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The role of HIV in the household introduction and transmission of influenza

in an urban slum, Nairobi, Kenya, 2008-2011


By


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Master of Public Health

Global Epidemiology




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An abstract of

A thesis submitted to the Faculty of the

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2013

# Abstract

The role of HIV in the household introduction and transmission of influenza

in an urban slum, Nairobi, Kenya, 2008-2011

By

Michael C. Judd

Little is known about how HIV affects the transmission dynamics of influenza in sub-Saharan Africa. In this retrospective cohort study of 176 households with known HIV status in an urban slum in Nairobi, Kenya, we used population-based household and clinic surveillance data gathered from 2008 through 2011 to examine the association between the HIV status of household members and their risk of introducing influenza to the home. We also examined the association between the HIV status of laboratory-confirmed influenza index cases in households and the risk of developing influenza-like illness (ILI) among their household contacts.

ILI in a household member was defined as reported or diagnosed cough or sore throat with fever $\geq 38.0°C$. Persons with ILI seeking medical care at the local study clinic and consenting to provide nasopharyngeal and oropharyngeal swabs were tested by real-time reverse transcription PCR for influenza infection. Log-binomial models using generalized estimating equations (GEE) to account for household clustering evaluated the association between laboratory-confirmed household influenza index case status among all household members and individual HIV status, as well as the association between secondary ILI status among household-contacts and the HIV status of the household influenza index case.

We observed that HIV-positive individuals were not at an elevated risk for introducing influenza to their households, compared to HIV-negative individuals (Risk ratio (RR), 1.35; 95% confidence interval (CI), 0.65 - 2.78). However, our results suggested that HIV-positive index cases were more likely to spread influenza in their households than HIV-negative index cases (RR, 2.36; 95%CI, 1.19 - 4.66), potentially implicating HIV-positive index cases as seeders of household influenza epidemics. Large sample size prospective studies measuring median CD4 counts and clinically confirming reported secondary ILI cases are needed to further evaluate the role of HIV in household influenza transmission. HIV-positive individuals should continue to be a priority for influenza vaccination in regions with high HIV seroprevalence.

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**Acknowledgements**

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**CHAPTER I: LITERATURE REVIEW**

<u>Influenza characteristics and epidemiology</u>

The influenza virus is a major cause of respiratory illness worldwide, resulting in

significant morbidity and mortality (1). Although it is vaccine-preventable, about

20% of children and 5% of adults develop symptomatic infection each year (2).

The virus is transmitted predominantly by respiratory droplets expelled during

coughing or sneezing (2,3). The severity and type of clinical symptoms depend

on one's age, degree of susceptibility, immunosuppression, and other

comorbidities (2). Infection is usually self-limiting and lasts about one to three

days. Viral shedding overlaps this period, with an average length of five days.

However, young children <5 years of age have been known to be infectious for

several weeks, often shedding virus at high titers for longer periods than adults

(2,4). They also have the highest rates of hospital admission for severe infection

(5,6). In contrast, school children aged 5-18 years are the most commonly infected

age group (7), while persons aged ≥65 years are at highest risk for mortality (2),

partially due to the tendency of the virus to exacerbate existing health conditions

(8).

<u>Virology</u>

The influenza virus displays great antigenic diversity and comes in three distinct

viral subtypes (A, B, and C), although only types A and B are known to cause

widespread outbreaks in human populations (2). Nicholson *et al* notes that

"influenza viruses are classified into subtypes based on antigenic differences

between their two surface glycoproteins, hemagglutinin and neuraminidase" (2).

There are 15 hemagglutinin subtypes and 9 neuraminidase subtypes identified

for influenza A viruses, while only one subtype of hemagglutinin and one

subtype of neuraminidase have been identified for influenza B viruses (2).

Transmission

Transmission patterns and circulating influenza strains vary geographically and

temporally. In temperate regions, sustained influenza epidemics occur in the late

Fall to early Spring months in the Northern and Southern Hemispheres (9). In

contrast, influenza viruses circulate continually in tropical regions, and

epidemics occur sporadically with peaks seen predominantly during periods of

high rainfall (2,10). A recent study of an influenza A subtype from 2002-2007

determined that most temperate epidemics are seeded by viruses originating

from East and South-east Asia, and that international trade is responsible for

spreading the viruses to the Americas and Europe (10).

Emerging strains and pandemic influenza

Via the processes of antigenic drift and antigenic shift, influenza mutates rapidly

(2); when a particularly transmissible novel strain emerges, a pandemic can occur.

The most recent pandemic was caused by the 2009 influenza A (H1N1) strain (11).

Emerging first in Mexico from a cross-species, or "zoonotic" transmission from

pigs, (a common influenza reservoir) and spreading quickly around the world

(12), this particular strain clustered in households and schools, with the majority

of the reported cases occurring in school children aged 5-18 years (9,13,14).

Cowling *et al* indicates that the virus possessed "characteristics broadly similar to

those of seasonal influenza A viruses, with comparable rates of viral shedding,

clinical illness, and household transmission" (15).

At the time of this publication, a novel influenza A (H7N9) strain has emerged in

China, and is associated with contact with infected poultry, causing severe

disease in humans (16), much like the highly pathogenic avian influenza A

(H5N1) virus reported first in 1997 (17). Uyeki and Cox maintain that intensified

surveillance for human and animal cases of influenza A (H7N9) will reveal more

of the viral epidemiologic characteristics (16).


Health and economic burden

Influenza epidemics exert a significant impact on health and the global economy.

In the early 2000s, Thompson *et al*. estimated that in the United States, influenza

caused hundreds of thousands of hospitalizations (18) and tens of thousands of

deaths (19). In 2007, Molinari *et al* estimated that the annual economic burden to

the United States was around $16 billion (20). The picture of influenza burden on

health and the economy is very similar in Western Europe (6), with significant

economic losses caused by worker absenteeism and lowered productivity among

the returning convalescent workers (21). Recent population-based studies show

that influenza is also associated with significant health and economic burdens in

developing countries in Asia (22,23) and Central America (24).

Prevention and treatment

To prevent or lessen such health and economic burdens, vaccines and antiviral

medications are used. Other less common strategies include isolation, quarantine,

and other social distancing measures (25). Influenza prevention efforts come in

the form of trivalent inactivated vaccines and live attenuated influenza vaccines,

and are produced annually in advance of the respective influenza seasons in

temperate regions. Since 2010, the Advisory Committee on Immunization

Practices has recommended yearly vaccination with trivalent inactivated vaccine

for all individuals aged 6 months or older, or live attenuated influenza vaccine

for healthy non-pregnant people aged 2–49 years (26). A recent meta-analysis of

17 randomized controlled trials and 14 observational studies found that both

vaccine types provided immunity for greater than 60% of study participants,

with children responding best to live attenuated influenza vaccines (27). In terms

of post-exposure prophylaxis, four licensed antiviral medications are commonly

used to reduce severity and duration of illness: amantadine, rimantadine,

zanamivir, and oseltamivir (26). Suzuki *et al* indicates that "these antiviral agents

can be used for controlling and preventing influenza, but they are not a

substitute for vaccination" (28). Amantadine is an antiviral drug with activity

against influenza A viruses, but not influenza B viruses (28). Rimantadine is similar to amantadine, but is not available in most parts of the world (2). Meanwhile, zanamivir is effective against both influenza A and B strains, and is licensed for the treatment of individuals 12 years of age and older (2). Oseltamivir was indicated for pandemic H1N1 influenza A, but widespread resistance among seasonal strains has been reported since 2010 (26), and new antiviral treatments are in the pipeline.

