Author's response to reviews

Title: Effect of meteorological variables on the incidence of hand, foot, and mouth disease in children: a time-series analysis in Guangzhou, China

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

Re: 1530366807826672 - Effects of meteorological variables on the incidence of hand, foot, and mouth disease in children: a time-series analysis in Guangzhou, China

Many thanks for your email dated on January 12, 2013, and attached comments from two reviewers. Here we have now revised our manuscript according to the reviewers’ comments. A point-to-point response to the reviewers’ comments is attached below this letter.

We are very grateful for your consideration of publishing our manuscript in *BMC Infectious Diseases*.

Yours sincerely,

Yuantao Hao
Corresponding author

**Responses to Reviewer #1: Liang Lu**

1. **The author should give more reasons for choosing children as the study population.**

   We have added the below sentences (see page 8, line 4).

   “According to our data, 99.5% HFMD cases were children aged 0–14 years. Therefore, we focused on the incidence of HFMD among children aged 0–14 years in this study. The form of child care impacts HFMD infection. In China, children aged 0–2 years are usually cared for at home, 3–5 years attend kindergartens, and 6–14 years go to school. Children aged <1 year obviously differ from those aged 1–2 years in daily activity. To investigate which age groups are the most susceptible to meteorological changes, we conducted the analyses for different age subgroups (<1, 1–2, 3–5, and 6–14 years) using the models of the best fit to the overall data.”

2. **And why choosing weekly data for the analysis?**
Weekly meteorological variables were actually calculated from daily records by the National Meteorological Information Center. But we can only obtain the data of weekly meteorological variables from National Meteorological Information Center. We have now made this point clear in the “Meteorological data” part (see page 8, line 12).

3. **It is usually to include public holiday as a confounding factoring in time series analysis based on daily observations, but this study was a weekly scale analysis, I wonder how the author defined the holiday in the analysis, which was not described in the manuscript.**

We did not control for this variable due to weekly data. Instead, we included two indicator variables for summer semester holiday and winter semester holiday to control holiday effects. We have revised the sentence into “**HFMD activities could be different in school holiday vs. school day, so holiday (in summer and winter) effects were controlled in all models as indicator variables**”. We have also indicated that the use of weekly meteorological data rather than daily data is one of the limitations of this study (see page 16, line 20).

4. **It is appropriate to include influenza in the model, but the definition is not clear by “the influenza period was used as an influenza indicator.”, what do the authors mean by “period”?**

Due to different epidemic levels of influenza, the HFMD epidemic can be influenced between the different years because media attention may lead to behavior changes. Therefore, we incorporated indicator variables for years to account for between-year changes in different epidemic levels of influenza. The below explanations are now added to the “Surveillance data of hand, foot, and mouth disease” part (see page 9, line 10).

“**Due to different epidemic levels of influenza, the HFMD epidemic can be influenced between the different years because media attention may lead to behavior changes. Therefore, we incorporated indicator variables for years to account for between-year changes in different epidemic levels of influenza.”**

5. **The study further examined for subgroups by age, I wonder what is the criterion for dividing age groups, e.g., why choose “0-2”, to my understanding, children with 0-1years old should be different from 1-2 in daily activity, which should affect the disease transmission.**

In China, children aged 0–2 years are usually cared for at home, 3–5 years attend
kindergarten and 6–14 years go to school. The data were hence stratified into three age groups: 0–2 years, 3–5 years, and 6–14 years before. We agree that children with 0-1 years old should be different from 1-2 in terms of daily activity. Therefore, in the revised version, we have stratified our analyses into four age groups: <1 year, 1–2 years, 3–5 years, and 6–14 years. We have added these explanations in ‘Surveillance data of hand, foot, and mouth disease’ part (see page 8, line 4).

6. **In Figure 1, there was a surprising increase in wind speed, to me, it is absolutely abnormal, would the authors please double check their data?**

We have carefully checked our data and also confirmed with National Meteorological Information Center that the increase in wind speed was the real situation.

7. **Again in Figure 1, it seemed obvious increased in the years of 2010 and 2011, which, to some extent, might be due to data quality; would the author please clarify this concern?**

We have added the below sentences to ‘Discussion’ part (see page 13, line 18).

