Author’s response to reviews

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

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Version: 1 Date: 12 Dec 2017

Author’s response to reviews:

Article Reference: INFD-D-17-01215R1

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

Dear editors,

We appreciated the great help and efforts which the editors and the reviewers have given to our manuscript. The editors and reviewers’ comments and suggestions were incorporated into the revised manuscript. We believe we have adequately addressed all excellent points and questions raised by the editors and reviewers below, and in the revised manuscript.

We provided both a clean copy as well as a copy using track changes. A point-to-point response to the comments and suggestions is detailed below. References used in the response were listed in the last part of responses to each reviewer.
All authors declare that they have no potential competing interests regarding the revised submitted manuscript. They also have read the manuscript and agree the work is ready for submission to the BMC Infectious Diseases, and accept responsibility for the manuscript’s contents.

Thank you very much for your consideration!

Sincerely yours,

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We would like to thank the reviewers for their helpful comments. The followings are our response to the reviewers’ comments point by point.

Response to the comments of Reviewer 1:

Pamela Palasanthiran (Reviewer 1):

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.

Thank you for the comments! The followings are our response to the comments and revision lists point by point.

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).

Thank you for the comments! There were studies conducted in Beijing investigating space-time patterns of HFMD and the effects of weather factors on this disease. Wang et al. used spatial filtering combined with scan statistics methods to detect HFMD clusters in Beijing from 2008 to 2012, finding that the most likely space-time cluster was located in the southwest of Beijing. Dong et al. used geographically weighted regression model to explore the seasonal influence of weather factors on incidents of HFMD from 2008 to 2011 in Beijing. They found that mean temperature, wind speed and total precipitation were all positively correlated with HFMD while the relation with relative humidity was negative. Weather factor influenced HFMD depending on season and the effects of mean temperature and wind speed were greater in the summer than in the winter. We added the comparison of these studies conducted in Beijing in the discussion section of the revised manuscript and showed the detailed information in Table S1 of supplementary material. (Page 16, Line 38-58)

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.
Thank you for the comments! The demographic and socio-economic characteristics could affect the HFMD incidence. The resolution of this study was township level. However, for now we could just obtain data of these factors (child population density, GDP per capita, number of health agencies, proportion of children in nursery, proportion of children in primary school) in district level, which were inappropriate to be added in the Bayesian CAR models. But as potential confounding factors, they should be considered in this study. We collected relevant data and observed the spatial distribution of the above factors in district level, which were showed as Figure S2-S6 in supplementary material. From these figures, we did not find obvious association with HFMD clusters. Further statistical analysis considering potential demographic and socio-economic confounders in high resolution should be conducted if available. (Page 17, Line 1-10)

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.

Thank you for the comments! The HFMD data was not public and for now we could not collect data of longer time span. It would be better to analyze data from a much longer time period to quantify seasonal and interannual variability and associated factors. We conducted this study with data of three years considering the data availability, which has been indicated in the section of limitations. (Page 17, Line 19-22)

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 uM) 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 smallpox 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.

Thank you for the comments! Fine particulate matter (PM2.5) is a major atmospheric pollutant and it can suspend in the air for a long time. It has a small size and a relatively large surface area, which makes it easy to absorb viruses in the air. A study in Shandong province of China suggested that wind can promote air pollutants where the enterovirus can survive and thus accelerate the spread [1]. There is a high level of PM2.5 pollution in Beijing and that might be associated with the spread of HFMD. But further study is still needed for this hypothesis. On the other hand, behaviorally, children would spend more time on indoor activities when the wind blow hard and window opening hours would be reduced, causing lack of ventilation, which increase the chance of contact transmission in small space. Even the droplets with HFMD virus could go just several meters, it will increase the contact transmission in the indoor environment. This might be the indirect reason that strong wind would increase the HFMD risk. We have added this explanation in the discussion section of revised manuscript. (Page 19, Line 18-21)

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?

Thank you for the comments! From time-series decompositions of HFMD cases (Figure 1), there was an evident seasonal pattern with a peak occurring between May and July, which corresponds to early summer in Beijing each year. After the seasonal pattern was removed, there was an oscillating inter-annual pattern with peaks at the start and towards the end of the study period in HFMD incidence. Thus, there was seasonal pattern in warmer months in our study, which was consistent with studies conducted in Shandong and Henan province of China [2]. We compared the seasonality of HFMD peaks in our study with other studies in the discussion section. (Page 15, Line 28-40)

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

We are sorry for this error. It has been revised in the revised manuscript. (Page 42)
References:


Response to the comments of Reviewer 2:

Ping-Ing Lee (Reviewer 2):

This study shows that the incidence of HFMD is significantly associated with some meteorological factors, including mean temperature, relative humidity, wind velocity and sunshine hours. It has been a common finding that the incidence of HFMD and other enteroviral infections show specific geographic distribution in different countries. The underlying mechanism remains obscure. It is therefore worthwhile to have some data from Beijing.

Thank you for the comments! The followings are our response to the comments and revision lists point by point.

Minor comments:

1. The definition of "severe disease" should be mentioned.

Thank you for the suggestion! We have added the definition of severe disease as ‘HFMD cases associated with meningitis, encephalitis, and severe complications, including neurological, cardiovascular and respiratory problems’ to the note of Table 1. (Page 38)
2. Although not the objective of this study, it will be interesting to know whether there were differences in the incidence of HFMD between those cared at home and those cared at day care centers.