Studying influenza at the household level

Influenza epidemics worldwide usually occur in structured environments like places of employment, schools, and homes. However, household settings have been particularly important sites for researchers to investigate a variety of influenza characteristics since they provide "detailed information on the dynamics of infection within well-defined clusters of individuals" (29). As Suess *et al* states, household settings are commonly used to "examine basic influenza parameters in seasonal viruses, such as the duration of infectiousness, susceptibility and infectiousness of children versus adults, and the therapeutic and prophylactic effectiveness of antivirals and vaccines" (30). Therefore, studying risk factors for influenza susceptibility and infectiousness at the household level has played an important role in creating novel strategies for the control of influenza transmission.

Influenza in immunocompromised populations

As well as influenza study at the household level, the study of influenza epidemiology within immunocompromised populations is vital to the design of comprehensive transmission control and prevention. In general, Kunisaki and Janoff stated that "high rates of influenza infection and complications are suggested to occur among people with impaired immune defenses" (31). It has also been consistently shown that immunocompromised individuals shed influenza for longer periods than the general population (31–37).

The largest population of immunocompromised individuals worldwide is the estimated 34 million people living with HIV (38). Among these individuals, influenza is a common cause of respiratory illness (39). Although studies of seasonal and pandemic influenza have found that HIV-positive individuals are not more susceptible to infection than the immunocompetent population (40–43), it has been widely accepted that those with HIV experience more severe clinical symptoms, leading to elevated rates of influenza-associated hospital admissions and mortality (31,33,34,41,44,45). Additionally, expert opinion and clinical case reports have suggested that HIV-positive patients may shed influenza for prolonged periods (32,34,45,46). However, no prospective follow-up studies have evaluated the implications of prolonged viral shedding by HIV-positive persons on influenza transmission to household contacts.

Influenza and HIV in sub-Saharan Africa

Like elsewhere in the world, influenza is a major cause of respiratory illness in sub-Saharan Africa (47–49). The major difference is that this region is home to 69% of HIV-infected individuals worldwide (38). It is thought that this widespread immunosuppression may modify influenza transmission dynamics, but this area of research is still in its infancy. The only study considering the effects of HIV on influenza infection in sub-Saharan Africa supported existing literature that influenza patients with HIV experience higher mortality rates than those without HIV (50).

No studies have evaluated HIV-associated influenza transmission patterns. This knowledge gap can be attributed to two primary challenges in data gathering. First, HIV testing coverage remains low in sub-Saharan Africa (51), with most individuals unaware of their status (52). Second, there is a paucity of comprehensive influenza data in the region due to sub-optimal population coverage, weak surveillance infrastructures, inconsistent reporting, and a lack of standardized protocol among participating countries (48,49,53).

Influenza and HIV in Kenya

While the picture of influenza transmission in sub-Saharan Africa as a whole remains incomplete, recent studies have begun to characterize influenza epidemiology (54–56) and household transmission patterns (57) in Kenya, a sub-Saharan East-African country bearing an estimated national HIV prevalence of

7.1% (51). A preliminary ecologic study examining the association between non-specific respiratory illness and HIV status indicated that living with at least one HIV-positive individual increases the incidence of influenza-like illness (ILI) among household members, compared to ILI incidence among members in exclusively HIV-negative households (CDC-Kenya, unpublished data). However no individual level studies have yet evaluated the relationship between HIV and influenza co-infections in Kenya.

<u>Thesis rationale</u>

If more was known about the effect of HIV on influenza transmission dynamics in household settings, vaccination programs could be enacted to reduce transmission by effectively targeting the individuals at highest risk for seeding and/or perpetuating household epidemics and thus mitigating influenza epidemics at large, especially in regions with high HIV seroprevalence. In the absence of action, HIV-positive individuals will continue to face a higher risk for influenza-related mortality (50,58), especially in sub-Saharan Africa where access to care is suboptimal. Therefore, to reduce the risk of influenza transmission and its subsequent health burden, it is imperative to understand the role of HIV in the epidemiology of influenza transmission in household settings. We begin to explore the interaction of these infections at the household level by using 2008 through 2011 household and clinic surveillance data gathered from 176 households with known HIV status in an urban slum in Nairobi, Kenya.

**CHAPTER II:  MANUSCRIPT**

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

**ABSTRACT**

**Introduction:** Little is known about how HIV affects the transmission dynamics of influenza in household settings in sub-Saharan Africa. In this retrospective cohort study of 176 households with known HIV status in an urban slum in Nairobi, Kenya, we used population-based household and clinic surveillance data gathered from 2008 through 2011 to examine the association between the HIV status of household members and their risk of introducing influenza to the home. We also examined the association between the HIV status of laboratory-confirmed influenza index cases and the risk of developing influenza-like illness (ILI) among their household contacts.

**Methods:** ILI in a household member was defined as reported or diagnosed cough or sore throat with accompanying fever ≥ 38.0°C. Persons with ILI who also sought medical care at the free clinic located in the study site, and who consented to provide nasopharyngeal and oropharyngeal swabs, were tested by real-time reverse transcription PCR for influenza virus infection. Index cases of influenza in households were defined as laboratory-confirmed influenza cases

occurring at least two weeks after a previous household case of ILI. The secondary ILI attack rate (SAR) was defined as the proportion of household contacts who developed ILI within 14 days after the laboratory-confirmed influenza index case was identified. HIV status was assessed via home-based testing and counseling or at the local study clinic. Log-binomial models using generalized estimating equations (GEE) to account for household clustering evaluated the association between laboratory-confirmed influenza index case status in the home and individual HIV status of the household members, as well as the association between secondary ILI status of household contacts and the HIV status of the influenza index case in the home.

**Results:** HIV-positive household members were not at an elevated risk for introducing influenza to their homes, compared to HIV-negative household members (relative risk (RR), 1.35; 95% confidence interval (CI), 0.65 - 2.78), when controlling for age group of the household member, household size, and general type of circulating influenza strain (seasonal or pandemic 2009 influenza A/H1N1). However, HIV-positive index cases were more likely to spread influenza to their household contacts than HIV-negative index cases, when adjusted for age group of the household-contact (RR, 2.36; 95%CI, 1.19 - 4.66).

**Conclusion:** Our results suggest that HIV-positive influenza index cases may seed household epidemics. Large sample size prospective studies and clinical study of median CD4 counts among index cases and secondary cases, as well as

laboratory or clinical confirmation of reported secondary cases are needed to further evaluate the role of HIV in influenza transmission in the home. HIV-positive individuals should continue to be a priority for influenza vaccination. Additionally, HIV status must be considered when analyzing influenza susceptibility data at the household level in a region with high HIV seroprevalence.

**INTRODUCTION**

Influenza has a significant impact on global morbidity and mortality (59). Epidemics worldwide have been suggested to occur primarily in structured environments like workplaces, schools, and homes (25,60). However, household settings have been particularly important sites for researchers to investigate a variety of influenza characteristics (29). While well-documented elsewhere in the world (15,61–63), little is known about influenza introduction to households and transmission within households in sub-Saharan Africa (57,64). In particular, the transmission dynamics of influenza may be altered by widespread immunosuppression due to the highest worldwide HIV seroprevalence in this region (38). However, no cohort studies of households have evaluated this hypothesis.