> “During the four-year study period, HFMD cases in Guangzhou city increased every year. In particular, there were obvious increases in the number of cases in the years of 2010 and 2011, which could be explained by higher incidence in reality, by improved diagnostic methods, and increased efforts in detecting and reporting HFMD. In addition, the trend may also be influenced by incomplete reporting in 2008 and the H1N1 pandemic in 2009.”

8. **The definition of the patient was mainly based on clinical symptoms, did the author try to do a sensitivity analysis based on those lab-confirmed patients? And how much of the patients were lab-confirmed?**

We agree with the reviewer that it is important to do a sensitivity analysis using lab-confirmed data. Something like this, cases were diagnosed by clinical diagnosis and/or lab. Either clinically diagnosed cases or lab cases were reported to CDC, so it is not possible to do sensitivity analysis. This was one of the limitations of our study (see page 17, line 1). In Guangzhou, 7.5% of patients did a laboratory testing.

**Minor comments:**

9. **In Abstract, “Over the last decade, Asian countries have encountered frequent and**
widespread hand, foot, and mouth disease (HFMD) outbreaks occurred predominantly among children.” This sentence is grammatically wrong.

We have now revised this sentence into “Over the last decade, major outbreaks of hand, foot, and mouth disease (HFMD) have been reported in Asian countries, resulting in thousands of deaths among children”.

10. In Abstract, “This study provides quantitative evidence that the incidence of HFMD cases in children were associated with high average temperature and relative humidity.”, what is “incidence of HFMD cases”, as the outcome variable in the model is count of HFMD, so I wonder how comes incidence?

Across years denominators were not changed dramatically, so the count was used as outcome, actually it meant the incidence.

Responses to Reviewer #2: Edmond Ma

Major Compulsory Revisions

1. This study provides further evidence showing that HFMD activities are associated with meteorological factors, in particular temperature and relative humidity. This is consistent with the other studies’ findings. The current study adds merits to the current knowledge by quantifying the associations, which are not very well documented. However, the speculations that such association will be differ in different age group is not clearly explained. Is this due to chance or there is a genuine biological mechanism that could account for this results. In fact the results shown are actually not conclusive. This differential association is observed for temperature but not humidity. An one percent of incase in temperature may lead to rise of HFMD cases by 1.9% to 2.4% among different age group. However, 1% increase in relative humidity may only lead to an increase of 1.7% - 1.8% of HFMD cases among different age group. The authors need either deleting this part of subgroup analysis or providing stronger argument for conducting this analysis and revise the relevant results and discussion part to better reflect what have been found.

We thank the reviewer’s comments. We agree that the main analysis should be based on children aged 0-14 years. The relevant results are now provided in Table 3 and Figure 2. However, we still want to know which age groups are the most susceptible to meteorological changes, we therefore estimate the effects in different age groups (<1,
1–2, 3–5, 6–14 years) using the lag1 model. In the new analysis, we also considered winter semester holiday as an indicator variable, so the results have been changed. The results of subgroup analysis are now provided in the last paragraph of “Results” part. We have also revised the relevant “Materials and Methods”, “Results” and “Discussion” part to better reflect what we have found.

Minor Essential Revisions

Abstract

Background

2. “..(HFMD) outbreaks that occurred predominantly…” should write as “ (HFMD) outbreaks that occurred predominantly…”

We have now revised this sentence into “Over the last decade, major outbreaks of hand, foot, and mouth disease (HFMD) have been reported in Asian countries, resulting in thousands of deaths among children”.

3. “This study aims to quantify..” should write as “This study aims at quantifying..”

Changed as suggested.

Results

4. “Temperature and relative humidity had the high effects on …” should write as “Temperature and relative humidity have large effect on …”

Changed as suggested.

5. “A 1%..” should write as “An one percent…”

Done.

Introduction

6. 1st para: replace “locations” by “countries”

Done.

7. 1st para: “Among these countries,..” instead of “Of these,…”

Done.
8. **1st para**: better say “there is no vaccine or effective curative treatment available”.

   Changed as suggested.

9. **4th para**: regarding the surveillance data, what’s mean by the reported accuracy rate? is this sensitivity or specificity?

