**Title:** Epidemiology of Respiratory Viral Infections in Two Long-Term Refugee Camps in Kenya, 2007 - 2010

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**Version:** 2  **Date:** 6 January 2012

**Author's response to reviews:** see over
Dear Editors,

Thank you for reviewing our manuscript. The reviewers' comments were helpful and have gone along in improving the final version. We received comments from two reviewers and in line with their comments, we made changes to the manuscript. Please see detailed point-by-point response below. In addition, we have corrected a few typos in the document. One key change we made in that regard is the name of one of our co-authors – we changed Lilian Waiboci-Muhia to Lilian W. Waiboci.

We would like to now re-submit the revised manuscript, “Epidemiology of Respiratory Viral Infections in Two Long-Term Refugee Camps in Kenya, 2007 – 2010” to BMC Infectious Diseases. The epidemiology of respiratory virus infections (RVI) in tropical regions is complex. Variations in climatic conditions and population distribution contribute to differences in rates and seasonality of virus-associated respiratory infections. The data we present is based on a surveillance programme for RVI that was established jointly by several governmental and non-governmental agencies in two refugee camps in Kenya. This is the first comprehensive report of the findings of the programme. We feel the manuscript and its findings will be of interest to the wide readership of BMC Infectious Diseases. In addition, your open-access policy means the manuscript will be available, free of charge, to a large group of practitioners across Kenya and other developing countries. We are confident the manuscript will add to the overall knowledge of RVI in Africa.

Submitted with this cover letter you will find the revised manuscript document and the additional files for the figures and tables.

Thank you for your consideration.

Sincerely,

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I enjoyed reading this study which highlights the importance of viral respiratory pathogens in an African refugee population.

Major Compulsory Revisions
None

Minor Essential Revisions

1. The internal control PCR was described as targeting the "ribonucleoprotein (RNP) gene". I believe the PCR is more accurately defined as the human ribonuclease (RNase) P gene PCR.

   Response: We have corrected the phrase to read “the test results were discarded for any specimen whose human ribonuclease P (RNP) gene (internal control) was negative.”

2. How was discordance between nasopharyngeal and oropharyngeal sample PCR results dealt with? Were both samples tested in all cases?

   Response: The initial study was not designed to assess relative sensitivity of OP and NP swabs. We were interested in simply maximizing sensitivity for detecting influenza. So, for two of the three years of the study, the NP and OP specimens once collected were placed in the same container and tested as one specimen. However, during the final year of the study, we started a sub-study comparing nasopharyngeal and oropharyngeal swabs, during this time, if either specimen were positive, then an individual was classified as positive (see Kim et al, 2011). We have included clarification to that effect within the “clinical specimens” sub-section of the methods.

3. Given the known persistence of some of the viruses in the nasopharynx, especially in younger infants, were criteria for patient re-presentations used and if
so what where they?

Response: We did not use such criteria for the analysis primarily because the surveillance protocol did not provide information to use for such exclusion.

4. 268 specimens were discarded due to failure to meet the criteria set out in the methods section, but what criteria were used to determine “poor sample quality” in the additional 115 excluded specimens?

Response: This too is described under “Specimen processing” in the methods section on page 8. The 268 were discarded in the field before shipment and the 115 at the laboratory in Nairobi following the criteria noted. Additional clarification was added to the sentence.

5. Can the authors provide figures for the overall numbers of ILI and SARI cases presenting to the hospitals during the surveillance period (or at least the number of people who were approached but refused to participate)? This would permit an assessment of the representativeness of the results.

Response: Unfortunately, we did not collect this data. We have highlighted this limitation in the discussion section.

6. Table 2 legend states the rates are for 2008-2010, is this correct or should it read 2007-2010?

Response: this is an error and we have corrected it. Thank you. It now reads 2007 – 2010.


Response: Another error which we have corrected. It now reads Sept 2007 to Aug 2010.

8. There is duplication of results in the figures/tables: the detailed results in Table 2 maybe makes Figure 2 redundant?

Response: We have deleted Figure 2. Figures 3 and 4 are now Figures 2 and 3.
9. I found several typos...e.g. double comma in the legend for figure 2; inconsistent use of full stops in figure/table legends.

**Response:** We have corrected the typos mentioned. We have also reviewed the manuscript for additional typos. Thank you again for this observation.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.

