component of direct costs	self-reported during the initial interview and follow-up interviews
Child care cost	Cost paid for childcare of other children in the household while the respondent was ill or taking care of the patient. These costs are borne by the patient	Component of direct cost	Self-reported during the initial interview and follow-up interviews
Lost work days	Workdays lost by any of the household members due to influenza-associated illness	Component of in-direct costs and used to estimate the household productivity loss cost	Self-reported during the initial interview and follow-up interviews
Household lost work days	Average number of days when the household missed work opportunities	Used to estimate the household productivity loss cost	Collected during the initial and follow-up interviews. Calculated as the total numbers of work days opportunities missed by all the household members divided by the number of people in the household who lost such opportunities
Household daily income	Self-reported daily income for the household	Used to estimate the household productivity loss cost. The midpoint value of the income category was used to represent household income	Estimated from the self-reported household monthly income. For each case-patient, the daily income was calculated by dividing the average monthly income amount (for each income category reported) by 30 days. The income categories were ≤5,000; 5,001-10,000; 10,001-25,000; 25,001-50,000; 50,001-100,000 and ≥100,000.
Household productivity loss	The monetary loss of productivity per household due the illness	Component of indirect costs	Self-reported during the initial interview and follow-up interviews
Lost school days	School days not attended by any member of the household due to influenza infection	Component of indirect costs but was not quantified in monetary terms	Self-reported during the initial interview and follow-up interviews

Appendix Table 7.2: Overall costs, direct and indirect costs, related to influenza-associated illness among inpatients, Jul 2013 - Aug 2014

Expenditure item	Costs among inpatients (US$ǂ)					
	<5 years		≥5 years		Total	
	n	Median(IQR)	n	Median(IQR)	n	Median(IQR)
Direct cost	76	64.96(38.18-94.80)	14	78.85(45.23-88.57)	90	65.31(39.57-90.47)
Healthcare prior to hospital/clinic visit	88	2.11(0.00-7.78)	17	5.56(0.00-7.22)	105	2.11(0.00-7.78)
Total facility-based medical costs	83	52.12(28.90-73.24)	15	54.68(38.57-60.12)	98	52.46(32.79-69.79)
Medications	83	3.89(1.11-15.11)	15	17.56(2.44-22.00)	98	5.95(1.11-16.78)
Hospital bed fees	83	20.00(11.11-30.00)	15	15.00(11.11-20.00)	98	20.00(11.11-27.78)
Procedure fees (non-/surgical)	83	0.56(0.00-4.44)	15	3.33(0.00-4.44)	98	0.56(0.00-4.44)
Diagnostic tests	83	2.22(0.00-4.44)	15	5.56(0.00-15.56)	98	2.22(0.00-5.00)
Routine health facility service management cost[a]	83	16.13(9.68-22.58)	15	9.68(9.68-12.90)	98	12.90(9.68-19.35)
Total transportation costs	88	2.22(0.00-6.39)	17	2.22(0.78-7.78)	105	2.22(0.00-7.00)
Personal car/taxi	10	8.00(5.56-11.11)	5	11.11(2.22-38.89)	15	10.00(4.44-22.22)
Matatu/bus	70	6.67(3.33-13.33)	17	4.67(2.33-12.00)	87	6.67(3.00-12.67)
Motorbike/bike/tuktuk	15	3.33(2.22-6.11)	2	16.39(7.78-25.00)	17	3.33(2.67-7.78)
Healthcare after discharge	88	0.50(0.00-3.89)	17	0.00(0.00-3.89)	105	0.33(0.00-3.89)
Child care cost	88	0.00(0.00-0.00)	17	0.00(0.00-0.00)	105	0.00(0.00-0.00)
Indirect cost (Average household productivity loss[b])	81	25.93(11.11-58.33)	15	38.89(19.44-77.78)	96	30.09(12.04-59.72)
Total cost per episode[c]	76	91.35(69.07-136.54)	14	122.39(75.01-163.35)	90	92.98(69.45-141.30)
Total cost per episode paid out of pocket	76	60.85(39.33-88.41)	14	122.39(75.01-163.35)	90	68.00(45.93-107.22)

IQR – Interquartile Range; NA-Not applicable; [a]Routine healthcare facility management costs for healthcare service costs per day (equipment maintenance, electricity, water, stationary, e.t.c); [b]Estimated by multiplying the average days when the household lost income opportunities by the household average daily income; [c]Sum of direct and indirect costs.
ǂ 1 US$=90 Kenya Shilings

Appendix Table 7.3: Overall costs, direct and indirect costs, related to influenza-associated illness among outpatients, Jul 2013 - Aug 2014

Expenditure item	Costs (US$ǂ)					
	<5 years		≥5 years		Total	
	n	Median(IQR)	n	Median(IQR)	n	Median(IQR)
Direct cost	100	6.39(4.14-11.11)	55	3.95(3.67-6.95)	155	5.47(3.73-10.17)
Healthcare prior to hospital/clinic visit	110	0.00(0.00-1.89)	58	0.00(0.00-0.00)	168	0.00(0.00-0.00)
Total facility-based medical costs	108	3.73(3.50-4.64)	57	3.83(3.50-5.56)	165	3.80(3.50-4.75)
Medications	108	0.50(0.28-1.38)	57	0.60(0.28-1.78)	165	0.58(0.28-1.44)
Hospital bed fees	-	N/A	-	N/A	-	N/A
Procedure fees (non-/surgical)	108	0.00(0.00-0.00)	57	0.00(0.00-0.00)	165	0.00(0.00-0.00)
Diagnostic tests	108	0.00(0.00-0.00)	57	0.00(0.00-0.00)	165	0.00(0.00-0.00)
Routine health facility service management cost[a]	108	3.23(3.23-3.23)*	57	3.23(3.23-3.23)*	165	3.23(3.23-3.23)*
Total transportation costs	112	0.00(0.00-0.78)	58	0.00(0.00-0.00)	170	0.00(0.00-0.56)
Personal car/taxi	1	0.56(0.56-0.56)	0	-	1	0.56(0.56-0.56)
Matatu/bus	42	1.72(1.11-2.78)	6	5.00(0.56-15.33)	48	1.72(1.11-3.22)
Motorbike/bike/tuktuk	17	1.56(1.11-4.44)	5	2.78(2.22-3.33)	22	1.94(1.11-4.44)
Healthcare after discharge	112	0.00(0.00-4.17)	58	0.00(0.00-0.00)	170	0.00(0.00-1.89)
Child care cost	112	0.00(0.00-0.00)	58	0.00(0.00-0.00)	170	0.00(0.00-0.00)
Indirect cost (Average household productivity loss[b])	106	0.00(0.00-16.67)	56	2.78(0.00-13.89)	162	0.00(0.00-16.67)
Total cost per episode[c]	100	11.36(4.94-24.61)	55	9.23(4.60-23.51)	155	10.89(4.75-23.78)
Total cost per episode paid out of pocket	100	8.056(4.19-22.78)	55	9.23(4.60-23.51)	155	8.67(4.18-23.33)

IQR – Interquartile Range; NA-Not applicable; [a]Routine healthcare facility management costs for healthcare service costs per day (equipment maintenance, electricity, water, stationary, e.t.c); [b]Estimated by multiplying the average days when the household lost income opportunities by the household average daily income; [c]Sum of direct and indirect costs.

ǂ 1 US$=90 Kenya Shilings; *No variability as the same amount was used for all patients

Chapter 8: General Discussion

8.1 Introduction

The main objective of this thesis was to generate information needed to inform influenza prevention and control policies, particularly those related to influenza vaccination in Kenya. In order to achieve this objective, we conducted several epidemiologic studies in Kenya seeking to address the specific research questions listed below:

i) What is the morbidity and mortality burden of influenza-associated disease in Kenya, and which segments of the population are most affected?
ii) What are the risk factors for influenza infection and/or severe influenza in Kenya?
iii) What is the economic burden of influenza-associated disease in Kenya?