Thank you for the suggestion! The HFMD incidence for children cared at home and those cared in nurseries was 292.7 and 243.3 per 100,000 people from 2010 to 2012. The related data has been added to the result section of the revised manuscript. (Page 14, Line 4-7)

Response to the comments of Reviewer 3:

Alexandre Manirakiza (Reviewer 3):

It is clear that the focus on the relationship between meteorological factors and HFMD incidence in Beijing. In the introduction, the authors referred to previous studies in which epidemiological characteristics, meteorological variables and spatiotemporal patterns of HFMD have been studied at different scales of China, and even at national level of this country.

The demographic and socio-economic characteristics of cases could affect the HFMD incidence, why these factors are not taken into account in the analysis model as confounders?

Thank you for the comments! We aimed to quantify spatio-temporal characteristics of HFMD and the relationship between meteorological factors and HFMD incidence with Bayesian conditional auto regressive (CAR) model approach as some previous studies did [1,2]. There are also studies exploring the association between the demographic or socio-economic factors and infectious diseases [3]. The demographic and socio-economic factors like child population density, GDP per capita, number of health agencies, proportion of children in nursery, proportion of children in primary school could affect the HFMD incidence. We added the analysis, discussed in the discussion section of the revised manuscript and showed the results in supplementary material. (Page 17, Line 1-10)

The authors assumed that a period of three years enough and state that analyze data from a much longer time period should be necessary. Hence, they assume that this study is an ecological one. This is somehow contradictory to the objective of the study.
Thank you for the comments! The HFMD data was not public and for now we could not collect data of longer time span. It would be better to analyze data from a much longer time period to quantify seasonal and interannual variability and associated factors. We conducted this study with data of three years considering the data availability, which has been indicated in the section of limitations. In this study, we explored the association between meteorological factors and HFMD at the population level. The meteorological data were also represent the conditions of the whole city, rather than the individual level. The objective of this study was to quantify spatio-temporal characteristics of HFMD and the relationship between meteorological factors and HFMD incidence in Beijing, which was set based on population. We acknowledged this as a limitation. (Page 17, Line 19-22)

In conclusion (line 46): please change "….prevalence of HFMD…” in "….incidence of HFMD…”

Thank you for the suggestion! We have changed the ‘prevalence’ to’ incidence’ in the revised manuscript. (Page 17, Line 34)

References:


Response to the comments of Reviewer 4:

Dadja Essoya Landoh, M.D., MPH (Reviewer 4): Reviewer's report:

Authors in this study used a time series analysis with parameters estimation to estimate the temporal and spatial variability of hand-foot-mouth disease in Beijing. This is an interesting topic and manuscript is well written. Many studies have been conducted in China in similar studies have been conducted. However some particularities have been pointed out and this could be shared with researchers worldwide to more understand meteorological linked to HFMD.

Thank you for the comments! The followings are our response to the comments and revision lists point by point.

Some minors concerns

1. Why the authors have chosen to use the Bayesian Conditional Autoregressive model rather than the Autoregressive Integrated Moving Average. ARIMA may be more appropriate to show seasonality.

Thank you for your question! Autoregressive integrated moving average (ARIMA) model emphasizes the importance of “time” for disease management studies and have been widely used in modelling the temporal dependence structure of time series [1-2]. However, the Bayesian conditional auto regressive (CAR) model could be used to quantify both the spatial and temporal patterns of infectious diseases. It could solve problems like spatial autocorrelation and potential dependence between the covariates faced by traditional statistical methods [3], which was recommended when analyzing the spatial and temporal patterns of infectious diseases and exploring risk factors simultaneously [4]. So Bayesian CAR model seemed more appropriate as we aimed to quantify spatio-temporal characteristics of HFMD and the relationship between meteorological factors and HFMD incidence in this study.

2. A time span of three years was used in this study. This could have affected the power of the model.

Thank you for the suggestion! The time-series of three years in this study was short. It would be better to analyze data from a much longer time period to quantify seasonal and interannual variability and associated factors. But for now we could not collect data of longer time span, so we conducted this study with data of three years considering the data availability, which has been indicated in the section of limitations. (Page 17, Line 19-22)
3. The role of precipitation is reported in most of studies even those conducted in china. The authors should give the likely explanation in the discussion of the fact that this factor was not significant in their study.

Thank you for the suggestion! Precipitation may directly promote virus to attach to the small particles in the air or objects surfaces or indirectly affect individual behavior and thus influence the individual vulnerability to virus infection. But it was not significantly associated with HFMD incidence in our study, which was consistent with the study conducted in Shandong Province, China [4]. As a temperate city, Beijing has relatively lower (54.9mm during the study period) mean monthly precipitation than that in cities with humid climate. The low precipitation might be the reason that it was not significant, considering the threshold effect of precipitation on HFMD [5]. Besides, this study was conducted in the time scale of month, while other studies were at weekly or daily basis, which could also contribute to the difference [6]. We have added the explanation of the fact that precipitation was not significant in the discussion section of the revised manuscript. (Page 16, Line 26-36)

References:


