Author's response to reviews

Title: Risk factors of febrile respiratory illness and mono-viral infections in a semi-closed military environment: a case-control study

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Version: 2 Date: 11 April 2015

Author's response to reviews: see over
Dear Editor,

Revised manuscript of “Risk factors of febrile respiratory illness and mono-viral infections in a semi-closed military environment: a case-control study

Thank you so much for assisting to get our manuscript peer-reviewed, and for the many useful comments from the reviewers to improve our manuscript further. We are very grateful.

Febrile respiratory illness (FRI) results in substantial burden in semi-closed environments worldwide such as in the military setting. This study aims to identify risk factors for FRI and mono-viral infections in a tropical military setting.

Our findings showed that increasing age, smoker, recruit-camp, stay-out personnel with ill household members and stay-in personnel with ill bunkmates were independent risk factors of FRI in a semi-closed military setting. However, staying in camp with none ill in bunk and at home was a protective factor against FRI. The analysis of the predominant mono-viral infections as well as the contact risk factors identified in this study is likely to be novel in the context of a semi-closed environment, to our best knowledge. Furthermore, the findings illustrated the importance of contact patterns both in camp and at home for potential FRI transmission. Lastly, these findings will have much significant impact on the prevention and control strategies and policies in reducing the burden of FRI.

In view of the high relevance and impact, we hope you will consider our revised manuscript as a Research Article for publication in BMC Infectious Diseases. Please kindly find the point-to-point reply to the reviewers’ comments in Appendix 1.

Thank you.

Yours sincerely,

Dr. Vernon Lee

Associate Professor
Reviewer’s report 1

Title: Risk factors of febrile respiratory illness due to viral infections in a semi-closed military environment: a case-control study

Version: 1 Date: 23 February 2015

Reviewer: Delphis Vera

Reviewer’s report:
This manuscript describes clearly and concisely some risk factors for febrile respiratory illness in a semi-closed environment. The conclusions are well supported and address the specific scientific question.

Authors: Thank you.

However, there are some observations related to study methodology.

Major Compulsory Revisions

1. Provide more detail on control selection, e.g. same-barrack, by-sex, age, symptom-onset?

Authors: The controls were not matched or restricted by barrack, sex, age or symptom-onset. This is because of the fact that we were interested to evaluate most of these variables as potential risk factors of FRI. Nevertheless, the controls were recruited during the same week as the cases. This is to ensure that both cases and controls had similar chance of exposure to a particular respiratory pathogen circulating in the same environment around the same period of the year to minimize potential misclassification bias. These points have been added from line 151-159.

2. Explain why risk factors, such as frequent hand washing, allergy, and military ranks were not considered.

Authors: We agree that frequent hand washing is a relevant risk factor to evaluate. However, it is very challenging to accurately assess how frequent hand washing was performed by the soldiers, and the accessibility and availability of clean water for hand washing may be significantly limited out in the field. Hence, the likelihood of recall bias and information bias would be significantly high as the soldiers may also tend to report the expected favorable hand washing behavior in military camp.

An allergy is a hypersensitivity disorder of the immune system. Symptoms include red eyes, itchiness, and runny nose, eczema, hives, or an asthma attack. We did not consider allergy because the symptoms are very broad to specifically define as an allergy, and aim of this study is
not to study clinical signs and symptoms that are associated with FRI. Furthermore, there would be significant potential information bias as it is less likely to be clinically diagnosed compared to asthma, diabetes, hypertension and heart disease.

We did not consider military rank due to fact that there is a significant number of cases that were recruited from the recruit camp, where the population is mainly made up of recruits as compared to non-recruit camp, where the population is mainly made up of higher ranks (p<0.010). As such, it would be biased to include military rank as one of the variables.

We have added the above justifications as part of limitations from line 428-441.

3. State whether or not there were outbreak situations during the study period, and explain the effect of known control measures, such as respiratory hygiene and case isolation might have had on your passive surveillance data.