These research questions were addressed in chapter 2 to chapter 7 of this thesis. In this final chapter, we present a synthesis and overview of the key findings of the studies included in this thesis, as well as compare our findings to published research conducted elsewhere. In this chapter, we also highlight the strengths and weaknesses of the studies; discuss the implications of the findings from these studies, make recommendations for further research that is needed, and finalize with the general conclusion.

8.2 Summary of key findings and comparison to related research

8.2.1 Morbidity and mortality burden of influenza in Kenya

5.2.1.1 Morbidity burden

Research question (i) was addressed through studies presented in chapters 2, 3 and 4. In chapter 2, we provided a comprehensive summary of published studies describing the morbidity burden of influenza in Kenya. Ten studies met the inclusion criteria set in the systematic review. Of the ten studies reviewed, four presented data on influenza-associated hospitalizations and outpatient visits; five presented data on hospitalizations alone; and one study presented data on outpatient visits only. From this literature review, we established that published data on the burden of influenza in Kenya was expanding. In general, the review showed a high burden of influenza among young children, especially those aged less than two years. Indeed, studies included in our literature review showed that there were an estimated 3 to 5 cases of influenza per 1,000 among children less than five years who were hospitalized with severe acute respiratory illness (SARI); and these rates were 7-10 times higher than those observed in persons aged five years or older. Additionally, we found that rates of influenza-associated hospitalization were higher among residents of the refugee camps of Kakuma and Dadaab compared to the rates in general communities in other parts of Kenya. Rates of hospitalizations associated with influenza infection were similar to rates reported in South Africa (1), Asia (2-7), and Latin America (8). However, some of the rates were up to seven times higher than those reported in the United States (9-14) and Europe (15, 16).

In chapter 3, we found that influenza was associated with a high burden of hospitalization for SARI among children aged less than six months in Western Kenya with an estimated incidence of 6 cases per 1,000 persons. These findings were similar to findings from another study in the same region which reported an incidence rate of 8 cases per 1,000 persons (17). These findings are also consistent with data from several other countries (10, 11, 18), which have shown a considerable burden of disease in young infants. Another important finding from this study was that influenza was associated with a high burden of non-medically attended SARI and ILI in the community which may be similar or even higher than the medically-attended burden.

5.2.1.2 Mortality burden

Using statistical models in chapter 4, we found that influenza was associated with a higher mortality rate for all-respiratory conditions among persons aged ≥50 years (35 per 100,000 person-years), and among children aged less than five years (17 per 100,000 person-years) compared to persons who were aged 5-49 years (5 per 100,000 person-years). We also found that influenza was associated with a higher mortality rate among persons with pulmonary tuberculosis (PTB) who were aged ≥50 years (42 per 100,000 person-years) compared to their younger counterparts; children aged less than five years (2 per 100,000 person-years), and persons aged 5-49 years (7 per 100,000 person-years). Our findings on all-respiratory mortality associated with influenza among children aged less than five 5 years were similar to findings from South Africa (19). However, estimates of the mortality rates in our study were more than ten-fold higher than rates reported in the US (20, 21) and Europe (22). Consistent with our findings, high respiratory mortality rates associated with influenza among elderly persons were also reported in studies conducted in South Africa (23) and elsewhere (21, 22, 24).

8.2.2 Risk factors for influenza infection and/or severe influenza in Kenya

Research question (ii) was addressed through studies that were presented in chapters 4, 5, and 6. Through these studies, a) we describe the role chronic medical conditions such as HIV/AIDS and TB may have on influenza disease burden in Kenya, and b) we characterize the seasonality and meteorological factors that are associated with influenza activity in Kenya.

5.2.2.1 Association of HIV/AIDS and TB with transmission and burden of influenza in Kenya

In chapter 4, we presented findings on the mortality burden of HIV/AIDS and PTB related deaths. Here we found substantially high PTB related mortality rates that were associated with influenza activity; 15 per 100,000 person-years in the general population, and 42 per 100,000 person-years among older persons aged ≥50 years. We also observed that influenza was associated with higher mortality rates among older patients with PTB compared to those with all-respiratory conditions (7 vs. 5 per 100,000 person-years among persons aged 5-49 years; and 42 vs. 34 per 100,000 person-years among those aged ≥50 years). This was consistent with findings from a study conducted in

South Africa that reported very high mortality rates associated with influenza among patients with TB compared to those without TB (25). Although we did not have sufficiently large numbers to model HIV/AIDS related deaths, we observed a relatively higher mortality burden of deaths using a direct estimation method.

In chapter 5, we presented findings of a study that sought to understand the potential effects of HIV infection on household influenza transmission dynamics in an urban informal settlement in Kenya. In this study, we analyzed data from household contacts of HIV-infected influenza index cases and compared them to contacts of their HIV-negative counterparts. It was previously reported that HIV-infected individuals shed influenza viruses in higher titers and for longer periods of time than HIV-negative individuals thereby increasing the likelihood of transmission to their household contacts (26, 27). Similarly, we found that household contacts of HIV-infected influenza index cases were about twice as likely to develop ILI compared to the household contacts of their HIV-negative counterparts.

5.2.2.2 Seasonality and meteorological factors associated with influenza activity in Kenya

In chapter 6, we investigated the seasonality and climatic factors that were associated with influenza activity in Kenya. The overall aim of this study was to characterize influenza activity which could possibly be used to inform the future timing for influenza vaccination activities in Kenya. In this study, which also analyzed and presented data by four different regions (western Kenya, Nairobi and central Kenya, northern/northeastern Kenya, and coastal Kenya), we found that there were multiple periods of increased influenza activity annually in Kenya. The findings from our study confirm reports that have suggested year-round influenza activity with multiple peaks of influenza activity in tropical countries (28, 29). On average, there were two epidemics that occurred each year in most of the regions, and these lasted for a median duration of 2-4 months. The first epidemic occurred between February and March, and the second between July and November. This finding was consistent across the four different climatic regions studied. The second epidemic was responsible for a relatively higher burden, accounting for nearly 60% of influenza cases annually. The period between April and May had the least influenza activity in Kenya.

In studies conducted elsewhere, influenza activity had previously been shown to be negatively associated with specific humidity (28, 30) and temperature (28, 31), and positively associated with rainfall (28). In our study, we found that specific humidity was significantly but negatively associated with influenza activity. As noted elsewhere (28), we were also able to confirm a hypothesis that influenza was more likely to circulate when both temperature and specific humidity were below the thresholds of 18^{o}C and 11g/Kg respectively, independent of the study site. However, contrary to a previous hypothesis that influenza activity was associated with rainfall in the tropics (28), we found no significant independent association between influenza activity and rainfall.

8.2.3 The need for data on economic burden of influenza in Kenya

To address research question (iii), we conducted a costing study for influenza-associated hospitalizations and outpatient visits which is presented in chapter 7. The aim of this study was to gain understanding of the cost of influenza-associated illness in Kenya, which may ultimately be useful in conducting economic evaluations of prevention strategies such as vaccination. We estimated the cost-per-episode of laboratory-confirmed influenza-associated illness in Kenya using data collected from five study sites in Kenya. Here we found that the mean cost-per-episode of influenza-associated hospitalization was US$118; mean cost was US$114 among children aged less than five years, and US$137 among patients aged five years or older. Among outpatients, the mean cost-per-episode of influenza-associated outpatient visit was US$20; with a mean cost of US$21 among children less than five years old, and US$17 among older patients. These costs were comparable to costs reported in Bangladesh (32) But because of the relatively lower cost of healthcare in Kenya, our estimates were substantially lower than estimates reported in developed countries such as the US (33) and Germany (34).

A sub-analysis of the data collected showed that an episode of influenza-associated illness resulted in a substantial economic burden to the households. For a hospitalized influenza case, the overall resultant cost to the families that was paid out-of-pocket was 40% of the average monthly household income. For an outpatient case, the resultant cost to the families – which was paid out-of-pocket – was 11% of the average monthly household income. When we extrapolated the estimated costs to the general Kenyan population, depending on the annual incidence which varies with the type and sub-type of influenza virus in circulation, the mean annual combined cost of hospitalization and outpatient visits associated with influenza illness ranged from US$ 9 to 32 million. Although the estimated cost-per-episode of influenza-associated outpatient visit was lower than the cost of hospitalization, the annual national economic burden of influenza was higher for outpatient visits compared to hospitalization due to the relatively high incidence of outpatient illness associated with influenza.

