Reviewer's report

Title: Spatio-Temporal Analysis on Enterovirus Cases through Integrated Surveillance in Taiwan

Version: 2 Date: 2 September 2013

Reviewer: Deok Ryun Kim

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Major Compulsory Revisions
1. The authors should mention the case definition of mild EV.
2. The authors may add information about all age groups of mild EV cases in order to explain relationship to 0-14 age group of severe EV cases.
3. The authors may consider another correlation coefficient to account for temporal trend and time lag effect. For example, cross correlation coefficient between time series data.
4. The authors used administrative boundaries in the spatial analysis, which has nothing to do with spatial process of the disease, and the local variation of the disease is obscured under this spatial analysis. I would suggest using a smaller scale to identify local clustering of the disease.
5. What was the justification for using 5% of maximum cluster population size, which is extremely conservative for infectious disease modelling. The authors should try with a larger scale.
6. Why the authors kept ages for all other analyses except for the cluster analysis of the severe EV cases.
7. In Figure 4, how come a county with zero cases (year 2003) creates spatial clustering? Similarly, identification of counties with lower incidence as spatial cluster (in 1999-2000, 2005) is questionable?

Minor Essential Revisions
1. To make it consistent, the authors should write “EV-71” throughout the manuscript.
2. What is the unit of the analysis?
3. The authors should mention what age group was used for the mild EV cases.
4. What was the source of geo data used in the spatial analysis?
5. How many cities and counties were used to identify the clusters?
6. Please move this text “Space-Time permutation was applied for detecting the mild EV clusters…” after the sentence “After identifying the space-time clusters of the severe EV cases, …”.
7. Reference is needed for the directional distribution method.
8. The authors should provide the median age of mild and severe EV cases because the distribution of the ages is skewed.

9. The sentence "The distribution of severe EV aged 0-14 incidence during the study period was high ranging from central to southern..." is not correct. The authors should recheck their data.

10. The authors should add county or city names in Figure 1. What is CI in the legend of the figure?

11. What are EV71%, CA%, CB%, and ECHO% in Table 1. The last column of these rows needs to be filled. Why the cell values of 1999 are quite different from the other years? Footnote is needed for the single star (*).

12. The county names need to be added in Figure 4, as the names have been used in the text while describing Figure 4.


14. The titles in Figures 5 need to be properly written.

15. Does it mean that there was no overlapping of cluster over time? I refer to Fig 5B.

16. It is not clear whether the authors talked about the cases from the five cities during April to June, 2008. I refer to Fig 7.

17. The geographic size of detected clusters may be mentioned. And, the direction is not easy to understand. What does it mean by "Moving Direction of the Center"?

18. The authors should describe the benefits and limitations when using the integrated information from different enterovirus surveillance systems.

19. The lag effect between mild and severe EV case was before/after 2002. After 2002, the severe EV cases occurred 2 weeks earlier than mild cases. It seems that the authors are talking about the pattern change is exceptional cases. And, they stated that one or two weeks of mild cases can help to predict severe EV cases. The authors should add one more sentence in support this conclusion.

20. The reason for the highest local risk in Penghu County does not make sense. The authors should add reference(s) in support to their statement.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**
I declare that I have no competing interests.