Reviewer's report

Title: Viral aetiology of acute respiratory infections among children and associated meteorological indicators in southern China

Version: 1 Date: 9 September 2014

Reviewer: Jesse Papenburg

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Major Compulsory Revisions

1. The authors explore associations between meteorological factors and detection of respiratory viruses in children 0-16 years old with signs / symptoms of acute respiratory infection in Shantou, China. Results of multiple comparisons and logistic regression models are presented. A greater emphasis on the exploratory nature of these analyses must be presented. Multiple comparisons increase the risk of false-positive associations. Even more importantly, regarding meteorological factors and respiratory virus circulation, there are inherent autocorrelation structures in the data. In other words, the number of viruses detected during a week is related to the counts from the previous weeks and future weeks. The same is true for temperature, humidity and wind velocity. Because of the autocorrelation within each individual time series, the correlation of two unrelated time series can be spuriously but significantly high due to chance alone or due to the confounding effect of an unmeasured seasonal covariate. Since the authors did not account for this autocorrelation (for example, though the use of time series analysis methods), the observed associations must be interpreted cautiously.

2. It is very surprising to see such high rates of positivity for EV and HRV, and especially such a high rate of co-detection of EV-HRV. 215 of 558 infections (39%) were dual infections of EV-HRV, and HRV-EV were co-detected in 307 samples!!! This is shocking. The authors mention in the Discussion that because of the genetic relatedness of EVs and HRVs, PCR can sometimes not distinguish between the two targets and will generate a signal for both even though only one of the two is present. Their analysis of differences in Cp between the two targets is insufficient, in my opinion, to exclude the possibility that many EV-HRV co-detections were, in truth, infection with one of those two picornaviruses. Because the primary outcome of their study is co-infections, this is a major problem. I believe that this must be addressed by sequencing (of at least a proportion of HRV-HRV co-detections) to determine the validity of these results.

Minor Essential Revisions

1. Last sentence of the Background. Please be more specific when stating your objectives. Some information regarding time, place and patient population should be included here. Also, the term "seasonal factors" is quite vague; I suggest using "meteorological factors" instead.
2. It is unclear if the study setting is a walk-in clinic, emergency department or some other outpatient facility. Please specify.

3. Please mention if any patients were admitted to hospital.

4. Statistical analysis (p. 6). Chi-square tests compare the differences in the distributions of categorical variables (or differences in proportions), not simply any difference.

5. Please describe in the Methods how the regression models were built, i.e., how decisions were made regarding which variables should be included in the final model. Also, please define what the outcomes of the models were.

6. Please explain (in the Methods) how the results in Table 3 were obtained. What are you comparing using Chi-square (as mentioned in the notes for Table 3)? What does "most favourable" mean? "Favourable" is not a statistical outcome.

7. In the first sentence of the Discussion, change "seasonality" to "meteorological factors".

8. Please complete Reference # 12

9. Table 4 (notes). "adjusted for age" and "all variables with p<0.05..." should be in separate sentences; they are not related.

10. The last two sentences ("These findings...") of the first paragraph of p. 4 are not the way that most experts in respiratory virus epidemiology interpret the literature. The importance of interactions between viruses is not understood at this point, and the majority of acute viral respiratory illnesses are likely due to the effect of one primary pathogen. Such a vague mention of interactions between other classes of microorganisms (bacteria, fungi and parasites) seems beyond the scope of this article, unless a specific point is brought up that could be used as an analogy for respiratory viruses.

11. I do not understand the last sentence of the first paragraph of the Background. The viruses studied (not just novel coronaviruses) are clearly the causative agents of primary infections. I do not understand what is meant by "secondary" and "bystander".

Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare that I have no competing interests