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**REVIEWER 2: COMMENTS AND POINT-BY-POINT RESPONSE**

**Title:** Epidemiology of Respiratory Viral Infections in Two Long-Term Refugee Camps in Kenya, 2007 - 2010

**Version:** 1  **Date:** 22 November 2011

**Reviewer:** Brad Gessner

**Reviewer's report:**

This is a nicely written and informative paper. I have a few suggestions and questions, mostly related to the case definitions and the Discussion (especially the final paragraph).

**Abstract**

Results: I don’t really understand the point of the data on <1 year olds, since the median age was 1 year. I would delete this sentence, which I find difficult to interpret, and replace with other more interesting data.

**Response:** The objective was to highlight differences in virus prevalence for the under 1s (Figure 1), however I see the point. We removed this sentence and
added new ones. In the sixth line of the results, the sentences “The rate of SARI hospitalization was highest in children.....” and “The ratio of rates for children....” were added.

Conclusion: I agree with the sentence until “and make up…” The authors have not presented data that these viruses were part of the causal chain leading to respiratory illness. The finding of virus in the nasal or oral pharynx does not ensure this, as a substantial proportion of persons in the community also may have some of these viruses. This is acknowledged by the authors in the limitation section of Discussion. I think the conclusion should end with “high rates of illness.”

Response: We agree with the reviewer that our study did not present data establishing causal links between positivity for virus by RT-PCR and disease. We have changed the word “illness” to “infection” in the part of sentence that read “substantial portion of respiratory illness”. However, we do believe that the identified virus was most likely relevant to the clinical illness. While asymptomatic carriage is common in some viruses (especially rhinoviruses and some adenoviruses), infections with the viruses focused on during this study have been shown to be associated with clinical illness rather than asymptomatic carriage (van Gageldonk-Lafeber et al., 2005, Graat et al., 2003, Edwards et al., 1985, Jansen et al., 2011). We accept the concept, however, that systematically controlled studies (like what is ongoing with PERCH studies) are limited, so modification is well advised.

Background

Paragraph 1. I would delete the clause “now vaccine-preventable”. I assume this means influenza, which makes up a tiny proportion of the viruses identified. I would also recommend deleting “treatable” and just stating “viral causes”. This is particularly true given that the phrase follows a sentence on developing countries, most of which have neither influenza vaccine nor anti-virals. Also, the discussion on vaccines is much clearer at the end of paragraph 2.

Response: we removed the clause “treatable-now vaccine preventable”
Methods

Case definition. Could the authors indicate the degree to which the clinical signs required for these case definitions were followed and how they were obtained? For example, if a CRF indicated “fever” but didn’t have a temperature was the patient excluded and if this happened to how many? Over how many seconds was respiratory rate counted; 10, 15, 30, or the recommended full 60 seconds?

Case definition. For ILI, was this restricted to children that could talk, since sore throat depends on this? For SARI in children >1 week and <2 months old it appears that SARI included all patients with any fever regardless of the presence of respiratory symptoms. Is this really true?

Response: The same surveillance officers have been working on this project since its inception. We conducted at least 3 months of piloting before the reported data was collected. Our case definitions for ILI and SARI are standardized case definitions currently in use in more than 10 other sites in Kenya and many more sites in the region. A temperature of $\geq 38^\circ$C is required for ILI and SARI among adults, and respiratory rate measurement is for the full 60s. There was no restriction of ILI to children that could talk and the SARI classification above was used for children younger than 2 months as stated in the manuscript. For every patient, surveillance officers recorded specific signs and symptoms so that case classification could be validated. Therefore, we think it is very unlikely that cases misclassification occurred. We added the sentence beginning “For every patient…” to the last paragraph of the Case Definitions subsection of the Methods section.

Case definition. Please indicate how these case definitions differ from those described by the WHO and why.

Response: The case definition for ILI is identical to the ILI case definition proposed by WHO. (http://www.who.int/csr/disease/swineflu/WHO_case_definition_swine_flu_2009_04_29.pdf). While to our knowledge there is no approved WHO case definition for SARI, our case definition was based on the pneumonia case definitions recommended in WHO’s guidelines for Integrated Management of Childhood Illness. We have included references to both the ILI case definition and the IMCI guidelines in the manuscript. An additional reference (#28 in the manuscript) has been added to the manuscript.
Data collection. Why were incidence rates calculated only for those <5 years?