8.3 Strengths and weaknesses of the studies

8.3.1 Strengths of the studies

Our studies were based on epidemiologic data that were collected from population-based platforms with well-defined catchment populations that facilitated estimation of disease burden. Most of the studies included in our systematic review presented in chapter 2 and the studies presented in chapters 3, 4, and 5 originated from areas where the Kenya Medical Research Institute (KEMRI) and the US Centers for Disease Control and Prevention (CDC) research collaboration has conducted research activities since 2001 (35). The Western Kenya health demographic surveillance system (HDSS) which generated most of these data serves as a platform that has been used for a

wide range of disease-specific observational studies (e.g. malaria, rotavirus, diarrhea, HIV/AIDS, TB, respiratory disease and other important infectious and non-infectious diseases among the community), and clinical trials (36). Over the years, a substantial amount of investment has also gone into training the personnel that carry out the research activities in this region. A similar amount of training and investment was conducted KEMRI and CDC among the surveillance officers who were deployed to collect data from the influenza sentinel surveillance sites located across the country.

Estimates of the morbidity burden associated with influenza and RSV that we presented in chapter 2 to chapter 4 were based on laboratory-confirmation of these pathogens rather than on clinical case definitions. Notwithstanding the huge amount of resources required to set-up and implement case-based surveillance with laboratory-confirmation, these data enabled us to estimate rates over relatively shorter periods of time using direct estimation methods. This would be a potential limiting factor if we were to rely on statistical models alone to estimate disease burden as these require data collated over sufficiently longer periods of time; preferably five or more years (37, 38).

The influenza surveillance system in Kenya has a broad representation of sites from across the country as it was initially designed to cover each of the previous eight provinces in Kenya. This had the benefit of allowing us to capture data on seasonality that was presented in chapter 5, and the cost of influenza related illness that was presented in chapter 7 - that reflected the diverse geographical and climatic regions in Kenya. Another positive aspect of the studies presented in this thesis is that the data on influenza surveillance were collected year-round and for multiple years. This provided us with a basis for assessing the seasonality patterns and generating the time series datasets for the statistical modeling methods used in chapter 4 and 6.

8.3.2 Limitations of the studies

Our studies had some important limitations. A weakness in the estimation of the morbidity burden of influenza-associated illness studies described in chapter 2 and 3 was that we had few data for older age groups; largely because of the low healthcare seeking behaviors as has previously been documented in our setting (39, 40). Because of this limitation, we were not able to sufficiently estimate influenza-associated disease burden in older populations. Indeed, modelling studies conducted elsewhere have suggested a high mortality burden of influenza-associated hospitalizations among the elderly (9, 24). This was also a limitation with the study described in chapter 7 where we estimated costs of influenza-associated illness in Kenya. More specifically, the implication of this limitation is that we potentially underestimated the economic burden of influenza as we did not incorporate any adjustments for cases of influenza in the community who did not seek healthcare.

As in most sub-Saharan African countries, there is an absence of systematically collected, and robust vital statistics data in Kenya. For this reason, we used the verbal autopsy (VA) data to estimate excess mortality associated with influenza and RSV as presented in chapter 4. Whereas this is among the few studies to use VA data in estimating excess mortality attributable to a respiratory illness in a resource limited setting (41, 42), the extent to which such estimates vary from estimates generated using clinician certified cause-of-death data remains to be determined. The government of Kenya has collected vital statistics data in Kenya since 1963. However, at the time when we conducted our analysis, these data were only available in paper format and digitization of these data was still ongoing.

Lastly, because of the limited data available through our hospital-based surveillance platforms, we could not sufficiently explore the burden influenza among persons with underlying medical conditions such as HIV/AIDS, TB , cardiovascular diseases, cancer, asthma, and diabetes. Although we showed a substantial mortality burden associated with PTB using VA data from Western Kenya, the study findings that we presented in chapter 4 lacked sufficient data to model the mortality burden associated HIV/AIDS.

8.4 Implications of the study findings

8.4.1 Risk groups for influenza infections in Kenya

The World Health Organization through the Strategic Advisory Group of Experts (SAGE) on immunization have identified pregnant women, young children, the elderly, healthcare workers, and persons with chronic medical conditions as being at increased risk of severe outcomes due to influenza infection. SAGE suggests that they should be targeted for influenza vaccination (43). The findings that we present in this thesis that show a disproportionately high burden of influenza among young children, especially those aged under two years, support this recommendation and highlight the potential benefits of influenza vaccination in Kenya. Despite the fact that we did not estimate the burden of influenza among pregnant women, our findings showed a high burden of influenza-associated hospitalizations among children aged less than six months. These findings highlight the potential value of vaccinating pregnant women against influenza in Kenya (44), which would not only protect them from severe outcomes associated with influenza infections (45) but also provide the needed protection to the infants (46). A review of published data showed a relatively high burden of influenza-associated hospitalizations in the refugee camps, compared to the general communities in Kenya, which may warrant consideration for targeted influenza control programs. Although it remains to be determined whether these high rates were observed as a result of the relatively centralized access to care, the unique challenges experienced in refugee

camp settings (such as crowding due to high population densities, poor sanitation, and malnutrition) may result in elevated risk of respiratory infections including influenza (47, 48).

Consistent with the SAGE recommendations, our findings also suggested a substantial mortality rate associated with influenza in elderly persons, young children, and persons with PTB. Targeting persons with chronic medical conditions such HIV/AIDS with influenza vaccination could be beneficial to them, and also help to break the chain of influenza transmission as it has been suggested that they shed the virus for longer periods (49). The relatively high burden of non-medically attended influenza-associated infections underscores the limitation of using hospital-based surveillance estimation methods which need to be considered for overall economic burden evaluations. This highlights the need to implement influenza surveillance beyond the health care facility-based surveillance, possibly using technology-based platforms such as Google Flu Trends (50) and other internet-based options, to best inform public health policy in this setting.

8.4.2 Timing of influenza activity and control options in Kenya

Unlike in temperate regions where influenza epidemics exhibit clear seasonality with peaks during winter months (51, 52) and Figure 8.1, the presence of multiple influenza epidemics each year in tropical countries presents a challenge for the determination of the optimal timing for influenza vaccination.

The evidence from our studies confirms that influenza circulates in Kenya year-round and that there are multiple epidemics of influenza that occur annually. Here we found that influenza circulates at relatively higher rates during the months of February and March, with a relatively dominant influenza epidemic from July to November. This pattern was consistent across the different climatic zones that we considered in Kenya. Considering that influenza circulated in Kenya year-round, influenza vaccination could potentially be implemented throughout the year using the most current vaccines as recommended by WHO (53). WHO continuously analyzes the antigenic and genetic characteristics of the circulating influenza viruses and makes recommendations on the influenza strains to be included in the two vaccine formulations each year; the Southern Hemisphere (SH) recommendations are made in September to inform production and availability for use the following April, while the Northern Hemisphere (NH) recommendations are made in February for vaccine production and availability for use in September (54). Evidence from our study suggests that the months of April to June would be the optimal periods for annual vaccination campaigns in Kenya (Figure 8.1), using the SH recommended vaccine, in order to offer protection during the dominant influenza activity period of July to November considering the potential effect of waning immunity over time (55, 56). This evidence is currently being considered in the planned influenza vaccination pilot project in Kenya where it will be evaluated alongside other vaccine delivery strategies for efficiency, coverage and cost-effectiveness. The evidence that we present in this thesis on the timing of influenza activity could also be an important reference for other countries in the tropics that want to follow the WHO's recommendations to initiate influenza vaccination programs.