Among individuals living with HIV, influenza is a common cause of respiratory illness (39). Although studies of seasonal and pandemic influenza have found that HIV-positive individuals are not more susceptible to influenza infection than the general population (40–43), it has been widely accepted that these individuals may experience more severe clinical infections, leading to elevated rates of hospital admissions and mortality (31,33,34,41,44,45). Additionally, expert opinion and clinical case reports have suggested that HIV-positive patients may shed influenza virus for prolonged periods (32,34,45,46). However, no prospective follow-up studies have evaluated the implications of prolonged viral

shedding by HIV-positive persons on influenza transmission to household contacts.

While the picture of influenza transmission in sub-Saharan Africa as a whole remains incomplete, recent studies have begun to characterize influenza epidemiology (54–56) and household transmission patterns (57) in Kenya, a sub-Saharan East-African country bearing a substantial HIV burden, with an estimated national prevalence of 7.1% (51). In this context, a weakened immune system may lead to a prolonged respiratory illness infectious period. Thus an increased dose and duration of pathogen shedding could theoretically increase the risk of transmission to household-contacts.

In this retrospective cohort study of 176 households we use household and clinic data from 2008 through 2011 to describe i) the effects of HIV status of household members on their risk of introducing influenza to the home, and ii) the effects of HIV status of index cases of influenza in the home on the risk of developing influenza-like illness (ILI) among their household contacts. This study was undertaken in a population-based infectious disease surveillance (PBIDS) site in Kibera, a large and densely populated urban slum in Nairobi, Kenya. We hypothesized that HIV-positive individuals were more likely to introduce influenza to their households than HIV-negative individuals and that household-contacts of HIV-positive influenza index cases were more likely to develop secondary ILI than household-contacts of HIV-negative influenza index cases.

**METHODS**

<u>Study site</u>

We analyzed respiratory illness data from a Kenya Medical Research Institute (KEMRI) and Centers for Disease Control and Prevention-Kenya (CDC-K) population-based infectious disease surveillance (PBIDS) site in Kibera, Nairobi, Kenya from 2008 through 2011. The surveillance system and this study site have been previously described (56,57,65–67). Briefly, Kibera is a sprawling urban slum in Nairobi, Kenya with a population density of 70,000 persons/km$^2$, suboptimal sanitation infrastructure, no endemic malaria, and an estimated 14.8% HIV seroprevalence in 2008 (52). Homes are usually single room structures built with mud, wood, and metal sheeting, and strewn along unpaved roads (57,68). A majority of slum inhabitants work outside the home in Nairobi (65).

Since 2006, approximately 28,000 study participants have been enrolled in this KEMRI/CDC-K study site. All individuals living in households >4 months are eligible for enrollment. Trained community interviewers regularly visit and survey all participating households in their native language for recent symptoms indicative of diarrhea, fever, jaundice and respiratory illness. Community interviewers encourage persons who report illness to go to the Tabitha Clinic, a local CDC-supported medical facility operated by Carolina for Kibera (Chapel Hill, NC), for diagnosis and free medical care (56,65). Interviews in Kibera occurred bi-weekly until September 2009, after which visit frequency increased

to weekly in 3 of 10 site clusters, and then to weekly across the entire site from 1 February 2010 onward.

The baseline HIV status of study participants was ascertained from a 2008 home-based testing and counseling (HBTC) program, previously described (52). All PBIDS enrollee adults (18 years or older) were   offered the option to consent and participate in HBTC, while limited enrollment was offered to persons less than 18 years of age. Among 24,450 people who were offered HBTC, 82% accepted (52); individuals not accepting HIV testing at enrollment and individuals enrolled after 2008 had access to voluntary clinic-based testing at the free medical facility. No comprehensive HBTC program has been implemented within the study site since 2008.

Household respiratory illness surveillance

At each household visit, participants are questioned about respiratory symptoms occurring within the past 2 weeks, including sore throat, cough, and fever ≥38.0°C. Persons >5 years of age are personally interviewed. If persons >5 years are not at home or are unable to answer questions, a proxy member of the household who is knowledgeable about the health of the participant is interviewed. For children ≤5 years of age, the mother or other primary caretaker is interviewed.

Case definition: Influenza-like illness (ILI)

Influenza-like illness (ILI) in a household member was defined as a measured fever ≥38°C and sore throat or cough among individuals of all ages. ILI could be home reported or diagnosed at the study clinic.

Clinic-based testing for influenza

Tabitha Clinic in Kibera provides outpatient care and refers patients for hospitalization to a district hospital 3 km away. When an ill study participant visits the study clinic, a standardized questionnaire is conducted. If the patient presents with symptoms indicative of ILI and consents to testing, staff perform a laboratory procedure to identify respiratory illness etiology. The protocol has been previously described, and is performed solely at this medical facility (56). Briefly, nasopharyngeal and oropharyngeal (NP/OP) specimens are collected upon patient consent and stored at 4°C for 0-24 hours. These specimens are then sent to KEMRI/CDC-K labs in Nairobi in a single viral transport medium at 4°C to be tested by real-time reverse-transcription polymerase chain reaction (RT-PCR) for influenza types and subtypes, among other respiratory pathogens. If swab specimens test positive for influenza, clinic staff notifies the ill study participant within 48-72 hours.

Household influenza index cases and secondary cases

We used clinic data recorded during the study period to identify all laboratory-confirmed influenza cases and linked them to their households by their study identification numbers. Only households of known HIV status in which no member other than the influenza case had reported or been diagnosed with ILI within the past 2 weeks were eligible. In households where >1 laboratory-confirmed influenza case occurred within a two-week period, the first with a confirmed NP/OP swab specimen was designated as the index case. If laboratory confirmation occurred on the same day, the younger household member was designated as the index case with the assumption that children are more susceptible to infection than older age groups (7).

After the influenza index cases were identified, we defined a secondary ILI case as any household-contact of the index case who developed ILI within two weeks. We selected a two-week follow-up period to account for approximately two influenza infectious periods (4), plus a short time lag to account for increased viral shedding duration among HIV-positive index cases (33). ILI was determined to be the best indicator of true influenza infection (69). Therefore we assumed that if a household contact of an index patient with influenza developed ILI, that household contact was infected with influenza. However, there was no clinical confirmation of secondary cases of influenza-like illness.

The overall secondary attack rate (SAR) was defined as the proportion of household contacts developing ILI within 14 days after index case identification.

## Case definitions: HIV-related

Individual HIV status was defined as the result of an HIV test recorded up until eighteen months after household influenza index case identification. An HIV-positive household was defined as one in which ≥ 1 member(s) had been tested for HIV up until eighteen months after influenza index case identification, and ≥1 member(s) confirmed HIV-positive. An HIV-negative household was defined as any household that had ≥ 3 members testing HIV-negative or ≥ 50% of the household testing HIV-negative up until eighteen months after index identification, and none testing HIV-positive. We used the eighteen-month time lag to reduce missing values for HIV status estimates at the individual and household level while introducing minimal misclassification bias (refer to Supplemental Methods Table 1). Individuals of unknown HIV status from HIV-positive and HIV-negative households were included in analysis.

## Bivariate analysis

We used bivariate log-binomial generalized estimating equations (GEE) models accounting for household clustering to assess the crude association between potential risk factors for influenza infection and i) the introduction of influenza to households, as well as ii) the transmission of influenza to household contacts.

