Reviewer's report

Title: Spatio-temporal analysis of the relationship between meteorological factors and hand-foot-mouth disease in Beijing, China

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Reviewer: Pamela Palasanthiran

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MANUSCRIPT: Spatio-temporal analysis of the relationship between meteorological factors and hand-foot-mouth disease in Beijing China

China has a significant problem with hand-foot-mouth disease (HFMD). A national notifiable communicable disease surveillance and reporting system for hand-foot-mouth disease (HFMD) has been in place since 2008 and increasing numbers of HFMD in children are reported. This study adds to a number of publications on the theme of understanding HFMD transmission patterns in China to design control strategies. The factors investigated in past studies have broadly included epidemiological, population demographics and climatic influences, many of which are referenced in citation list in this study. The studies have either been national (China-wide) or at a regional level.

This current study is at a township level (Beijing) and investigates the relationship between meteorological factors and the incidence of HFMD in this city by 'spatio-temporal' mapping (so, space and time) relative to weather factors (so, meteorological).

Of note, a previous study from Beijing has investigated a space-time relationship of HFMD clusters wrt epidemiological factors in Beijing, using the same database as that used in this study under review (the Beijing CDC)*. Wang's study was however for a longer time period (2008-12). Therefore, the cases in this study by Tian et al (time period 2010 - 12 for the 3 years) are a subset of the cases investigated in the Wang JJ, 2014 paper, albeit with different factors investigated. This is indeed so, as the figures in Table 1 for 2010, 2011 and 2012 in both papers tally. Thus - from this demographic data, it is possible to obtain many epidemiological risk factors governing HFMD risk e.g. age groups and gender and childcare settings that could tie in with this study. Wang JJ et al. Epidemiological analysis, detection and comparison of space-time patterns hand-foot-mouth disease (2008 - 2012). PloS One, 2014:9(3)p.e927345. [reference 18 in this study]. There is also study by Dong W et al, 2016, (ref 38 in your study) investigating climate changes in Beijing and its influence on HFMD, using different methodology from this one under review (Tian et al), and over a longer time period (2008 - 12) but added the important factor of child population by areas.
Some comments:

1. The authors could set the context by referring specifically to what has already been investigated in China and Beijing, a synthesis of the findings, and what additional information this study adds. The authors have alluded to the studies, referred to some in the discussion, but not elaborated. It would also be useful to say what time periods the other studies cover, compared to the time period in this study. It appears studies encompass varying periods within the 2008 - 2012 reported periods, whilst this study by Tian et al is from 2010 - 2012 (3 years). This would set this study in context. It would be particularly pertinent to address what this study (Tian et al) adds to the study of Dong et al (2016) which also investigates climatic /meteorological factors, but takes child population into account (see point 2 of my comments)

2. The findings showing a relationship between HFMD and weather using the spatio-temporal modelling appear compelling. It is of course simplistic to associate climatic factors alone with the HFMD clustering, and this is acknowledged somewhat in your paper. However, to build some strength to your arguments, the following question is raised. Are there any other confounding variables that could explain the patterns you have found? An important correlation would be age distribution, by new birth cohorts, of the child population by districts shown - to see if age distribution influenced the clustering? In other words, could "age" have accounted for the frequency pattern, and more importantly - as new birth cohorts get added per year, so - a new group with put serological protection. For example - were there proportionately more children aged < 2 years (the peak ages for HFMD in Xing et al Epidemiological characteristics of HFMD in China 2008-12. Lancet ID, 2014;14(4):308-18) in the "clustered" areas? thereby, possibly confounding or explaining the clusters? Your Table 1 provides the ages but they are not by districts, and the data does not provide an analysis by correlation of clusters by district and ages. Note that a negative correlation could add weight to the meteorological findings explaining the cluster zones. The same reasoning could extend to other confounding factors: population size, socio-demographics, gender, social proximity of at risk groups like nurseries.

3. You state in the limitations that the study period was short (3 years). Is there a reason why the period 2008 - 2012 could not have been reviewed using your methods? A longer period of analysis would have been more robust. This is also pertinent as HFMD is known to come in cycles/periodicity of 2 -3 years.

4. The statement in your discussion hypothesising high wind velocity contributing to spread of HFMD. This hypothesis is an important one as your study finds this a positive association. If wind is a real factor in spread, this would lend weight to you findings. Could you provide some evidence to support this as a plausible explanation? It has been raised before as a possible mechanism of enteroviral (EV) transmission, but so far is only a theoretical possibility. It is counter intuitive as viral transmission of EV is via
"contact"+/− "droplet" spread. An infectious inoculum probably only goes several meters as the droplet nuclei (smallest droplets e.g. 2.5 μM) would not remain airborne for long (drops to surface after a certain travel distance (meters); if however, as postulated, the droplets are carried distances by wind, it would not be expected to be viable for long. However, there may be emerging data to support this? Note: fungal spores and some robust pathogens Coxsella burnetti (agent causing Q fever ), or small pox can be transmitted for several kilometres - but as far as we know, this has not been so convincingly demonstrated for enterovirus. This is an important point as wind velocity and increased prevalence is one of the findings of your paper - but the mechanism of why this may be so is unconvincing.

5. The seasonality of the peaks: EV demonstrates a known seasonal pattern (warmer months, and is seen worldwide. How would this be different in your study? Would it also explain the findings?

6. Please note that the legend for Figure 3 says it is "Figure 4". (There is an error.)

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

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