As we found in one of the studies presented in this thesis (chapter 6), climatic factors did not appear to play a major role in determining influenza activity. Indeed, specific humidity was the only variable that was independently and negatively associated with influenza activity. However, from the analysis of influenza activity patterns, not all periods of increased activity or onset of influenza activity were associated with the lowering of specific humidity. This suggests that specific humidity alone may not necessarily be a good predictor of influenza activity. This could support the hypothesis that influenza transmission in the tropics is mainly through direct or indirect contact with secretions (58), and perhaps influenced by influenza activity in the temperate countries and the level of movement and interaction with people in these countries. Other than through vaccination, which has been shown to be the most effective way of preventing influenza infections (59), the Government of Kenya could also consider other influenza control programs targeting adoption and observation of good behavioral practices such as respiratory hygiene and handwashing (60).

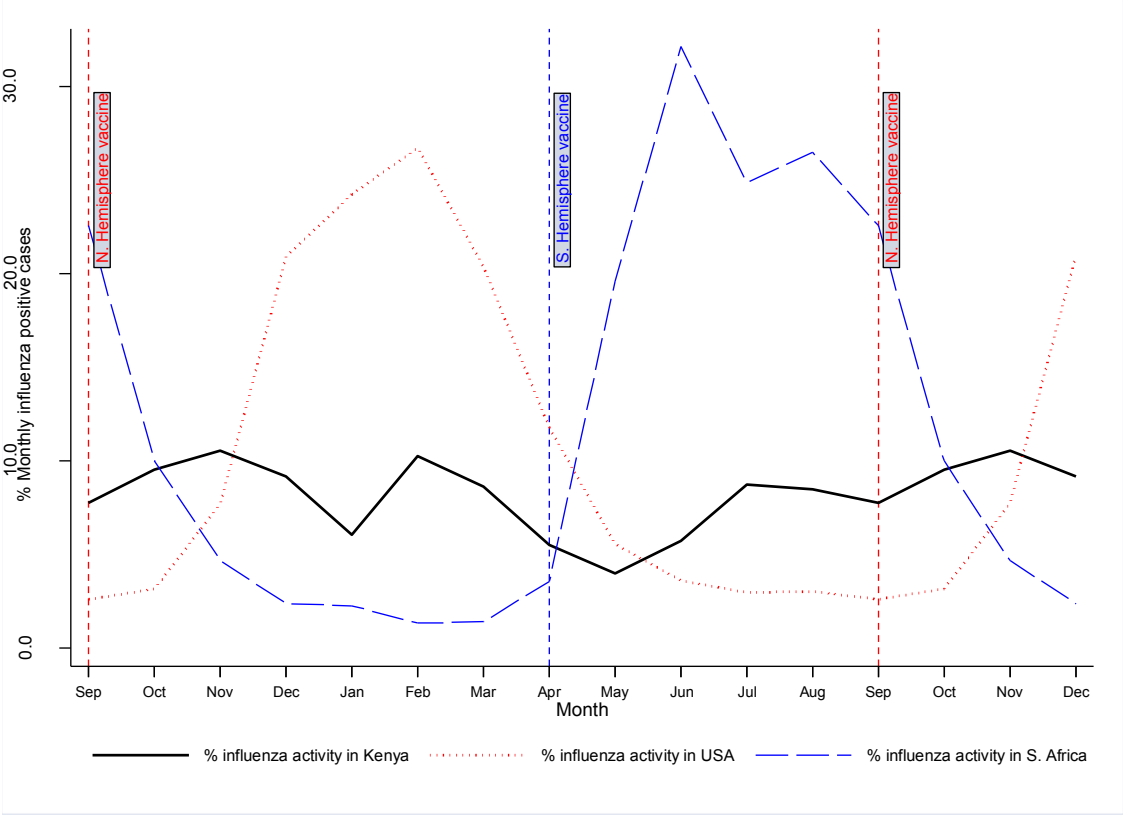

Figure 8.1: Monthly influenza activity in Kenya, USA, and South Africa. Data for Kenya is from influenza surveillance data collected over the period 2007 to 2013 and presented in chapter 6. Data for USA and South Africa were obtained from Flunet (57). All data presented exclude data collected during the pandemic H1N1 period of 2009 and 2010.

8.4.3 Considerations for influenza vaccination program in Kenya

The Kenya Ministry of Health (KMoH) through the Kenya National Immunization Technical Advisory Group (KENITAG) recently (in 2016) conducted a detailed review of published data on influenza in Kenya to inform policy recommendations and priority setting. The review process considered most of the data and findings presented in this thesis and concluded that there was sufficient evidence to prioritize influenza vaccination of children under two years of age. In this regard, it recommended for a pilot vaccination program in Kenya that targets children aged 6-23 months given the limited experience with influenza vaccination in Kenya. The main objective of this pilot program is to understand the technical and operational requirements that would potentially inform a larger scale-up of influenza vaccination in the future [KENITAG's unpublished report to the KMoH].

In this pilot vaccination program, the KMoH is targeting to vaccinate approximately 600,000 children aged 6-23 months within five Counties in Kenya (Nairobi, Mombasa, Nakuru, Nyeri, and Kakamega). Among the possible vaccine delivery strategy options currently considered are a) conducting a year-round vaccination program where influenza vaccines are available throughout the year at the health facilities (using the most currently available SH or NH vaccine formulation); b) conducting year-round vaccination with targeted vaccination campaigns during 1-2 months preceding the two periods of increased influenza activity; and c) only using targeted vaccination drives in the months preceding the two periods of increased influenza activity. Different counties would be selected for one of the vaccine delivery strategies listed above. As part of the pilot vaccination program, the KMoH in collaboration with CDC and other partners are also planning to collect data on knowledge attitudes and practices among caretakers of the children targeted for vaccination, as well as healthcare workers. Additional data will also be collected on uptake of influenza vaccination, and the cost of vaccine delivery which will in turn be used to determine the cost-effectiveness of the possible vaccine delivery strategies.

8.4.4 Economic burden of influenza in Kenya

The evidence that we present in this thesis on the cost of influenza-associated illness in Kenya, and for the first time in tropical Africa, shows an important economic burden associated with influenza infections. Indeed we showed that influenza infections burdened households where nearly half of the average monthly household income was used to resolve influenza-associated hospitalizations. For a vaccine-preventable illness like influenza, these limited household resources would potentially be re-directed to other competing priorities such as food and education. We also found a substantial health facility-based cost-per-episode of influenza-associated illness which represents potential savings for the Government of Kenya. Notwithstanding the relatively lower cost associated with an episode of influenza-associated outpatient visit, the resultant annual economic burden was higher than the burden associated with hospitalization due to the relatively higher incidence of outpatient illness associated with influenza.

Whereas our findings highlight an important societal economic impact of influenza-associated illness, further studies should explore the cost-effectiveness of targeted influenza vaccination strategies in Kenya. Indeed the KMoH, through the recommendation for a pilot vaccination program in Kenya by KENITAG, recommended for further efforts to conduct a full economic evaluation of the potential impact of influenza vaccination programs and strategies in Kenya. The data that we present in this thesis could be a useful basis for implementing such economic evaluations in the future.

Our study findings, which show that households commit nearly half of their monthly income to resolving an episode of influenza-associated illness, also suggest the potential benefits of a more vibrant national health insurance scheme to provide accessible, affordable, sustainable, equitable and quality social health insurance for the Kenyan population and cushion them against sudden financial expenses associated with an illness. The existing National Health Insurance Fund has a limited overall insurance coverage of approximately 11% of the population as the membership is compulsory only for salaried employees and voluntary membership for self-employed and other informal sector workers (61).

8.4.5 Lessons for other African countries

The general process of documenting data on influenza that is presented in this thesis was instrumental in informing the recommendations by the KENITAG for influenza vaccination in Kenya. This makes Kenya one of the very few Sub-Saharan African (SSA) countries to make such recommendations. Other than South Africa which has a national vaccination policy for influenza that targets the risk groups for influenza infections as recommended by SAGE (young children, pregnant women, the elderly, healthcare workers and persons with chronic medical conditions) (62), most of the SSA countries are yet to develop such policies. Given the similarity in demographics, cultural practices, and comorbidities with some other Africa countries, the findings from this thesis (as relates to disease burden, risk groups, and seasonality) could be applicable to other tropical African countries. Similar approaches to disease burden documentation could be replicated and used to inform and catalyze the development of influenza control policies in these countries.