*P* values and crude risk ratios assessed statistical association and direction of effect, respectively. These potential risk factors included individual HIV status, age group of household member, household size, and general types of circulating influenza strains. Individual HIV status was treated as a time-varying covariate; during the study period, if a household member had unknown HIV status at index case identification, but was tested within 18 months after index identification, the status from the test result was applied retroactively to the unknown status. Individual HIV status was categorized into indicator variables for "HIV-positive", "HIV-negative", and "HIV-unknown" statuses. Age in years was calculated at the time of index case identification from known birthdates, rounded to one decimal place, and categorized into infant (≤ 2.0 years), pre-school (2.1-4.9 years), school-aged (5.0-17.9 years) or adult (≥ 18.0 years). We measured household size as the maximum count of members present within 2 weeks of index case identification, and dichotomized it at the mean (≤ 7 persons or > 7 persons). We classified the general types of circulating influenza strains by year of observation: index cases observed during 2008, 2010, and 2011 were assumed to be seasonal influenza A and B strains, while index cases observed during 2009 were assumed to be pandemic influenza A (H1N1).

We then performed Pearson Chi-square tests at $\alpha = 0.016$ (adjusting with the Bonferroni method for multiple comparisons) to identify significant differences in the distribution of influenza risk factors between i) laboratory-confirmed

influenza index cases and secondary ILI cases, and ii) secondary ILI cases and their household contacts with no secondary infection.

<u>Multivariate analysis</u>

We used multivariate log-binomial generalized estimating equation (GEE) models accounting for household clustering to evaluate relationships between the dependent and independent variables. Our models assumed that all the secondary ILI cases were infected by the index cases. The first model included all 1,050 study participants, and assessed the association between individual HIV status of household members and their risk of introducing influenza to the home as the index case, adjusted for age group of the household member, household size, and general type of circulating influenza strain at time of index case identification. Our second model included all non-index case household contacts (n=874), and assessed the association between the HIV status of the index case and the risk of developing ILI among the household contacts, adjusted for age group of the household contact. The primary exposure in both models (i.e. individual HIV status) was split into two indicator variables, respectively comparing "positive" and "unknown" categories, with "negative" as the referent.

The variables included in the multivariate models demonstrated a significant association with the respective outcomes in bivariate analyses and substantially

changed the regression coefficient of the primary exposure variable (by >10%)

after being added to the model. We evaluated these models for multicollinearity

by measuring condition indices and variance decomposition proportions (70)

and for effect modification and confounding by using the Score test and a

hierarchical backwards elimination procedure (71). Ninety-five percent

confidence intervals (95% CI) were calculated around point estimates of the risk

ratio (RR) for our primary exposures using the exchangeable correlation

structure and robust standard error estimator (72). Statistical analysis was

performed using SAS 9.3 for Windows (SAS Institute, Cary, NC) and Stata 12 for

Mac (College Station, TX).

Ethics Statement

The protocol and written consent forms were reviewed and approved by the

ethical review committees of the Centers for Disease Control and Prevention and

the Kenya Medical Research Institute. The Emory institutional review board

determined that this secondary data analysis did not require their approval. The

Emory IRB form can be found in the Appendices.

**RESULTS**

<u>Kibera population</u>

The source population consisted of 632 households with a laboratory-confirmed influenza index case identified from January 1, 2008 through December 17, 2011. Figure 1 shows the progress of index cases and their household contacts through the study. After exclusions, our sample consisted of 1,050 individuals (176 index cases, 874 household contacts) living in 176 households.

Overall, 6% of sampled individuals were aged ≤2.0 years, 10% were aged 2.1-4.9 years, 36% were aged 5.0-17.9 years, and 47% were aged ≥ 18.0 years. Forty-seven percent of the sample was male. Overall HIV seroprevalence was 6%, although when 530 (50%) individuals with unknown HIV status were excluded from this estimate, the average (95% CI) HIV seroprevalence was 13% (10 – 15). Adults ≥ 18.0 years contributed 77% of known HIV status, while 74% percent of individuals aged ≤2.0 years, 81% of individuals aged 2.1-4.9 years, and 74% of individuals aged 5.0-17.9 years had not been tested for HIV. Forty-five percent of those tested for HIV were male. Yearly HIV seroprevalence from our sample ranged between 11% and 16% during the study period. No individuals with known HIV-negative status seroconverted by the end of the study period.

Households

The median (range) household size was 6 (2-15) persons. The mean (95% CI) age per household was 19.4 (18.6-20.2) years. Approximately 32% of households had ≥1 individual(s) testing HIV-positive, with 26% of households having only 1 individual testing HIV-positive, and 6% of households having 2. The median (range) number of individuals tested for HIV per household was 3 (1-7) persons.

Index cases

We identified 176 laboratory-confirmed influenza index cases that met our study inclusion criteria. Selected demographic and clinical characteristics for these cases are shown in Table 1. Figure 2 shows temporal incidence of influenza index cases by six-month intervals. Among the index cases, the median (range) age was 8.3 (0.2 – 48.1) years, and 49% were male. HIV seroprevalence was 6%, although when 109 (62%) index cases with unknown HIV status were excluded from this estimate, the average (95% CI) HIV seroprevalence was 15% (6 – 24). They were most frequently school-aged, and lived in mostly HIV-negative households of less than average size (7 persons). The index cases were similar to the secondary cases, except that there was a significantly higher proportion of school aged children among the index cases than among the secondary cases (42% vs. 23%, p = 0.01).

Secondary ILI cases and household contacts with no respiratory infection

There were 72 (8%) secondary ILI cases out of 874 total household contacts. Selected demographic and clinical characteristics for secondary ILI cases and their household-contacts with no respiratory infection are shown in Table 1. The average (95% CI) crude SARs due to seasonal influenza A and B strains (2008, 2010, and 2011) were 9% (1-17), 10% (4-15), and 6% (2-11), respectively. Similarly, the average (95% CI) SAR due to 2009 pandemic influenza A (H1N1) was 6% (4-9). The median (range) age among secondary cases was 6.3 (0.3 – 52.4) years, and 46% were male. In contrast, the household contacts with no respiratory infection had a median (range) age of 19.2 (0.1 – 66.1) years. There were significantly larger proportions of infants and pre-school age children among secondary cases than among household contacts with no respiratory infection (22% vs 3%, p < 0.01; 19% vs 8%, p = 0.01). Secondary ILI cases had an HIV seroprevalence of 7%, although when 36 (50%) individuals with unknown HIV status were excluded from this estimate, the average (95% CI) HIV seroprevalence was 14% (2 – 26). Household contacts with no respiratory infection had a similar HIV seroprevalence. Healthcare seeking among household contacts was minimal, with 6 (8%) secondary cases and 20 (2%) of household-contacts with no reported ILI seeking treatment for respiratory symptoms.

Risk factors for influenza introduction to the household

Crude analyses to determine potential risk factors for the introduction of influenza to the household are presented in Table 2. We found that being HIV-positive, being an infant, of preschool age, or school age, living in a household of less than average size, and being observed during the years when seasonal influenza A and B strains were circulating were all factors significantly associated with being a household influenza index case.

Multivariate analysis of influenza introduction to the household

The adjusted multivariate model describing the effect of HIV status on influenza introduction to the household is presented in Table 2. Among the 1,050 study participants in 176 households, HIV status was not significantly associated with influenza index case status when controlling for age of the household member, household size, and general type of circulating influenza strains. Instead, age of the household member was significantly associated with influenza index case status, when controlling for HIV status of household members, household size, and general type of circulating influenza strains.