Authors: There was the influenza A (H1N1)pdm09 pandemic in June to September 2009 during the early part of the study period. Seasonal influenza vaccines were provided to most soldiers immediately before or during the early part of the epidemic and subsequently A(H1N1)pdm09 vaccine was provided to selected units after it became available, as illustrated in Figure 1. The ratio of relative risks for pandemic H1N1 infection before and after pandemic vaccination for the recruit camp relative to other camps was 0.14 (95% CI 0.016-0.49) for influenza A(H3N2), 0.44 (95% CI 0.035,1.8); and for influenza B, 18 (95% CI 0.77,89) [1]. Furthermore, an estimated 70% (RR = 0.30; 95% CI 0.11-0.84), 39% (RR = 0.61;0.25-1.43) and 75% (RR = 0.25; 95% CI 0.11-0.50) reduction in the risk of influenza A(H1N1)pdm09, influenza A(H3N2) and influenza B infections, respectively, in the recruit camp during the post-vaccination period compared with during the pre-vaccination period was observed [2]. This control measure is likely to have reduced the incidence of FRI, and hence, vaccination status was accounted for as a potential confounding factor when assessing the effect of other epidemiological variables.

Enhanced respiratory hygiene and other measures like cohorting of staff were practiced during the first wave of the influenza A (H1N1)pdm09 pandemic. This would have also limited the risk of transmission of respiratory viruses during that particular period compared to other periods within this study. Furthermore, patients with confirmed influenza A (H1N1)pdm09 infection were isolated in hospitals to prevent transmission. Contact tracing was performed to identify close contacts and most contacts were quarantined at home for a 7-day period. “Ring prophylaxis” with oseltamivir (Tamiflu, Roche), at a dose of 75 mg daily, was administered to coworkers of the patient with confirmed infection for a period of 10 days after exposure [3]. There was a significant reduction in the overall reproductive number (the number of new cases attributable to the index case), from 1.91 (95% credible interval, 1.50 to 2.36) before the intervention to 0.11 (95% credible interval, 0.05 to 0.20) after the intervention [3]. As such, vaccination types, which were used differently during the different study period (Figure 1), were used as a surrogate to account for the potential bias due to the enhanced protective and preventive measures applied during the influenza A (H1N1)pdm09 pandemic. Nevertheless, this bias should be minimal as we recruit a number of controls in the same period and camp as the cases.

We have added the above justifications as part of limitations from line 416-428.
4. If outbreaks were detected during the study period, explain what consideration has been given to the fact that outbreak situations tend to alter the effect of known risk factors; e.g. regardless of age and or sex, during an outbreak, being next to an infected individual is a risk factor in itself.

Authors: Please refer to the authors’ reply for Comment 3. Thank you.

5. Provide more detail on the statistical analysis performed, e.g. how covariates were added to the regression model; and the resulting power of each (regression) analysis conducted separately for each virus (decreased sample size may lead to decreased power).

Authors: Univariate that were significantly associated with the outcome of FRI were included in a multivariable logistic regression model to determine the independent factors. Selected variables with high co-linearity were dropped. The best model was determined using backward stepwise regression method.

The five most common mono-virus infection were due to influenza B with 541 cases, influenza A (H1N1)pdm09 with 526 cases, coxsackie/echovirus with 523 cases, adenovirus E with 467 cases, and rhinovirus with 378 cases.

Power calculation for the rhinovirus with cases of 378 vs 1247 non-FRI controls was performed as an example.

<table>
<thead>
<tr>
<th>RR</th>
<th>P0</th>
<th>0.1</th>
<th>0.2</th>
<th>0.3</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.2</td>
<td>0.34</td>
<td>0.54</td>
<td>0.64</td>
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<td></td>
</tr>
<tr>
<td>1.4</td>
<td>0.84</td>
<td>0.97</td>
<td>0.99</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>1.6</td>
<td>0.99</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td></td>
</tr>
</tbody>
</table>

Power calculation for the rest of the respiratory viruses should have higher power than the rhinovirus analyses since the number of cases is greater than cases with rhinovirus infection.

We have added the above details from line 207-209.

6. Please, state the prevalence for FRI and each separate virus considered in your study, and explain the effect it may have on OR values as proxies to RR values.

Authors: The prevalence for FRI is about 17%, influenza B is 1%, influenza A(H1N1)pdm09 is 1%, coxsackie/echovirus is 1%, adenovirus E is 0.8%, and rhinovirus 0.6%. Relative risk is used frequently in the statistical analysis of binary outcomes where the outcome of interest has relatively low probability. Odds ratio (OR) would be very similar to relative risk when the probability of developing a particular outcome among soldiers is small. As such, OR values as proxies to RR would be similar for the mono-virus infections, whereas the OR of the risk factors for FRI likely exaggerates, to some extent, the effect relative to RR.