8.5 Recommendations for further research

8.5.1 Additional burden data needed

The morbidity burden of influenza among pregnant women in Kenya remains to be determined and, as recently recommended by KENITAG, further research is needed to document disease burden in this group which is also identified by SAGE as a priority group for influenza vaccination.

KEMRI and US CDC are currently conducting a prospective cohort study among pregnant women in Western Kenya. These data, once available, will be used to determine the burden of influenza-associated respiratory illness among pregnant women. Data from this study will also be used to compare the birth weights of infants born to mothers with and without influenza-associated illness during pregnancy, as well as estimate the burden of influenza-associated illness among infants aged 0-2 months in mothers with and without influenza infection during pregnancy.

Similarly, additional data on influenza-associated disease burden is needed for older persons, and persons with chronic medical conditions such as HIV/AIDS, TB, cardiovascular diseases, cancer, asthma, and diabetes. As highlighted elsewhere in this thesis, we were not able to adequately characterize the morbidity burden due to influenza in older populations in Kenya primarily because of the low healthcare seeking behaviors (39, 40). Additionally, future research is needed to determine the impact of comorbidities such as malaria and malnutrition on the influenza disease burden in the Kenyan population. A recent study in western Kenya, where malaria is endemic (63), showed that although uncommon, coinfection of influenza with malaria was associated with a longer duration of hospitalization than single infections among children 24–59 months of age (64).

Statistical modelling methods, rather than the direct estimation methods used on hospital-based surveillance data, could be useful tools in estimating disease burden among older populations using household morbidity data or incorporating age-specific adjustments for healthcare seeking in cases of ARI that are reported in the hospital based surveillance. The latter would require that more accurate data are available on healthcare utilization for respiratory illness. These data, once available, will be helpful in conducting an evaluation of the economic impact of influenza in Kenya.

Most of the studies that have estimated excess mortality associated with influenza have used data with the cause of death certified by a clinician (19-21). As clinician-certified cause of death data become available in Kenya, after the ongoing efforts by the Government of Kenya to digitize these data are completed, further analysis may be warranted to compare and validate those estimates with the data that we present in this thesis. These data, once available, will also be useful in generating national estimates of excess mortality due to influenza Kenya which are needed to inform policy decisions.

8.5.2 Determinants of influenza activity in Kenya

As figure 8.1 suggests, the months of increased influenza activity in Kenya (February and March, and July to Nov) coincide with the peak months (or just after the peak months) of influenza activity in the NH and SH respectively. However, the two periods when Kenya experiences increased influenza activity have different weather conditions which suggests association with other important factors other than the meteorological variables that we investigated in chapter 6. Indeed, the period of February to March is typically characterized by dry and hot weather conditions, while

the period between October and November experiences rainy and humid weather conditions (65). Future studies could investigate whether the observed increase in influenza activity in Kenya is directly linked to the influenza activity in the NH and SH, and determine the associated factors that determine human influenza transmission (e.g. tourist activities, and migration patterns). Understanding the factors that influence influenza activity patterns would further help to inform decisions around influenza prevention and control programs in Kenya.

8.5.3 Cost effectiveness data

The data on the cost of influenza-associated illness that we present in this thesis are an important step towards making an economic evaluation of the impact of influenza in Kenya. More work needs to be done to conduct a full economic evaluation to include cost effectiveness and cost benefit analyses of the potential impact of influenza vaccination programs and strategies in Kenya. This will be useful in helping the Government of Kenya to make evidence based decisions around influenza control through vaccination by putting the costs of implementing the vaccination strategies in context to the prevented costs and gains in health in the Kenyan population. Additionally, carrying out sensitivity analysis to determine the break-even price for the vaccines to become cost-effective would help the Kenyan Government to negotiate with the companies that produce vaccines.

8.5.4 Priority setting for influenza control programs

There is need for further studies to be conducted on the overall knowledge attitudes and practices relating to vaccine acceptance, barriers to influenza vaccination uptake, and factors related to vaccination decisions in the general Kenyan population, and provider knowledge of influenza vaccine recommendations among healthcare practitioners. A previous study seeking to address these questions in Kenya was limited in geographical scope and may not have reflected the potential effect of the social and cultural diversity of the Kenyan population on attitudes and practices relating to influenza vaccination (66). These data, considered together with the influenza disease burden data and economic evaluations, would be helpful in priority setting for influenza control programs in Kenya.

8.5.5 The need for data to inform future RSV vaccination

Sub-analyses on data presented in chapters 3 and 4 of this thesis showed an important burden of respiratory syncytial virus (RSV) among children aged less than five years. Among these children the estimated incidence of hospitalization associated with RSV was nearly twice as high as the rate of influenza-associated hospitalizations. Similarly, the mortality rate associated with RSV among children less than five years was higher than the estimated mortality rate for influenza. This highlights the need for continued surveillance for RSV to generate data to inform possible future RSV vaccination interventions in Kenya.

8.6 Conclusion

Our studies showed a high morbidity burden of influenza among young children in Kenya. Our studies also showed substantial mortality rates among young children, elderly persons, and persons with HIV/AIDS and/or TB. We also found that influenza-associated illness resulted in substantial economic burden nationally, and especially to households that pay out-of-pocket. These findings suggest the potential benefit of influenza vaccination in Kenya to reduce morbidity and mortality associated with influenza among young children, elderly persons, and persons with chronic medical conditions. While more work is needed, there is a possible health and economic benefit to influenza vaccination in Kenya that warrants further investigation.

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Summary

Globally, a large fraction of human respiratory tract infections are associated with viruses, quite notably influenza A and B, and RSV. Whereas seasonal influenza has long been recognized as a cause of morbidity and mortality in countries with temperate climates, recent studies have shown that influenza causes a significant burden of disease in countries in the tropics, such as Kenya, as well. To develop successful influenza prevention and control strategies in Kenya, it is important to be able to adequately describe its epidemiology and economic impact.

The aim of this thesis is to contribute to the understanding of the epidemiological and economic burden of influenza in Kenya. The work described in this thesis provided estimates of the morbidity and mortality burden of influenza-associated infections, described the risk factors for influenza infection as well as the timing of influenza activity, and estimated costs associated with influenza infections as a basis for quantifying economic impact. The main research questions addressed in this thesis were:

1. What is the morbidity and mortality burden of influenza-associated disease in Kenya, and which segments of the population are most affected?
2. What are the risk factors for influenza infection and/or severe influenza in Kenya?
3. What is the cost and overall economic burden of influenza-associated disease in Kenya?

Chapter 1 provided a general introduction to this thesis. Here, we provided the background information, the rationale, and the research objectives of this thesis.

In chapter 2, we present the results of a systematic literature review of published data from 10 articles that described the disease burden associated with influenza in Kenya. Results from this review, showed that influenza virus was detected in 5-27% of all medically attended patients who presented with acute respiratory illness, and in 5-10% of those who were hospitalized with severe acute respiratory illness (SARI). We also showed that the incidence of hospitalizations with influenza among children aged less than five years ranged from 3-5 per 1,000, and were 7-10 times higher compared to rates among persons aged five years or older. This review also showed that the rates of hospitalization for influenza were highest among persons who lived in refugee camps, even without incorporating adjustments for eligible cases who were not tested as was done in most of the other studies. Overall, our review showed an expanding set of literature on disease burden associated with influenza in Kenya, with a substantial burden among children under five years of age. The rates of hospitalization with influenza that were reported among children aged less than five years were 2-3 times higher than those reported in temperate countries such as the United

States. In general, there were notable differences in the methodologies used in the studies that we reviewed, particularly relating the case definitions for the syndromes that were used for surveillance and testing for influenza cases, as well as the adjustment factors that were applied to generate the estimates of the incidence rates.