Risk factors for influenza transmission within the household

Crude analyses to determine potential risk factors for influenza transmission within the household are also presented in Table 2. We found that HIV status of

the index case and age of the household contact were significantly associated

with the development of ILI among household contacts. In the 10 households

with HIV-positive index cases, 8 (24%) of the 33 household-contacts developed

ILI, while only 21 (9%) of the 239 household-contacts developed ILI in the 45

HIV-negative households with HIV-negative index cases (p=0.002). In

exclusively HIV-negative households, 18 (8%) of the 239 household contacts

developed ILI. HIV status of the household contacts was not associated with

influenza transmission within the household.

Multivariate analysis of influenza transmission within the household

The adjusted multivariate model describing the effect of HIV status on influenza

transmission within the household is presented in Table 2. Among the 874

household-contacts in Kibera, the risk of being a secondary ILI case when the

household influenza index case was HIV-positive was about two times the risk of

being a secondary ILI case when the household index case was HIV-negative,

adjusting for age of the household-contact (95% CI: 1.19, 4.66).

**DISCUSSION**

To our knowledge, this is the first study to investigate the effects of HIV on influenza transmission dynamics in a household setting in sub-Saharan Africa. Our results support prior studies asserting that HIV-positive individuals are not at a higher risk for influenza infection than the general population (40–43). Our results also match the general consensus that young and school-aged children experience elevated influenza susceptibility (7,29,59,62,73), and that they often introduce influenza into their homes (74,75). However, our findings suggest that HIV status does confound the effects of age on influenza susceptibility, and therefore must be considered when predicting individual influenza susceptibility at the household level in a region with high HIV seroprevalence.

Most importantly, our study indicates that HIV-positive persons may play a significant role in seeding household influenza epidemics. Therefore, we recommend HIV-positive individuals continue to be a priority for influenza vaccination. Furthermore, we assert that it is crucial to identify additional effective preventive measures and post-exposure treatments for HIV-positive individuals in order to mitigate influenza transmission in populations with significant HIV burden.

Introduction of influenza to the household

We found that HIV positive individuals were not at an elevated risk for
introducing influenza to their homes, when adjusting for age of household
members, household size, and general type of circulating influenza strains.
Rather, children were more likely to introduce influenza to their homes than
adults, when adjusting for the HIV status of the household members, household
size, and general type of circulating influenza strains (Tables 1 and 2). Since it has
long been established that children are the most susceptible age group for
influenza infection, this result was expected. Prior observational studies and
simulation models have pointed to the importance of schools and the associated
frequent social mixing as the probable explanation for this age-related influenza
transmission phenomenon (74–76). Our study amends this phenomenon by
describing the confounding nature of HIV status on the relationship between age
and influenza susceptibility, and highlights the need to consider HIV status in
future studies of influenza susceptibility in structured environments like the
home.

Influenza transmission within the household

We showed that household contacts of HIV-positive influenza index cases were
about twice as likely to develop ILI than household contacts of HIV-negative
influenza index cases, when adjusting for age of the household contacts (Table 2).

Similarly, we also reported a 24% SAR among the 33 household contacts of the 10

HIV-positive index cases. This SAR is significantly higher than the observed 8%

SAR among the 303 household contacts in exclusively HIV-negative households.

There are a few potential explanations for these findings. First, expert opinion

and clinical case reports have shown that HIV-positive individuals have been

known to shed influenza virus at an increased dose for prolonged periods

(32,34,45,46). Second, the various adverse conditions prevalent in urban slums,

such as high population density, poor air quality, and poor community sanitary

infrastructure (68) could have increased the transmission potential for influenza

viruses. These factors could have worked in tandem, increasing the risk of

transmission to household-contacts.

On the other hand, we showed that in exclusively HIV-negative households, 18

(8%) of the 239 household contacts developed ILI. Since there have been no

studies on HIV-positive secondary ILI attack rates, this more specific SAR

facilitates direct comparison with prior observational studies. It is similar to

SARs observed in in the United States and Hong Kong, both of which take into

account seasonal influenza A and B strains and 2009 pandemic influenza A

(H1N1) and likely include no HIV-positive study participants (15,62). A

nationwide study of pandemic 2009 influenza A (H1N1) in the United States

reported a 10% crude SAR when a secondary case was defined as influenza-like

illness (62). A study in Hong Kong of individuals from outpatient clinics and

their household contacts compared seasonal and pandemic 2009 influenza A (H1N1), reporting 8% and 9% crude household SARs, respectively (15). While participant demographics and locally important comorbidities were likely different between these prior study populations and our study sample, the similar SARs suggest that social networks and hygienic behaviors were probably similar among household participants.

Regardless of HIV status, we observed that seasonal influenza A and B viruses produced crude average (95% CI) SARs of 9% (1-17) in 2008, 10% (4-15) in 2010, and 6% (2-11) in 2011, and that pandemic 2009 influenza A (H1N1) produced a crude average (95% CI) SAR of 6% (4-9). Due to sampling error inherent in all studies, our data do not appear to be meaningfully different than a 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 (15).

Finally, we found that children were at an elevated risk for secondary infection when adjusted for HIV status of the index case. This supports the conclusions from a recent systematic review of SARs among children during the 2009 H1N1 pandemic (14), as well as the vaccination recommendations from the Central European Vaccination Advisory Group, and two studies reviewing pandemic and seasonal influenza transmission (11,77,78).

Limitations and strengths

Our study is subject to certain limitations. First, there was an age-related case ascertainment bias for individual HIV testing, which was most visible among the index cases. This can be in part ascribed to overall sub-optimal coverage of HIV testing and counseling (52) and age-related testing restrictions; testing was only offered to study participants ≥ 18 years of age and emancipated minors (13-17 years of age), as well as children aged 13 years or younger whose biologic mothers were HIV-positive or were deceased. Therefore, younger individuals whom were often the household index cases or had secondary ILI could not be represented among the known HIV status estimates (52). This lack of a comprehensive HIV testing means that we could have underestimated or overestimated the effect of HIV status on household influenza transmission dynamics. However, because our overall HIV seroprevalence estimate of 13% is similar to the 2008 estimate of 15% measured via HBTC, and because study population HIV estimates ranged between 11% and 16% during the study period, it is likely that systematic bias due to missing values was minimal.

Additionally, there were several confounders to the relationships we evaluated that were not measured, including extent of vaccination coverage and prevalence of pharmaceutical treatment among all study participants, as well as median CD4 counts and prevalence of highly active anti-retroviral treatment (HAART) among HIV-positive individuals.

Influenza vaccination is the single most effective preventive measure for reducing influenza transmission. Regular vaccination campaigns have not been implemented in this study site, although children < 12 years of age were targeted in a pilot study during 2010-2011. However, the sample size was too small to reveal any significant effect on influenza susceptibility or transmission, and further analysis was not pursued. Because vaccination coverage probably did not reach a level sufficient for herd immunity, our oversight likely had little effect on our adjusted multivariate analyses.

Antiviral treatments have been shown to mitigate household transmission when the household index case is treated (63,79). Although we were unable to determine the population antiviral use among index cases, only two patients reported seeking clinical care, and 8% of secondary cases and 2% of household-contacts with no reported ILI indicated that they had used pharmaceuticals for their illness. Therefore our effect was probably not confounded by common antiviral usage. Even if all household-contacts not reporting respiratory illness but seeking care had been counted as secondary ILI cases, the SAR would have only increased to 11%, which is still within the range of observed SARs in cited literature.

We also did not measure median CD4 counts to determine severity of immune system decline among the 65 HIV-positive individuals in this study. Instead, we assumed HIV-positive individuals had progressed to a state of meaningful

immunosuppression, which had significantly affected their susceptibility and transmission potential for influenza as compared to their HIV-negative counterparts. If this was not the case, our estimates may have overstated the effect of HIV status. We also did not measure or stratify upon usage of highly active antiretroviral therapy (HAART) among HIV-positive individuals. Since HAART usage is on the rise in sub-Saharan Africa and has had a significant impact on lowering morbidity (80), we may have also overstated the effect of HIV on influenza transmission within the household.