We have added the above justifications as part of limitations from line 444-447.
Minor Essential Revisions

1. None.

Discretionary Revisions

1. Clarify the relationship between the study and the sentinel respiratory disease surveillance system. Did the sentinel surveillance include the questionnaire, or was it a study “nested” in the sentinel system?

Authors: The sentinel surveillance program included the questionnaire from the time of its inception. Going forwards, this analysis is being used to refine the questionnaire for the surveillance program.

We have clarified the above details from line 146-149.

2. Explain how bacterial causes were excluded.

Authors: The ResPlex I assay (Qiagen) was designed to amplify and detect DNA of six bacterial respiratory pathogens. They were Mycoplasma pneumoniae, Chlamydophila pneumoniae, Legionella pneumomophila, Streptococcus pneumoniae, Neisseria meningitides and Haemophilus influenza 1, 2, 3. FRI subjects with bacterial causes were not excluded. This is because one of the aims of the study is to determine the potential risk factors for FRI, regardless of any detected or undetected respiratory virus and/or bacteria. Secondly, it is not the aim of this study to identify the causal etiology of FRI, which in the first place is already very limited by using ResPlex assay, but more focused on understanding the demographic, health status and contact risk factors of FRI, as an outcome.

We have added the above justifications as part of limitations from line 447-452.

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.

Authors: Thank you for your comments.
Reviewer's report 2

Title: Risk factors of febrile respiratory illness due to viral infections in a semi-closed military environment: a case-control study

Version: 1 Date: 14 February 2015

Reviewer: Wen-Chien Ko

Reviewer's report:

1. This case-control study reveals the risk factors associated with febrile respiratory illness in a military environment. Basically, this study is well-designed and the manuscript is well prepared.

Authors: Thank you.

2. The viral etiological agents are detected by a multiplex PCR, and the nature of test, a commercial kit or home-made test, should be clearly indicated.

Authors: We used a multiplex PCR panel which included 18 different respiratory viruses based on the Resplex assays I and II (version 2.0, Qiagen, Inc., Valencia, CA, USA).

We have provided the details from line 188-192.

3. The list of respiratory viruses to be tested should be shown in details.

Authors: They are as following- Adenovirus E, Influenza A(H3N2), Rhinovirus, Coxsackie/Echovirus, Influenza B, influenza A(H1N1)pdm09, Enterovirus (EV), human metapneumovirus (hMPV), Parainfluenza 1 (hPIV-1), hPIV-2, hPIV-3 and hPIV-4, Coronavirus OC43 (CoV-OC43), CoV-NL63, CoV-229E, CoV-HKU1, respiratory syncytial virus A (RSV-A) and RSV-B and Bocavirus (BV).

We have provided the details from line 181-185.

4. Accordingly, the total list of viral pathogens detected in those with FRI deserves complete presentation in the text. It is interested to know the details of polyviral infections.

Authors: We agree and these details has been published in our previous article [4] and in more details another article [5].

5. Furthermore, were there cases of asymptomatic infections as revealed by the PCR technique?

Authors: There were no asymptomatic infections among cases as they all have fever as one of the criteria for recruitment. However, there were about 10% of non-FRI controls that had respiratory viruses as revealed by PCR, which were excluded from this study and these are subjects with asymptomatic infections. This has already been highlighted from line 226-228.
6. To conclude a protective effect of pdm-A(H1N1) vaccine against rhinovirus should be cautious. The comparison is done among the whole study period, and will be biased by the circulating virus and the administrated flu vaccines in other periods. For example, to assess the role of pre-pdmTIV vaccine, the preferred comparative groups will be those without flu vaccine, but not those with post-pdm TIV or pdm-A(H1N1) vaccine.

Authors: We would like to clarify that we did not conclude a protective effect of pdm-A(H1N1) vaccine against rhinovirus, even after adjusting for the various administrated flu vaccines in other periods. We were cautious with this these findings as it may have been due to non-specific interactions and interference between respiratory viruses, and could also have been due to the periodic nature of respiratory virus outbreaks, which is a challenge to account for in this study. Nevertheless, we do acknowledge the fact that the vaccine construct of pdm-A(H1N1) is also one of the three strains used for the post-pdm TIV or known as the seasonal vaccine.

We have further clarified from line 369-371, with the statement that these unexpected findings would still require more scientific and epidemiological evidence for further conclusion.

7. The format of cited references needs to be modified, according to the recommended style of the journal.

Authors: Thanks. We have amended.

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

Quality of written English: Acceptable

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

No competing interests.

Authors: Thank you for your comments.
References