   The reporting rate mentioned was calculated as: Reported cases / Found cases * 100%. The index was used to show the under-reporting rate.

10. **The authors may need to explain more on why they suspect the association between HFMD and meteorological factors would vary at different age groups, or such difference in association has any clinical or public health importance.**

   The below explanations have been added to the “Surveillance data of hand, foot, and mouth disease” part (see page 8, line 4).

   “According to our data, 99.5% HFMD cases were children aged 0–14 years. Therefore, we focused on the incidence of HFMD among children aged 0–14 years in this study. The form of child care impacts HFMD infection. In China, children aged 0–2 years are usually cared for at home, 3–5 years attend kindergartens, and 6–14 years go to school. Children aged <1 year obviously differ from those aged 1–2 years in daily activity. To investigate which age groups are the most susceptible to meteorological changes, we conducted the analyses for different age subgroups (<1, 1–2, 3–5, and 6–14 years) using the models of the best fit to the overall data.”

**Materials and Methods**

**Surveillance data of HFMD**

11. **1st para**: cross out “In which”

   Done.

**Results**

12. **6th para**: the authors reported that the relations between HFMD incidence and temperature rose relatively flat at temperature above 25 °C but a linear model is adopted in the subsequent calculations. The authors may either reconsider a non-linear model for a better estimation of the association or stating the linear
relationship may apply up to 25°C.

We now estimate the associations between HFMD incidence and meteorological variables based on children aged 0-14 years. For Lag0 model and Lag0–2 model, the risk ratio increased sharply before 25 oC but became relatively flat afterwards. However, the trends seemed linear for Lag1 model and Lag2 model, which was supported by the chi-square test for linearity. As a result, we used piecewise linear splines for Lag0 and Lag0–2 models, and linear regression for Lag1 and Lag2 models to estimate the effects. In the piecewise linear spline model, we used a breakpoint at 25 °C for temperature. The results are now provided in Table 3 and Figure 2.

13. Last para: Judging from the results shown in Table 2, I don’t agree with the sentence “the effects of temperature and relatively humidity on HFMD incidence were strongest in children 0-2 years, and progressively decreased with age.” Contrast to lag 1 model, the effect of temperature on HFMD incidence appears to be increasing with age in lag 2 model. The effect of humidity on HFMD among different age group is not very conclusive.

We have now revised our manuscript based on the new analysis.

Discussion

14. 4th para: “Furthermore, the findings that EV71…” complicated sentence and wrong gramma. Please rewrite.

We have rephrased this sentence as “Furthermore, the geographical distribution of EV71 strains in surface water was similar to that of clinical stool samples, suggesting that water serves as a potential reservoir and vehicle of the viruses, and thus high humidity and rainfall play an important role in HFMD infection”

15. 4th para: please change “physical activities” to “change of human contact”

Changed as suggested.

16. 4th para: change “this may lead to more contact in the child” to “this may lead to increase in contact among children”

Changed as suggested.
17. 5th para: It is well known in the literature that HFMD affects young children, especially those under 5 years old. It is also well documented in the literature that antibody against the enteroviruses decline with age, what the authors also quote. But this does not explain the difference in the association between HFMD and meteorological variables among different age groups, if such difference does exist.

We agree that the difference in serum antibodies in different age groups does not totally explain the differences in the association between HFMD and meteorological variables among different age groups. We think the differences in the association could be due to other reasons. One important reason is the difference in daily activities, and this is also the reason why we stratified the data into four age groups. We have now added more discussion into this paragraph (see page 15, line 13).

18. 7th para: Consider deleting the sentence “Although the research in Hong Kong...” and “Morover”.

We have deleted these two sentences as suggested.

19. Last para: Please delete ”Rainstorms and floods...this can increase the risk of household water contamination”. This is irrelevant since HFMD is NOT a food or water-borne disease!

We have deleted these two sentences.

Reference

20. Reference no. 31: please check proper citation. If this is online data, please use proper format, e.g. access on xx (date), cited xx (date).

Reference no. 31 is now in the correct style.

Table and Figure

21. Table 2 and Figure 2-4. No need breakdown into different age group.

The main results are now based on children aged 0-14 years.