In chapter 3, we estimated the age-specific burden of medically-attended, and non-medically attended influenza and RSV in Western Kenya. Here, we estimated the mean annual incidence of influenza-associated hospitalization for SARI among children aged under five years to range between 2-4 cases per 1,000 children. This was lower than the rate of hospitalizations among children aged less than five years for RSV which was estimated to range between 4-7 cases per 1,000 children. In this study, we also showed a substantial burden of influenza-associated hospitalizations among children aged less than six months (2-14 cases per 1,000 children) for whom there are no licensed influenza vaccines. For this group of children, vaccinating pregnant women is recommended as a means of protecting them from influenza infections during the period when they are not eligible for influenza vaccination. Our study also showed substantially high rates of influenza-associated outpatient medically-attended influenza-like illness (ILI) which ranged between 17-35 cases per 1,000 children. Overall, estimates of the rates of hospitalization and outpatient visits among children aged less than five years were several fold higher than estimates among older persons. Using adjustments for health seeking behaviors, we also estimated the incidence rates of influenza- and RSV-associated non-medically-attended SARI and ILI which were higher than comparable rates of medically-attended illness in the community.

Using verbal autopsy data collected through a health demographic surveillance system (HDSS) in Western Kenya, we estimated the overall and age-specific excess mortality rates associated with influenza virus and RSV (chapter 4). These rates were calculated for four mortality outcomes: all-cause mortality, all-respiratory deaths (including pneumonia), HIV-related deaths, and pulmonary tuberculosis (PTB) related deaths. The all-cause excess mortality rate associated with influenza was estimated at 14 cases per 100,000 person-years (PY) compared to 11 cases per 100,000 PY for all-respiratory deaths. The highest all-respiratory mortality rates associated with influenza were among persons aged fifty years or older (35 cases per 100,000 PY), and among children aged less than five years (17 cases per 100,000 PY). Mortality rates associated with influenza were particularly highest among persons with TB infections who were aged fifty years or older (42 cases per 100,000 PY). Similar to studies conducted in temperate countries, our estimates of all-respiratory mortality rates associated with RSV among children aged less than five years (39 cases per 100,000 PY) were higher compared to the influenza-associated mortality rates. Overall, we showed an important role of influenza and RSV on excess mortality in Western Kenya, particularly among children aged less than five years, older persons, and persons living with HIV/AIDS or those infected with TB.

In chapter 5 we presented findings from a household-based study that examined the association between the HIV status of household members and their risk of introducing influenza to the home, and whether the HIV status of index cases of influenza impacted the risk of developing secondary (ILI) among their household contacts. Here we showed that while the HIV status did not affect the likelihood of being an influenza index case, household contacts of HIV-infected influenza index cases had twice the risk of developing secondary ILI than contacts of HIV-negative index cases.

Using data collected from twelve influenza surveillance sites distributed across the country, we described the patterns and periods of increased influenza circulation, and assessed the relationship between three meteorological variables (temperature, rainfall, and specific humidity) and influenza activity (Chapter 6). In this study, we showed that there was year-round circulation of influenza in Kenya, with multiple epidemics that occurred annually and lasted a median duration of 2-4 months. On average, there were two epidemics that occurred each year in most of the regions in Kenya: the first epidemic occurred between the months of February and March, and the second between July and November. This pattern was consistent across the different climatic zones that we considered in Kenya. The epidemic that occurred in the second half of the calendar year, between July and November, was responsible for the highest number of influenza cases annually (accounting for nearly 60% of the cases). The months of April and May had the lowest influenza activity in Kenya. An assessment of the relationship between the meteorological variables showed that specific humidity was independently and negatively associated with influenza activity. Our analysis also confirmed the hypothesis that suggested that combinations of low temperature (<18^{o}C) and low specific humidity (<11g/Kg) were significantly associated with increased influenza activity. However, we did not find evidence in Kenya to show that temperature and rainfall were associated with influenza activity, as previously reported in other studies that were conducted elsewhere.

Chapter 7, reported results of a costing study that estimated the cost-per-episode of laboratory-confirmed influenza-associated illness in Kenya. This study was conducted in five health facilities, including four hospitals and one outpatient facility. In this study, we estimated that the mean cost-per-episode of influenza was US$118 among inpatients (US$114 for children aged less than five years, and US$137 for persons aged five years or older). Among outpatients, the mean cost-per-episode of influenza was US$20 overall (US$21 for children aged less than five year, and US$17 for persons aged five years or older). From our analysis, we showed that an episode of influenza-associated illness resulted in a substantial economic burden to the households. For a hospitalized influenza case, the overall resultant cost to the families that was paid out-of-pocket was 40% of the average monthly household income. For an outpatient case, the resultant cost to the families was 11% of the average monthly household income. The median number of work-day opportunities missed in households of influenza case-patients was two days (four days for households of hospitalized case-patients, and one day for households with an outpatient). Among households of

influenza case-patients that had school-age children, the median number of school-days missed was four days (three days for households of hospitalized case-patients, and four days for households with an outpatient). Overall, the national annual influenza-associated cost ranged from US$3-5 million for inpatients, and between US$6-26 million for outpatients.

In chapter 8, we provided a synthesis of the main findings of the studies that were included in this thesis, discussed the implications of the findings, and made some recommendations for further research. The studies that we presented in this thesis showed a disproportionately high morbidity burden of influenza among young children, especially those aged under two years, which highlighted the potential benefits influenza vaccination and supported the World Health Organization's (WHO) recommendation for targeting young children for vaccination. Our findings also suggested a substantial mortality burden in Kenya that was associated with influenza among elderly persons, young children, and persons with TB. This was also consistent with the WHO's recommendations which identified these groups as being at increased risk of severe outcomes due to influenza infection and are thus priority groups for influenza vaccination, together with pregnant women, persons infected with HIV, and healthcare workers. Furthermore, considering the relatively high prevalence of HIV-infection estimated at 5.6% in the general Kenyan population and the fact that our data suggested a higher risk of developing secondary ILI among household contacts of HIV-infected influenza cases, targeting persons who are infected with HIV with influenza vaccination could also help to break the chain of influenza transmission in the community as studies have suggested that immunocompromised individuals shed the virus for longer periods of time. The year-round circulation of influenza in Kenya that we showed, suggested that influenza vaccination could potentially be implemented throughout the year using the most currently available vaccines as recommended by the WHO. However, it is important to note that if annual vaccination campaigns were to be considered, our data suggested that the months of April to June would be the optimal periods for vaccination using the southern hemisphere recommended vaccine in order to offer protection during the dominant influenza activity period of July to November. The evidence that we present in this thesis on the cost of influenza-associated illness, suggested an important economic burden associated with influenza infections, which further highlighted the potential benefits of influenza vaccination in Kenya. The financial strain to families occasioned by out-of-pocket payments, that are nearly half their monthly household income, also suggest the potential benefit of a more vibrant national health insurance scheme for the Kenyan population. However, further studies are need on cost-effectiveness which would be used to conduct a full economic evaluation of the potential impact of influenza vaccination programs and strategies in Kenya. To understand the full impact of influenza in the Kenyan population, further studies are also needed on the burden of influenza among pregnant women, as well as an assessment of the impact of comorbidities such as malaria and malnutrition on influenza infections.

Samenvatting

Een aanzienlijk deel van wereldwijd voorkomende luchtweginfecties wordt veroorzaakt door virussen, in het bijzonder influenza A en B en RSV. Terwijl seizoensgebonden influenza in landen met een gematigd klimaat als een belangrijke oorzaak van ziekte en sterfte wordt gezien, tonen recente studies, dat influenza ook de oorzaak is van een forse ziektelast in de tropen, bijvoorbeeld in een land zoals Kenia. Om succesvolle preventieve en bestrijdingsprogramma's rond influenza in Kenia mogelijk te maken, is het allereerst belangrijk de epidemiologie en de economische impact van influenza te kennen.

