Author's response to reviews

Title: Estimating the case numbers of hand, foot and mouth disease among children under-five in Beijing during 2012, based on a telephone survey of healthcare-seeking behavior

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Response to reviewers

Reviewer #1: Mark Riddle

1 - In the methods section the authors describe use of the Beijing Immunization Information System to sample telephone numbers for the survey. What percent of the population has access to a phone? How representative is the sample given a proportion of the population does not have a valid phone number to be called? Roughly 35% were not able to be contacted. Why is this? Is this non-contacted population similar to the contacted population based on demographic (socioeconomic factors)? The authors should consider this potential bias and discuss generalizability of the results based on reliance of this phone system.

Author: We agree with the reviewer’s comments about the potential bias. Of the 20,000 phone numbers, about 35% were not contacted. About 98% of those phone numbers were valid. The main reason for not being contacted is refusal to answer unknown phone number. We have compared the distribution of age and gender between those contacted and non-contacted subjects. We found that there was no statistic significance between them. We also compared the distribution of age and gender between those participates and non-participates. No statistic significances were found. So we believe that 6,209 subjects could be representative in terms of gender and age. We have added this to the results section (page 7).

2 - Case definition issues. The differential diagnosis of HFMD is quite broad with some diseases being common. How did the author's rule out these other conditions to avoid misclassification in the self-reported case definition? Was this self-report definition validated in any way? Some of the common differential diagnosis are listed below:

• Enteroviruses
• Erythema Multiforme (Stevens-Johnson Syndrome)
• Herpangina
• Herpes Simplex
• Herpes Zoster
• Kawasaki Disease
• Pharyngitis, Viral
Toxic Epidermal Necrolysis

Author: We agree with the reviewer’s comments about differential diagnosis. For rash, we listed some common skills to differentiate from other diseases when conducting the telephone survey. These differential diagnoses were not added in the manuscript. As the reviewer request, we have added this in the methods section (page 4). Because of the difficulty for parents or legal guardians to differentiate HFMD from the similar symptoms of other disease, the definition of self-defined HFMF cases was quite broad. As results showed, only 9.1% of self-defined cases were finally diagnosed as clinical cases by physicians for children under 2 years, and 40.3% of self-defined cases were clinical cases diagnosed by physicians for children between 2 and 4.

In the methods section (page 6), we also added the definition of probable (clinical) cases and laboratory confirmed case in the electronic National Notifiable Infectious Diseases Reporting Information System (NNIDRIS), as well as a brief description of NNIDRIS.

3 - Results, page 5 describes that children ages 2-4 were more likely to seek healthcare than children under 2 (81 vs 75.2%, p=0.036). Based on table two, the 95% confidence intervals of these point estimates overlap, therefore it is unclear how this is a statistically significant difference. What test was used? Recommend including numbers as well as percents in the table so that statistical analysis can be checked.

Author: Thanks a lot for the review’s comments on this. These CIs were calculated using the normal approximation, since the sample size is more than 30 and the proportion isn’t close to 0 or 1. We have double checked 95% CIs in table 2. There was no wrong in these values. As the reviewer request, we have added the number of each subgroup for checking statistical analysis. Additional details about methods used for statistical analysis in this study have been added to the methods section (page 6).

4. Year to year variations - the analysis is based on a single year. The authors should consider how generalizable a single year of data is in the stability of HFMD estimates over time. Might the year analyzed have represented an epidemic and thus artificially skew the data? The authors need to consider such in their discussion.
Author: Thanks a lot for the review’s comments. There were variations in the annual incidence rate of HFMD in Beijing. We didn’t aim to generalize a single year to other years. The title of this manuscript is misleading, and we have revised the title to avoid being misunderstood. The estimate of the case numbers of HFMD in this study is limited to the year of 2012.

5. Discussion: There is not mention of incidence rates of HFMD to other countries or even regions in China. It would be most informative to compare the rates the authors describe with similar incidence estimates provided from other relevant regions/countries of the world.

Author: This information on the overall incidence rate of HFMD in China is now described in the text (page 9).

6. Statistics: the statistical methods section lacks adequate detail to assess the validity. It is unclear how confidence intervals were obtained for complex calculations such as estimated cases and estimated rates. The authors report median case numbers (Table 3) and 95% confidence intervals. This is not normally done, usually mean and 95% CI are reported, OR median and interquartile ranges.

Author: Thanks a lot for the review’s comments. 95% CIs of estimated cases and estimated rates were determined by Monte Carlo simulation. In table 3 and 4, “median” has been changed into “mean”.

Reviewer #2: Xianjun Wang

1) It is necessary to introduce the difference between laboratory-conformed cases, clinically diagnosed HFMD, and symptomatic cases or self-defined HFMD. Which data were included in the NNIDRIS?

**Author:** Thanks a lot for the review’s comments. Laboratory-conformed cases and clinically diagnosed HFMD were included in the NNIDRIS, which have been described in the methods section. Symptomatic cases were equal to clinically diagnosed cases or probable cases of HFMD. Additional information on the definition of self-defined HFMD has been added in methods section (page 4).

2) It is necessary to describe how to select samples for isolate in Beijing? And if these samples covered all clinically diagnosed HFMD with different symptoms.

**Author:** Thanks a lot for the review’s comments. Clinical samples, including throat swab, rectal swab, faecal sample, vesicular fluid, or cerebrospinal fluid, were collected from the first five HFMD cases with mild, probable disease who visited hospital outpatient departments every week, and from all severe cases and deaths. Additional details about clinical samples have been added to the methods section (page 6). These samples covered all clinically diagnosed HFMD with different symptoms.

3) It could be necessary to discuss if other diseases such as varicella could be included in self-defined HFMD by parents or guardians of children, which could influence the estimation of the burden of HFMD.

**Author:** Thanks a lot for the review’s comments. The definition of self-defined HFMD cases was so broad that such diseases as varicella or measles might be included in self-defined HFMD cases. The impact on the estimation of the burden of HFMD was discussed in discussions section (page 10).