Please include this information.

Response: reliable denominator data was only available for children <5 years. This clarification has been added to the “data analysis” sub-section in the methods.

Overall. Was any health utilization survey conducted? I’m particularly interested in hospital utilization for persons with SARI. Do the data presented represent 90% of all SARI or 5%?

Response: No. We did not conduct a health utilization survey in either of the camps. This is mentioned in the manuscript. Please see the data analysis sub-section in the methods section and the limitations paragraph in the discussions section. However, the camp hospitals are the only inpatient facilities in the two camps (Hagadera and Kakuma) and we believe the rates presented represent a good estimate of the true burden of disease because of our sense of fairly high health service utilization for severe disease in this somewhat closed setting. In the recent meta-analysis by Nair et al on global burden of RSV in young children (Nair et al., 2010), reported incidence ranges of RSV-associated severe ALRI were similar in studies with active and passive case ascertainment.

Overall. Could the authors provide some idea of population movements into and out of each of the refugee camps? This could be an important reason for some of the epidemiology. A static population over the study period should have a stable epidemiology similar to the resident population, while a dynamic camp will likely have a changing epidemiology.

Response: Dadaab camps near the Somalia border have had a highly dynamic population compared to Kakuma. The refugee population had grown by 150% in the three year period represented in the study (see methods section).

Results

Rates of hospitalization. A lot of emphasis is placed on the difference in incidence between <1 and 1-<5 year old. But this is misleading since children are only <1 for a year while they are 1-<5 for 4 years. Consequently, I think from the
data, more cases occur from 1-4 years of age than among those <1 year (except for maybe RSV and hMPV). I recommend making this point in the article.

Response: we presented rates per 1000 children per year which standardized the incidence among the different age groups for comparison.

Discussion

Paragraph 2, the entire part beginning with “Yet our…” This strikes me as a strange group of sentences and arguments. There are dozens and maybe hundreds of studies from Asia and Africa, so to find similar rates in 6 is not surprising, even if just by chance. When looking at several meta-analyses/reviews (meta-analyses published by Nair on RSV and influenza, review by Gessner on influenza in Africa, and the Rudan studies on ARI) show clearly that incidence rates for ARI vary wildly by time and place. The authors’ argument also is concerning scientifically, as there is no biologic reason to expect incidences to be similar across time or place, given dynamics in human immunity, environmental conditions, viral evolution, etc.. Please delete or revise this section. For example, if the authors want to compare their data to other studies, please use the meta-analyses and discuss similarities and differences between the refugee camps and other sites.

Response: Our manuscript reports rates of viral infection associated with severe respiratory infection. For comparison, we searched for studies showing rates of viral infection associated with severe disease in tropical and sub-tropical countries without specifically choosing studies with similar results. Most of the studies done in Africa or in other tropical settings have had limited study duration; many do not report incidence data and/or simply cannot be compared to this study because of major differences in methodology. While there may be no reason to expect similar findings, we thought it important to compare. We have incorporated additional information from one of the meta-analyses mentioned above. We have deleted the sentence before the “Yet our findings section…” and added the sentence beginning “in a meta-analysis….”

Paragraph 3, last sentence. Please move the term “among Alaska Natives” to
directly follow “5 times higher”. Additionally, the correct term is “Alaska Native people” and not “Alaska Natives”. Lastly, the sentence should make clear that the quoted study refers specifically to RSV, which has a peculiar epidemiology among Alaska Native children.

Response: Thank you for highlighting the proper terminology. We have made the appropriate corrections. Singleton et al (referenced paper) also reports non-RSV LRTI hospitalization rates for the same population. For example, while RSV rates are reported as having declined from 178/1000 children <1 year per year, the rates of non-RSV LRTI were reported as having increased to 215 per 1000 infants per year. We have combined this paragraph with paragraph 2.

Paragraph 5. Differences in the camps may simply reflect differences in population immunity, which may result from different in and out migration in the camps.

Response (now paragraph 4): While we cannot establish the real cause of the differences in the camps from this study and the different population dynamics may have contributed to it, there may be variations related to geographic location. There is distinct seasonality in the camp in eastern Kenya, near the Somali border; however, distinct seasonality has not been shown in the other camp closer to Sudan and Uganda (Kakuma). This is a topic that requires further exploration.