Dit proefschrift wil een bijdrage leveren aan een beter inzicht in de epidemiologie en economische impact van influenza in Kenia. In dit proefschrift worden schattingen van influenza geassocieerde ziekte en sterfte gepresenteerd, evenals van risicofactoren voor influenza, een vaststelling van het seizoen voor verhoogde influenza activiteit en tot slot een schatting van kosten van influenza als basis voor een berekening van de economische impact van de ziekte. De kernvragen die in dit proefschrift aan de orde komen zijn:

1. Wat is de ziekte- en sterftelast van influenza geassocieerde ziekte in Kenia en welk deel van de bevolking heeft daar het meeste last van?

2. Wat zijn de belangrijkste risicofactoren voor (ernstige) influenza in Kenia?

3. Wat zijn de kosten en economische impact van influenza geassocieerde ziekte in Kenia?

Hoofdstuk 1 omvat de inleiding van het proefschrift. Hierin worden aanleiding, achtergrond en onderzoeksvragen weergegeven.

In hoofdstuk 2 presenteren we de resultaten van een systematisch *literatuuronderzoek* op basis van 10 artikelen, welke de ziektelast met betrekking tot influenza in Kenia beschrijven. Uit de resultaten van deze studie blijkt dat het influenzavirus wordt vastgesteld bij 5-27% van alle medische consulten van patiënten met acute luchtwegproblemen, en bij 5-10% van de patiënten met ernstige luchtwegproblemen (SARI) die in een ziekenhuis worden opgenomen. De incidentie van ziekenhuisopnamen vanwege influenza bij kinderen onder de vijf jaar varieert van 3-5 per 1000 en deze cijfers blijken 7-10 keer hoger, wanneer vergeleken met cijfers van personen van vijf jaar en ouder. Het aantal ziekenhuisopnamen is het hoogst bij mensen uit de vluchtelingenkampen. Dit is zelfs zonder correcties voor gevallen, die mogelijk wel influenza hebben, maar niet zijn getest, zoals in veel andere studies is gedaan. Er is een uitdijende hoeveelheid literatuur rond influenza gerelateerde ziektelast in Kenia, met op de voorgrond de grote ziektelast ten gevolge van influenza bij kinderen onder de vijf jaar. Hat aantal ziekenhuisopnamen vanwege influenza bij kinderen onder

de vijf jaar is 2-3 keer hoger dan cijfers gerapporteerd uit landen, zoals de Verenigde Staten. Er zijn wel forse verschillen in methoden, zoals gebruikt in de bekeken studies, vooral rond 'case definitions' voor syndromen welke zijn gehanteerd bij surveillance en bij het testen van influenza gevallen, en rond correctiefactoren, welke zijn gebruikt om de incidentie te schatten

In hoofdstuk 3 berekenen we de leeftijdgebonden *ziektelast* ten gevolge van influenza en RSV bij mensen die wel of niet medische hulp opzoeken in West Kenia. We schatten de gemiddelde jaarincidentie van influenza geassocieerde ziekenhuisopnamen voor SARI bij kinderen onder de vijf jaar op 2-4 per 1000 kinderen. Dit is lager dan het aantal ziekenhuisopnames van kinderen onder de vijf jaar met RSV, welke varieert van 4-7 gevallen per 1000 kinderen. In deze studie zien we vooral een behoorlijk aantal influenza geassocieerde ziekenhuisopnamen bij kinderen onder de zes maanden (2-14 gevallen per 1000 kinderen), waarvoor geen influenzavaccins met licentie beschikbaar zijn. Voor deze specifieke groep kinderen wordt vaccinatie van zwangere vrouwen aanbevolen om op deze manier de kinderen te beschermen tegen influenza in de periode dat ze nog niet in aanmerking komen voor influenzavaccinatie. De studie laat ook een behoorlijk hoge influenza geassocieerde ziektelast onder polikliniekbezoekers zien, welke varieert van 17-35 gevallen per 1000 kinderen. Het aantal ziekenhuisopnamen en polikliniekbezoeken van kinderen onder vijf jaar is overigens vele malen hoger dan die van oudere personen. Als een correctie op hulpzoekgedrag wordt doorgevoerd, kunnen we ook de incidentie van influenza en RSV geassocieerde SARI en ILI van mensen, die géén medische hulp zochten, berekenen. Deze cijfers vallen hoger uit dan vergelijkbare cijfers van mensen die wél medische hulp zochten.

Met behulp van *'verbal autopsie'* gegevens, welke worden verzameld in het Health Demographic Surveillance System (HDSS) in West Kenia, zijn ruwe en leeftijdspecifieke influenza en RSV geassocieerde *sterftecijfers* berekend. (hoofdstuk 4) . Deze cijfers zijn berekend voor vier sterfterisico uitkomstmaten: totale sterfterisico, totale respiratoire sterfterisico (inclusief pneumonie), HIV gerelateerde sterfterisico en longtuberculose gerelateerde sterfterisico. Het geschatte, algemene, influenza geassocieerde oversterfterisico bedroeg 14 gevallen per 100.000 persoonjaren (PJ) in vergelijking met 11 gevallen per 100.000 PJ voor het totale respiratoire sterfterisico. Het hoogste influenza geassocieerde totale respiratoire sterfterisico komt voor bij mensen boven de vijftig jaar i.e. 35 gevallen per 100.000 PJ en bij kinderen onder de vijf jaar i.e. 17 gevallen per 100.000 PJ. Het influenza geassocieerde sterfterisico is vooral hoog onder tuberculose patiënten van vijftig jaar en ouder i.e. 42 gevallen per 100.000 PJ. Evenals studies uitgevoerd in landen met een gematigd klimaat laten onze berekeningen van het RSV geassocieerde totale respiratoire sterfterisico bij kinderen onder de vijf jaar, i.e. 39 gevallen per 100.000 PJ, ook zien, dat dit hoger is dan het influenza geassocieerde totale respiratoire sterfterisico. Influenza en RSV spelen een belangrijke rol in het oversterfterisico in West Kenia, vooral bij kinderen onder de vijf jaar, oudere personen en bij HIV respectievelijk TB geïnfecteerde personen.

In hoofdstuk 5 presenteren we de resultaten van een studie op huishoudniveau waarbij de relatie tussen *HIV status van familieleden en het risico om influenza* in het huishouden te introduceren is bestudeerd, en of de HIV status van influenza index gevallen invloed heeft op het risico voor secundaire ILI onder hun familieleden. Waar de HIV status geen invloed had op de kans om een influenza index geval te zijn, hadden de familieleden van HIV geïnfecteerde influenza index gevallen wel een tweemaal zo hoog risico om een secundaire ILI te ontwikkelen ten opzichte van HIV-negatieve index gevallen.

Met gegevens uit twaalf, over het land verdeelde, influenzasurveillance meetpunten, beschrijven we de *patronen van en de seizoenen met verhoogde influenza activiteit* en bestuderen we de relatie tussen drie *meteorologische variabelen* (temperatuur, regenval en bepaalde vochtigheid) *en influenza activiteit*. (hoofdstuk 6). In deze studie stellen we vast dat er het hele door jaar influenza activiteit in Kenia aanwezig is, met jaarlijks meerdere epidemieën, welke gemiddeld 2-4 maanden duren. Gemiddeld vinden er in de meeste regio's in Kenia twee epidemieën per jaar plaats: de eerste epidemie zo rond februari - maart en de tweede tussen juli en november. Dit patroon is consistent voor de verschillende klimaatzones, welke Kenia kent. De epidemie, die optreedt tussen juli en november, zorgt voor het hoogste aantal influenza gevallen (ongeveer 60% van alle gevallen in een jaar). De maanden april en mei geven de laagste influenza activiteit in Kenia te zien. Onze studie naar de relatie tussen meteorologische variabelen en influenza activiteit laat zien dat een bepaalde vochtigheid, onafhankelijk en negatief is geassocieerd met influenza activiteit. Onze analyses bevestigen de hypothese, welke claimt, dat een combinatie van lage temperatuur (<18C) en lage bepaalde vochtigheid (<11g/kg) significant zijn geassocieerd met een verhoogde influenza activiteit. We konden echter in Kenia geen bewijs vinden voor een verband tussen enerzijds temperatuur en regenval en anderzijds influenza activiteit , zoals andere studies in andere landen wel hebben gerapporteerd.