However, our study has the following strengths. Considering the paucity of HIV testing among study participants, we had to estimate a significant portion of individual HIV statuses. Therefore, we extended the follow-up period to 18 months after index case identification to maximize the number of study participants with known HIV status. Our estimation resulted in a 26% increase of known individual HIV statuses, allowing us to improve the power for detecting significant differences in measures of effect. We correctly estimated 119 (23%) HIV-negative statuses and added 16 (24%) more HIV-positive statuses unknown at the time of index identification. Given that the 2010 Kenya National HIV Estimate showed yearly HIV seroconversion to be <1% (81), it is unlikely that any individuals with unknown HIV status at the time of index case identification seroconverted within 18 months. Additionally, we measured our individual HIV status via HBTC and measured household transmission from home-reported

secondary cases. Relying on home-based measurements rather than clinic surveillance improved our ability to estimate the true seroprevalence of HIV and true incidence of secondary ILI. Finally, the active population-based study design allowed us to measure cumulative incidence of influenza infections, rather than a less representative point prevalence.

Recommended extensions of current study

More comprehensive HIV testing in Kibera would improve HIV prevalence estimates, effectively reducing this source of bias in the estimation of relative risk for influenza susceptibility and infectivity. Such an improvement would be especially relevant to individual level estimates of effect, where sample size for our primary predictor was sparse. It would also be worthwhile to assess clinical respiratory illness on a daily basis whenever a known HIV-positive household index case of influenza is identified. Average infection time has been reported as occurring within 3 days of symptom onset in the index patient (79). If household contacts are being infected due to prolonged shedding from the HIV-positive index case, then one might expect to see measureable influenza infection in household contacts occurring later on average than among exclusively HIV-negative households. If not, then perhaps the HIV-positive index case is shedding more influenza virus than HIV-negative index cases, or perhaps the explanation lies in a combination of a higher dose and prolonged shedding, or some other unknown mechanism.

Recommendations and conclusions

Our findings lay forth a preliminary role for HIV status in the introduction and transmission of influenza in household settings in Africa. We conclude that HIV status should be considered in future studies evaluating the risk factors for influenza susceptibility, especially in populations with high HIV seroprevalence, and that HIV-positive influenza cases may play a significant role in seeding household influenza epidemics. However, a better understanding of the effects of HIV on influenza transmission dynamics is needed, especially in regions of high HIV seroprevalence like sub-Saharan Africa. In the meantime, HIV-positive individuals should continue to remain a priority for routine vaccination, if not solely because HIV-positive individuals are at an elevated risk for severe clinical symptoms and mortality, but because vaccinating HIV-positive individuals may mitigate influenza transmission in the home. Post-exposure prophylaxis is also recommended to reduce household transmission.

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**TABLES**

**Table 1.** Selected Characteristics for Laboratory-Confirmed Influenza Index Cases and Their Household-Contacts
- Kibera, Kenya, 2008 - 2011.

| Characteristic, n (%) | Index cases[a] (n = 176) [A] | Household contacts | | *P* value (α = 0.02) † | |
|---|---|---|---|---|---|
| | | Secondary cases[b] (n = 72) [B] | Non-cases (n = 802) [C] | [A] vs [B] | [B] vs [C] |
| Household HIV Status | | | | | |
| Positive | 55 (31) | 20 (28) | 205 (26) | 0.59 | 0.68 |
| Individual HIV Status | | | | | |
| Positive | 10 (6) | 5 (7) | 50 (6) | 0.71 | 0.81 |
| Negative | 57 (32) | 31 (43) | 367 (46) | 0.11 | 0.66 |
| Unknown | 109 (62) | 36 (50) | 385 (48) | 0.08 | 0.75 |
| Age (years) | | | | | |
| < 2.0 | 26 (15) | 16 (22) | 24 (3) | 0.16 | <0.01 |
| 2 - 4.9 | 30 (17) | 14 (19) | 65 (8) | 0.65 | 0.01 |
| 5 - 17.9 | 74 (42) | 17 (24) | 289 (36) | 0.01 | 0.03 |
| ≥ 18.0 | 46 (26) | 25 (35) | 424 (53) | 0.18 | 0.01 |
| Persons per household | | | | | |
| ≤7 | 124 (70) | 42 (58) | 400 (50) | 0.07 | 0.17 |
| Year ‡ | | | | | |
| 2008 | 15 (9) | 9 (13) | 64 (8) | | |
| 2009 | 88 (50) | 33 (46) | 419 (52) | | |
| 2010 | 36 (20) | 20 (28) | 143 (18) | | |
| 2011 | 37 (21) | 10 (14) | 176 (22) | | |

[a] Study participants who had laboratory-confirmed influenza in a household of known HIV status where no other member had reported or been diagnosed with influenza-like illness (ILI) within the past 2 weeks. In households with >1 laboratory-confirmed influenza case within a two-week period, the first with a confirmed NP/OP swab specimen by RT-PCR was designated as the index case.

[b] Any household-contact of the index case with home reported or clinically diagnosed ILI within two weeks of index case identification. We assume that if a household contact of an index patient with influenza developed ILI, the household contact was infected with influenza.

† Pearson Chi-square test adjusted using Bonferroni method for multiple comparisons.

‡ Circulating influenza strains were of seasonal influenza A and B types in 2008, 2010, and 2011. All cases in 2009 are assumed to be pandemic influenza A (H1N1).

**Table 2**. Crude bivariate analyses and adjusted multivariate analyses using fitted log-binomial GEE models to account for household clustering in Kibera, Nairobi, Kenya 2008-2011.

| Predictors | Index case | | | | Secondary ILI case | | | |
|---|---|---|---|---|---|---|---|---|
| | RR | 95% CI | aRR* | 95% CI | RR | 95% CI | aRR† | 95% CI |
| HIV-positive household member | 3.30 | (2.00, 5.46) | 1.34 | (0.68, 2.66) | -- | -- | -- | -- |
| HIV-positive index case | -- | -- | -- | -- | 3.40 | (1.52, 7.63) | 2.36 | (1.19, 4.66) |
| Age (years) | | | | | | | | |
| < 2 | 17.66 | (10.19, 30.62) | 4.78 | (3.18, 7.17) | 6.73 | (3.99, 11.35) | 6.56 | (3.96, 10.85) |
| 2 - 4 | 7.882 | (3.87, 16.05) | 3.35 | (2.20, 5.09) | 3.20 | (1.87, 5.50) | 3.02 | (1.73, 5.27) |
| 5 - 17 | 4.10 | (1.84, 9.12) | 2.56 | 1.78, 3.67) | 1.00 | (0.61, 1.64) | 1.01 | (0.61, 1.66) |
| ≥ 18 | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Persons per household | | | | | | | | |
| ≤7 | 3.02 | (2.81, 3.25) | 2.45 | (2.17, 2.75) | -- | -- | -- | -- |
| Year | | | | | | | | |
| 2008 | 1.87 | (1.29, 2.70) | 1.32 | (1.13, 1.55) | -- | -- | -- | -- |
| 2010 | 2.30 | (1.99, 2.68) | 1.24 | (1.07, 1.44) | -- | -- | -- | -- |
| 2011 | 2.05 | (1.74, 2.41) | 1.40 | (1.24, 1.59) | -- | -- | -- | -- |
| 2009 | 1.00 | | 1.00 | | -- | -- | -- | -- |

* Risk ratio calculated for 1050 study participants, adjusted for age group of household member, persons per household, and year of observation.
† Risk ratio calculated for 874 household contacts, adjusted for age group of household-contact.

