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.
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.

METHODS

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].

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].

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%. 
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].

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.

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.

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.

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 MacOS 10.7.5 (StataCorp, College Station, TX).

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).

RESULTS

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 (Supplemental Figure 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) (Supplemental Figure 1).

Influenza types and subtypes for the household index cases are summarized in Supplemental Table 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).

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 1).

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 2).

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 (J. Wong, D. Nyachieo, L. Cosmas, et al, submitted) and
influenza viruses in particular in higher titers and for longer periods of time than HIV-negative individuals [10, 11].

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 [12].

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 [13] 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 [14, 15], our findings highlight the potential value of thoughtful delivery of effective influenza vaccines to HIV-infected individuals.
FOOTNOTE PAGE

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Conflict of interests:
None exist.

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Meeting where information was previously presented:
An abstract of this research was presented by Gideon Emukule at the Options for the Control of Influenza in Cape Town, South Africa, 5-10 September 2013.

Acknowledgements:
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REFERENCES


Table 1. Risk Factors for Introducing Influenza to Household as Index Case Among All Household Members (n = 1050), Kibera, Kenya 2008-2011.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Total, n (%)</th>
<th>Index cases, n (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>aRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-positive individual</td>
<td>65 (6)</td>
<td>10 (15)</td>
<td>3.30</td>
<td>(2.00, 5.46)</td>
<td>1.23</td>
<td>(0.55, 2.75)</td>
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<tr>
<td>HIV-unknown individual</td>
<td>530 (51)</td>
<td>109 (21)</td>
<td>1.21</td>
<td>(0.65, 2.24)</td>
<td>1.05</td>
<td>(0.74, 1.48)</td>
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<tr>
<td>HIV-negative individual</td>
<td>455 (43)</td>
<td>57 (13)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<tr>
<td>Age of individual, years</td>
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<tr>
<td>&lt; 2</td>
<td>66 (6)</td>
<td>26 (39)</td>
<td>17.66</td>
<td>(10.19, 30.62)</td>
<td>5.69</td>
<td>(3.67, 8.82)</td>
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<td>2 - 4</td>
<td>109 (10)</td>
<td>30 (28)</td>
<td>7.88</td>
<td>(3.87, 16.05)</td>
<td>3.83</td>
<td>(2.40, 6.11)</td>
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<tr>
<td>5 - 17</td>
<td>380 (36)</td>
<td>74 (19)</td>
<td>4.10</td>
<td>(1.84, 9.12)</td>
<td>3.08</td>
<td>(2.02, 4.71)</td>
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<tr>
<td>≥ 18</td>
<td>495 (47)</td>
<td>46 (9)</td>
<td>1.00</td>
<td>1.00</td>
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<td>Persons per household</td>
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<td>≤ 6</td>
<td>412 (39)</td>
<td>102 (25)</td>
<td>3.44</td>
<td>(3.18, 3.72)</td>
<td>3.14</td>
<td>(2.73, 3.61)</td>
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<tr>
<td>&gt; 6</td>
<td>638 (61)</td>
<td>74 (12)</td>
<td>1.00</td>
<td>1.00</td>
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**Gender**

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<tbody>
<tr>
<td>Male</td>
<td>496 (47)</td>
<td>87 (17)</td>
<td>1.15</td>
<td>(0.64, 2.06)</td>
<td>--</td>
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<tr>
<td>Female</td>
<td>554 (53)</td>
<td>89 (16)</td>
<td>1.00</td>
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</tr>
</tbody>
</table>

* 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) or severe acute respiratory infection (SARI) 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.

RR = risk ratio, computed using generalized estimating equations (GEE) log-binomial bivariate model; aRR = adjusted risk ratio, computed using GEE log-binomial multivariate model; CI = confidence interval
Table 2. Risk Factors for Secondary ILI Among Household Contacts of An Influenza-Positive Index Case (n = 874), Kibera, Kenya 2008-2011.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Total, n (%)</th>
<th>Secondary ILI(^b), n (%)</th>
<th>RR</th>
<th>95% CI</th>
<th>aRR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resided with HIV-positive index case</td>
<td>33 (4)</td>
<td>8 (24)</td>
<td>3.40</td>
<td>(1.52, 7.63)</td>
<td>2.36</td>
<td>(1.19, 4.66)</td>
</tr>
<tr>
<td>Resided with HIV-unknown index case</td>
<td>538 (62)</td>
<td>43 (8)</td>
<td>1.14</td>
<td>(0.65, 2.00)</td>
<td>1.27</td>
<td>(0.72, 2.21)</td>
</tr>
<tr>
<td>Resided with HIV-negative index case</td>
<td>303 (35)</td>
<td>21 (7)</td>
<td>1.00</td>
<td></td>
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</tr>
<tr>
<td>HIV-positive household-contact</td>
<td>55 (6)</td>
<td>5 (9)</td>
<td>1.22</td>
<td>(0.54, 2.76)</td>
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</tr>
<tr>
<td>HIV-unknown household-contact</td>
<td>421 (48)</td>
<td>36 (9)</td>
<td>1.12</td>
<td>(0.71, 1.77)</td>
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<tr>
<td>HIV-negative household-contact</td>
<td>398 (46)</td>
<td>31 (8)</td>
<td>1.00</td>
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<td>Age of household contact, years</td>
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<tr>
<td>&lt; 2</td>
<td>40 (5)</td>
<td>16 (40)</td>
<td>6.73</td>
<td>(3.99, 11.35)</td>
<td>6.56</td>
<td>(3.96, 10.85)</td>
</tr>
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<td>2 – 4</td>
<td>79 (9)</td>
<td>14 (18)</td>
<td>3.20</td>
<td>(1.87, 5.50)</td>
<td>3.02</td>
<td>(1.73, 5.27)</td>
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<tr>
<td>5 – 17</td>
<td>306 (35)</td>
<td>17 (6)</td>
<td>1.00</td>
<td>(0.61, 1.64)</td>
<td>1.01</td>
<td>(0.61, 1.66)</td>
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<tr>
<td>≥ 18</td>
<td>449 (51)</td>
<td>25 (6)</td>
<td>1.00</td>
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<tr>
<td>Persons per household</td>
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<td>≥ 18</td>
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<tr>
<td>Persons per household</td>
<td>661 (76)</td>
<td>48 (7)</td>
<td>0.64 (0.38, 1.08)</td>
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<tr>
<td>Persons per household</td>
<td>213 (24)</td>
<td>24 (11)</td>
<td>1.00</td>
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<td>Gender</td>
<td>≤ 6</td>
<td>&gt; 6</td>
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<tr>
<td>Gender</td>
<td>310 (35)</td>
<td>31 (10)</td>
<td>1.39 (0.81, 2.36)</td>
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<tr>
<td>Gender</td>
<td>564 (65)</td>
<td>41 (7)</td>
<td>1.00</td>
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Gender

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<tr>
<th>Gender</th>
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<th>Female</th>
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<tbody>
<tr>
<td>Gender</td>
<td>409 (47)</td>
<td>465 (53)</td>
</tr>
<tr>
<td>Gender</td>
<td>33 (8)</td>
<td>39 (8)</td>
</tr>
</tbody>
</table>

Any household-contact of the index case with home reported or clinically diagnosed ILI within two weeks of index case identification.

RR = risk ratio, computed using GEE log-binomial bivariate model; aRR = adjusted risk ratio, computed using GEE log-binomial multivariate model; CI = confidence interval
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.