Hoofdstuk 7 rapporteert over de resultaten van een *kosten van ziekte* studie waarbij de kosten per laboratorium bewezen influenza geassocieerde ziekte is berekend. Deze studie is uitgevoerd in vijf gezondheidinstellingen, vier ziekenhuizen en één polikliniek. We schatten de gemiddelde kosten per influenza episode op USD 118 voor ziekenhuispatiënten: USD 114 voor kinderen onder de vijf jaar en USD 137 voor personen ouder dan vijf jaar. Bij polikliniekpatiënten zijn de gemiddelde kosten per influenza episode USD 20: USD 21 voor kinderen onder de vijf jaar en USD 17 voor personen ouder dan vijf jaar. Uit onze studie blijkt dat een influenza episode een fors financieel beslag op een huishouden kan leggen. Voor een in een ziekenhuis opgenomen patiënt met influenza bedragen de totale out of pocket betaalde kosten 40% van het gemiddeld maandinkomen van een familie. Voor een polikliniekpatiënt bedragen de totale out of pocket kosten zo'n 11% van het gemiddeld maandinkomen van een familie. Het mediane, aantal gemiste werkdagen in families met een influenzapatiënt is twee dagen (vier dagen in families met een in een ziekenhuis opgenomen influenzapatiënt en één dag in families met een polikliniekpatiënt). In families met influenzapatiënten en schoolgaande kinderen, is het mediane, aantal gemiste schooldagen vier

dagen (drie dagen in families met een in een ziekenhuis opgenomen influenzapatiënt en vier dagen in families met een polikliniekpatiënt) Concluderend: de nationale influenza geassocieerde kosten op jaarbasis variëren van USD 3-5 miljoen voor ziekenhuispatiënten tot US 6-26 miljoen voor polikliniekpatiënten.

In hoofdstuk 8 geven we een synthese van de belangrijkste bevindingen uit de diverse studies van dit proefschrift, gevolgd door een discussie over de implicaties van die bevindingen en komen we tot slot met aanbevelingen. De studies, welke in dit proefschrift zijn gepresenteerd, laten een naar verhouding hoge *ziektelast* door influenza bij kinderen in Kenia te zien, vooral bij kinderen onder de twee jaar. Dit werpt nog eens een extra licht op de gezondheidswinst, die valt te boeken met influenzavaccinatie van jonge kinderen, hetgeen ook wordt ondersteund door de aanbevelingen vanuit de Wereldgezondheidsorganisatie (WHO). De studies suggereren ook een aanzienlijke *sterfte* onder jonge kinderen, ouderen en tuberculose patiënten in Kenia. Dit correleert ook met de aanbevelingen van de WHO, die juist deze groepen heeft geïdentificeerd vanwege hun verhoogd risico op een slechte afloop na een infectie door influenza en dus een hoge prioriteit verdienen om in aanmerking te komen voor een influenzavaccinatie, samen met zwangere vrouwen, HIV-geïnfecteerden en gezondheidswerkers. Daarenboven, als we de relatief hoge HIV prevalentie - geschat op 5.6% van de algemene Keniaanse populatie- in acht nemen, en het feit dat onze resultaten suggereren dat er een hoger risico is voor secundaire ILI bij familieleden van HIV-geïnfecteerde influenza gevallen, kan door influenzavaccinatie van HIV-geïnfecteerden de keten van transmissie van influenza in de bevolking beter worden doorbroken, vooral ook omdat diverse studies aantonen, dat immunogecompromitteerde individuen het influenzavirus langere tijd blijven uitscheiden.

De, in onze studies aangetoonde, het hele jaar door optredende *influenza activiteit* in Kenia, zou kunnen betekenen dat influenzavaccinatie ook het hele jaar door zou moeten plaatsvinden, daarbij gebruik makend van de beschikbare, door de WHO aanbevolen, vaccins. Het is echter belangrijk om zich te realiseren, dat mocht een jaarlijkse influenzavaccinatiecampagne worden overwogen de maanden april tot juni de meest aangewezen periode voor vaccinatie zijn en dat het vaccin van het zuidelijk halfrond dan het meeste aangewezen vaccin zou moeten zijn, vooral vanwege de, tijdens de dominante influenzaperiode (van juli tot november), geboden bescherming.

De uitkomsten van onze studie naar de *kosten* van influenza geassocieerde ziekte, impliceren in feite een behoorlijke financiële last voor families, waardoor we nog serieuzer moeten kijken naar de potentiële opbrengsten van influenzavaccinatie in Kenia. De financiële stress van families door out of pocket betalingen vanwege medische hulp voor een familielid met influenza , waaraan bijna de helft van het maandelijkse huishoudinkomen kan opgaan, vraagt ons ook na te denken over de meerwaarde van een nationaal, meer dynamisch, gezondheidsverzekeringsysteem voor de gehele Keniaanse bevolking. Daarvoor zijn echter eerst meer kosteneffectiviteitstudies nodig, waarvan de resultaten kunnen worden ingebracht in een allesomvattende economische evaluatie over de

potentiële opbrengsten van influenzavaccinatieprogramma's en strategieën in Kenia. Om de volledige impact van influenza op de Keniaanse bevolking beter te begrijpen is in ieder geval meer onderzoek nodig, o.a. naar influenza bij zwangere vrouwen, naast een evaluatie van de impact van comorbiditeit, zoals malaria en ondervoeding, op influenza.

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About the author

Gideon Osoma Emukule was born in Busia, Kenya on the 17th of March in 1975. He studied Mathematics and Statistics and obtained Bachelor of Science (BSc) degree in 1999 from Moi University, Eldoret. He enrolled for post graduate course on Biometry at the University of Nairobi and graduated with a Master of Science (MSc) degree in 2009. In 2014, he enrolled for a PhD in Epidemiology at the department of Primary and Community Care at Radboud University Medical Center, Nijmegen, The Netherlands and is scheduled to defend his thesis on 12th May 2017.

Gideon worked for International Child Support in Busia, Kenya as data analyst from 2000 to 2004. While at this position, where he worked with researchers who developed and tested solutions to real-world problems faced by the rural poor in education, agriculture, and public health, he gained valuable experience in data management, and data analysis. In June 2004, he joined the Kenya Medical Research Institute (KEMRI) and US Centers for Disease Control and Prevention (CDC) research collaboration program in Kisumu, Kenya where he worked as Senior Data Analyst. While at this position, he led the data management team working under the Global AIDS Program, and was responsible for providing statistical analysis support and overall oversight of the data processing. In 2007, he left his position to join Family Health International (FHI) at the Africa regional office in Nairobi, Kenya as a Senior Data Manager/Analyst. This move was in part motivated by the need to enroll for Master's degree at the University of Nairobi. While at this position, he provided technical leadership and support in the management of the monitoring and evaluation systems and statistical data analysis. Shortly after completing his MSc degree, he joined the US CDC-Kenya country office in Nairobi where he works as the lead statistician in the influenza program to date.

From 2010, Gideon provided statistical and technical support to the epidemiologists and other researchers in the design of studies, data collection instruments, review of study protocols and scientific papers, data analysis and interpretation of results for various research activities. He has also led and mentored a team of data analysts, data management specialists, and students who worked with the influenza program at CDC-Kenya. While at this position, he has also provided technical support to the Kenya Ministry of Health on implementing activities related to the influenza vaccine policy development. He also provided technical support and facilitated trainings to other countries in the East African region to strengthen influenza surveillance and generate data for policy recommendations.

Over the years in his professional life, Gideon was involved in research activities that span the areas of school and community development programs, HIV/AIDS programing, and influenza surveillance. Through these, he led and participated in several studies where he was able to publish 28 articles in peer reviewed journals, a part of which are included in this thesis.

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