Paragraph 6, sentence 3. The rates are not particularly elevated in the study populations, as the authors note in paragraph 2. Please delete this clause.

Last paragraph, first sentence. The word “cause” is problematic. I would write “viruses are associated with many cases of respiratory disease…”

Last paragraph. I’m confused by the statement on nosocomial infection. Are any of the cases in the study nosocomial? If not, please delete this part of the sentence. I’m also skeptical of all of the recommendations except vaccine at the end. For example, how will refugees reasonably wash their hands the multiple
times a day necessary to reduce infection risk? For crowding, small reductions will not reduce transmission for many viruses. Additionally, it is not a practical solution for refugee camps, given the premium on land. If the authors really want to recommend this, I think they are obliged to state what measures could reasonably be implemented (for example, would the international community purchase land on which to build houses?). Lastly, I don’t know what public health education would decrease viral transmission. In short, I find this paragraph’s recommendations unhelpful. Instead, I would think the appropriate interventions should be prioritizing vaccines if and when these become available and ensuring that persons with SARI have hospital access so that they can receive oxygen and antibiotics to treat secondary bacterial infections.

Response (now paragraph 5): There are several issues raised here. Please see below.

- **Causality:** See earlier comments to concerns expressed by the reviewer. We have modified the wording from “major cause of respiratory disease” to “major cause of respiratory infection”.

- **Nosocomial infection:** All the SARI cases reported in this study were hospitalized. Hospitalization occurred in a refugee setting with limited bed space and overcrowded wards. The camp hospitals have one pediatric ward for all children of all ages presenting with any illness requiring hospitalization. The same nurses and clinicians care for all the patients. They use the same instruments (e.g. stethoscopes) for all the patients. While we have not explored hospital acquired infection in this study, it is a reasonable concern that the hospital ward could serve as a setting and source of infection with these easily transmittable respiratory viruses for many children. Other studies have suggested that respiratory viruses may persist for days sometimes months on fomites/inanimate surfaces and these may be a source of continued transmission (Kramer et al., 2006). We have clarified this aspect by adding the two sentences beginning with “All SARI cases in this study...” and “While we have explored…”

- **Physical interventions to prevent infections versus vaccination:** Hand washing has been shown to decrease incidence of both respiratory infections and other infectious diseases that are major causes of morbidity and mortality in the refugee camps (Luby et al., 2005, Curtis and
Cairncross, 2003). While vaccination is ultimately the most effective method, vaccine producers do not readily avail these products to poor nations at affordable prices. For example, the availability of the influenza vaccine has not resulted in any appreciable utilization in Kenya and other countries of the region. It normally takes great concerted effort from the international community to provide these vaccines at a highly subsidized rate and then push for its roll out before widespread adoption occurs. Even then, refugee populations may still not benefit. Handwashing and hygiene promotion activities are currently being stepped up in the camps. Availability of adequate soap for handwashing at the household level is increasingly being prioritized by agencies. Health education activities on the importance of handwashing may help decrease morbidity due to respiratory viral infections. We think that successful promotion of hand hygiene is within the realm of feasibility in this setting, perhaps more so than the reviewer does. We appreciate, however, the skepticism and have qualified the concept with the statement: “Innovative and effective approaches need to be implemented to achieve sustained compliance with hand hygiene promotions”

The camps in Dadaab and Kakuma are located in wide open spaces where limitation of land is less due to availability and more due to local politics. As seen earlier this year, when the government of Kenya agreed to the opening of three additional camps in the Dadaab area to accommodate the additional number of refugees pouring into the country, political pressure can suddenly yield results. The refugee camps also have unique regular activities that encourage the gathering of large crowds in narrow spaces. From food and non-food item distributions (that occur twice a month at least), to registration activities, large numbers of refugees gather in confined spaces. Physical interventions and public education may help decrease infectious disease transmission in these settings especially if there is concern in the virulence of circulating viruses or if in the midst of an epidemic or pandemic. We think it is important to utilize these findings to contribute to the dialogue about reducing crowding in these settings.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I work for AMP which receives unrestricted support from Sanofi-Pasteur and
 References