GEE = generalized estimating equations; ILI = influenza-like illness; RR = risk ratio; CI = confidence interval

**Supplemental Table 1.** A comparison of several HIV status definitions to minimize misclassification while maximizing known HIV status, Kibera, Nairobi, Kenya 2008 - 2011.

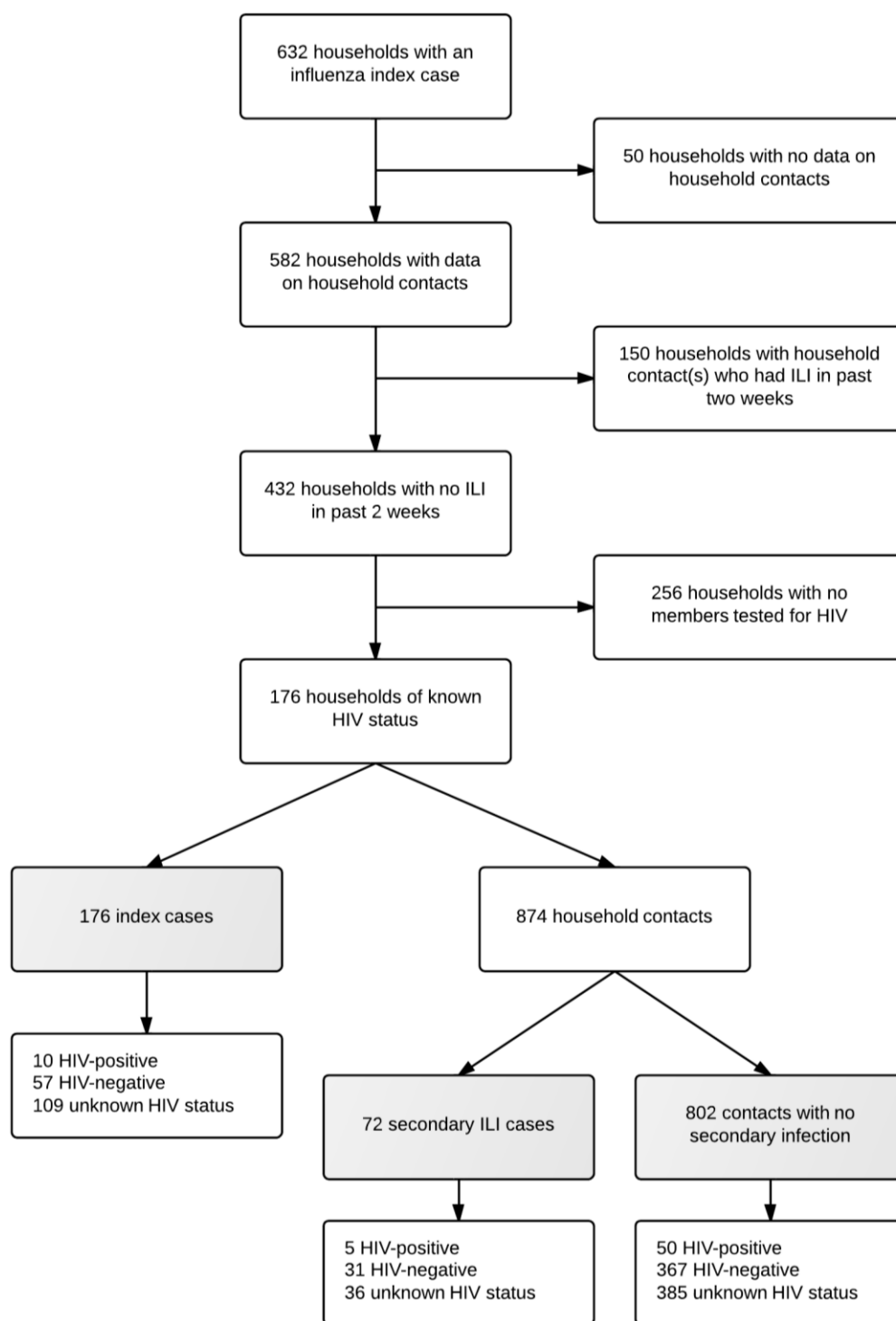| Months since index case identification | HIV-positive n (%) | HIV-negative n (%) |
|---|---|---|
| 0 | 49 (4.7) | 336 (32.0) |
| ≤ 2 | 50 (4.8) | 357 (34.0) |
| ≤ 4 | 53 (5.0) | 372 (35.4) |
| ≤ 6 | 58 (5.5) | 391 (37.2) |
| ≤ 8 | 60 (5.7) | 413 (39.3) |
| ≤ 10 | 61 (5.8) | 427 (40.7) |
| ≤ 12 | 61 (5.8) | 434 (41.3) |
| ≤ 14 | 62 (5.9) | 444 (42.3) |
| ≤ 16 | 64 (6.1) | 451 (43.0) |
| ≤ 18 | 65 (6.2) | 455 (43.3) |
| ≤ 20 | 67 (6.4) | 457 (43.5) |
| At end of study period | 67 (6.4) | 463 (44.1) |

**FIGURES**



**Figure 1.** Number of surveillance participants and exclusions from study analysis – Kibera, Kenya, 2008-2011. Individuals in gray boxes were subject of analyses.
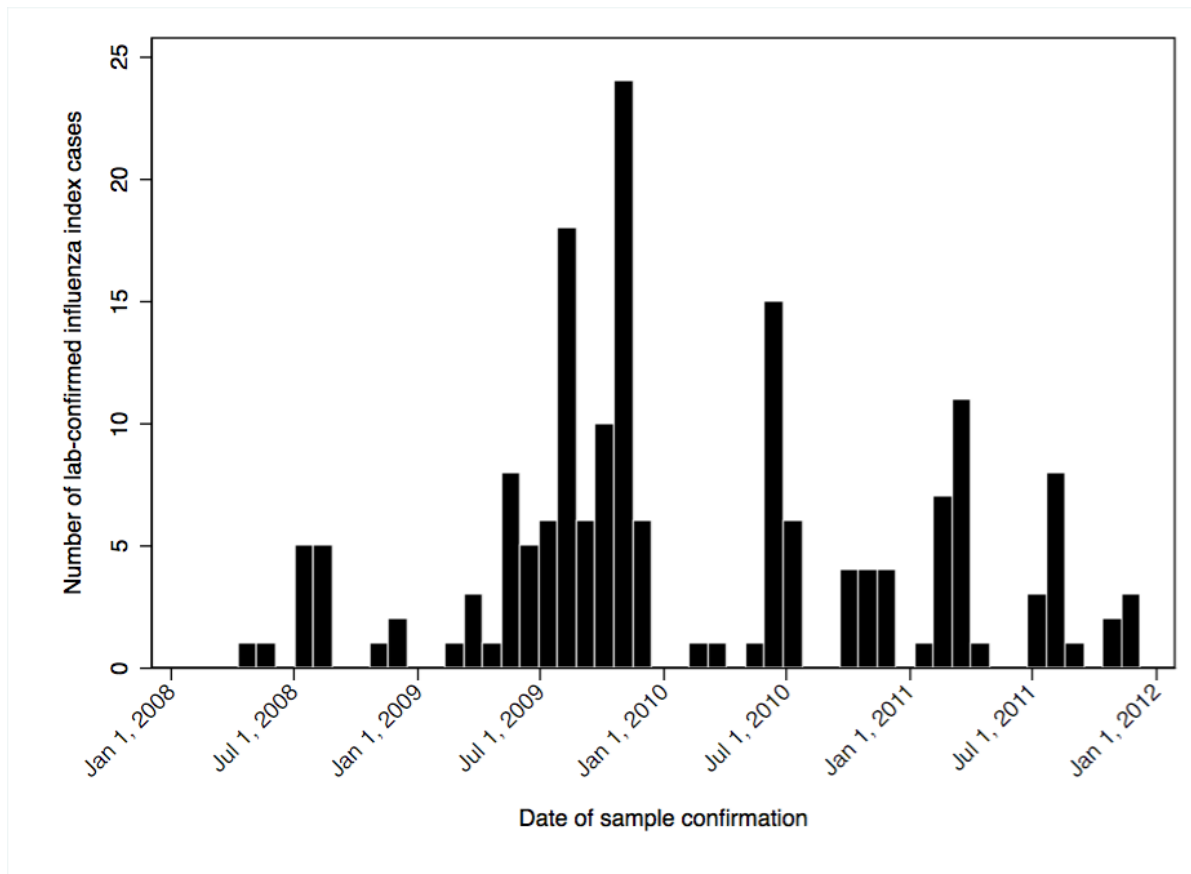
**Figure 2.** Number of laboratory-confirmed influenza index cases by sample confirmation date – Kibera, Kenya, 2008-2011. The x-axis indicates the sample confirmation date, and the y-axis indicates the number of lab-confirmed influenza index cases.

**CHAPTER III:  Public Health Implications**

In 2008, the UN HABITAT program indicated that "the urban population in sub-Saharan Africa is expected to double to nearly 800 million people by 2030" (82). Worldwide urban infrastructure has not kept pace with massive in-migration, resulting in the expansion and creation of densely populated slums with minimal access to government-sponsored basic sanitation services. As we have seen in Kibera, this chaotic and unregulated urban influx creates a variety of public health challenges and the potential for catastrophic epidemics (83). In this context, our additions to the understanding of influenza transmission have many implications for targeted interventions and future studies.

First and foremost, our cohort study of households in Kibera gives us a preliminary understanding of how HIV affects influenza transmission in densely populated urban slums in sub-Saharan Africa. Because household transmission is an important part of the overall perpetuation of influenza epidemics, and because HIV-positive individuals may facilitate such transmission, we believe that our study provides sufficient evidence to galvanize program planners and policy makers towards orchestrated, large-scale influenza vaccination campaigns in Kibera. These campaigns must effectively target the HIV-positive population. However, because of the ethical issues faced when targeting a certain group of individuals, we recommend that local authorities and NGOs work together to

provide free or low-cost influenza vaccines to clinics caring for HIV-positive

patients. We also suggest that they train their medical staffs on ways to educate

patients regarding the benefits of vaccination, and that they develop informative

literature to raise awareness within the community at large. It would also be

worthwhile to advise community members to bring their household contacts

with them when they go to clinics for vaccination. In the absence of action, HIV-

positive individuals will continue to face a higher risk for influenza-related

mortality (50,58), and their household contacts may face increased chances of

influenza infection.

Next, because we have shown that children are more likely to be susceptible and

infectious than adults, influenza vaccination awareness campaigns targeting

mothers could also facilitate increased vaccination uptake within the community.

Finally, providing inexpensive or free post-exposure antiviral treatments

effective against common influenza types and subtypes would be helpful for the

mitigation of influenza transmission among unvaccinated individuals.

Although we can take steps right now to prevent influenza transmission, it is still

vital to understand more about the role of HIV in influenza transmission

dynamics, especially in regions with high HIV seroprevalence. Therefore it is our

hope that this study will encourage researchers to conduct future prospective

studies with larger sample sizes and more clinical intervention to verify or refute

the validity of our results. Such studies would benefit from increased HIV testing within the community, so home-based counseling and testing campaigns like the one conducted by Dalal *et al* in 2008 (52) should be repeated and expanded to the Kibera community at large, and not just within the existing CDC-K/KEMRI surveillance site.

On a more general level, our research illustrates the importance of developing infectious disease surveillance programs in informal urban settlements. As Patel *et al* indicates, "collected data in slum populations are generally not included when health statistics are reported" (83). Ignoring the health of these fringe populations cannot continue; developing infrastructure and building capacity to estimate the incidence of a variety of important infectious diseases within the world's urban slums must be accomplished. This would not only satisfy our moral calling to respect and engender positive human health, but it would have implications for the safety of the population at large. After all, although HIV incidence may be declining (38), urban populations in sub-Saharan Africa seem to only be getting bigger and denser. And while established populations may reap the health benefits associated with stable urban life, the spread of disease never ends at the margins of the marginalized.

# APPENDICES

## Ethics Statement

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).

The Emory Institutional Review Board determined this secondary data analysis thesis did not require formal evaluation, as shown below.

EMORY UNIVERSITY | Institutional Review Board

April 1, 2013

Michael Christian Judd
Rollins School of Public Health
Emory University
Atlanta, GA 30322

RE:     **Determination: No IRB Review Required**
        **eIRB#: n/a**
        **Title: n/a**
        **PI: Michael Christian Judd**

Dear Mr. Judd:

Thank you for requesting a determination from our office about the above-referenced project.  Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definition(s) of "research" or "clinical investigation" involving "human subjects" as set forth in Emory policies and procedures and federal rules, if applicable.  Specifically, in this project, you have reviewed de-identified data that has no linked individual identifiers from the CDC Global Disease Protection Kenya Influenza Project.  Use of such information is not considered human subjects research.

Please note that this determination does not mean that you cannot publish the results. If you have questions about this issue, please contact me.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data.  If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,


Martha C. Patterson, BA
Research Protocol Analyst

**Additional Discussion**

Interpreting the effect of household size on influenza introduction risk

Overall, secondary cases and index cases occurred more often in households of less than average size (7 persons). We posit that in the smaller households, individuals are more likely to be nuclear families and thus have closer physical contact, whereas larger households may be multiple nuclear families, intergenerational families, or unrelated individuals with strong social connections. Most (90%) resided in a single room (68). The physical size of the dwelling was not measured in this study, but if households of less than average size lived in smaller dwellings than larger households, it is likely that they had more frequent physical contact. This increased physical contact establishes a suitable context for potential disease transmission, especially highly transmissible respiratory pathogens like the influenza virus.

Additional study limitations

There are additional reasons why our results may have understated the true effect of HIV on influenza susceptibility and infectiousness. Asymptomatic infection accounts for close to 1 in 3 infected persons (4). Therefore, on top of the probability that some influenza-positive individuals did not seek clinical care, others may not have been counted as primary cases or secondary cases due to a lack of symptoms to report. Fever may not have been observed either. All of these issues may have biased our estimates towards the null.

Second, we assumed that all household members were exposed uniformly to the

index case. This could be misleading if a household-contact shares a bed or

otherwise spends more time with the index case than other household-contacts

(such as mother-contact with child-index).

Next, because ILI was used as a proxy of influenza infection, some

misclassification might have occurred. However, a study reviewing eight double-

blind, placebo-controlled studies in North America, Europe, and the Southern

Hemisphere determined that ILI was best symptomatic indicator of true

influenza infection (69). Therefore, misclassification bias was likely minimal.