Author’s response to reviews

Title: Measles Outbreak in an Office Building in the Crowded Metropolis of Beijing, China

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Responses to the Reviewers’ Comments and the Corresponding Revisions

We appreciate all the two reviewers for their careful evaluation of the manuscript. A thorough and detailed reply to each point raised by the reviewers together with the changes made to the manuscript is listed below.

We thank the editor for the suggestion, the format have been revised in the main text.

Response to Reviewer 1:

Comment: “Abstract line 9 "and residences" and line 21 qualify "wider distribution of cases" (should be potentially wide geographic distribution of cases")?); p12 line 4 "and spread to 9 of Beijing's 16 districts" - this indicates secondary cases did occur, or do you mean "infected workers from 9 of 16 districts"? and line 9 - same wording as abstract regarding "wider distribution of cases"; same statement is also repeated in Conclusion line 9.”

Response: We have corrected these sentences in p 2 line 9, p 2 line 18-19; p11 line 7 (deleted); p 14 line 1.
Comment: “The second aspect of focus is that there is insufficient time describing the response, yet quite a lot of time spent describing IgM and PCR results. As the main focus of the paper is on the outbreak setting and effective control I don't think it necessary to dwell on IgM evolution over time, nor even the change in vaccination status during the outbreak - these matters can be described with simple statements rather than excessive text and tables.”

Response: Table 2 has been deleted and the laboratory results were described with simple statements in p8 line 11-12. Figure 1 has also been modified.

Comment: “Yet there is minimal description of the vaccination and active surveillance approach, which must be inferred from the figure and the discussion - these should be properly described in the methods and results. Lines 9-11 on p.7 are the only reference to the vaccination response in the results, yet are poorly written and do not give the reader any appreciation of the vaccination process or key decision points in the evolution of the response.”

Response: We have added descriptions on active surveillance and outbreak response immunization in p10 line 2-4, p10 line 11-14.

Comment: “In addition, most of the "Outbreak Setting" section on p.7 should be moved to the beginning of the Results so that readers can understand the significance of the "Chronology of the Outbreak".”

Response: We have moved "Outbreak Setting" section to the beginning of the Results in p 6 line 2.

Comment: “Also in the "Outbreak Setting" include the population numbers for the building and each of the subsections (Company A, Company B, commercial, other).”

Response: The population numbers were added in p6 line 8, 10 and 11.

Comment: “Another example - the risk of the elevator is mentioned twice in the discussion, yet only in results once to describe what floors the elevator services - nothing about how the investigators came to determine it was an important exposure site (Discussion p. 12 line 17).”

Response: We have supplemented risk assessments of different locations in the results (p 8 line 15-22 and table2) and a discussion on elevators in p12 line 3-5.

Comment: “Also "the working area of the source case" is first mentioned on p.10 as having the highest attack rate. This is interesting. His working area should be described in the outbreak chronology or outbreak setting sections - how many co-workers? was the area physically separated from the rest of Company A? did the index case also work in this area?”

Response: The descriptions on Company A and the working area of the source case was added in the results p6 line 9-12.
Comment: “By contrast we are given too much detail about - as we are already told the criteria by which cases are confirmed, and this is not a paper investigating specificity and sensitivity of measles diagnostic methods, much of the detail can be omitted. Particularly, p. 8 lines 20-21 can be simplified "Forty four percent (19/43) of cases were IgM positive and 81% (34/43) were PCR positive for measles" - please add how many were confirmed by clinical evidence alone? I suggest deleting Table 2.”

Response: We have deleted table 2, and simplified the descriptions on Laboratory results in p 8 line 11-13.

Comment: “In the Discussion, p.14, lines 20-22, there is reference back to the relative performance of IgM and PCR, yet it is not apparent about the point of including this. Do the Beijing measles control guidelines not recommend confirming measles with PCR and caution about the sensitivity of IgM in the first few days following rash? If this is the case then it does deserve a paragraph in the Discussion, if not, then omit the sentence.”

Response: We have deleted the sentence.

Comment: “My final major concern is where the local guidance appears to vary from international guidance, yet I am unable to substantiate the reasons for this. This is mainly along two lines - requiring MCV for adults not vaccinated in the past 5 years and a longer infectious period for cases with pneumonia. It may well be this is what the Beijing measles control guidelines state, but I am unable to verify that and the references provided do not substantiate the claims made. This applies to p.11 lines 3-4 and lines 10-11, p13 lines 3-8.”

Response: We have corrected or deleted these sentences in p 9 line 11, p 10 line 9-10 and p 13 line 9-11.

Comment: “I note that reference 4 does not mention poor immunogenicity of Chinese measles vaccines, nor does it mention cold chain as a problem, except as a constraint in expanding the vaccination program prior to the 1980's. A major issue described by Ma seems to be inaccurate measurement of coverage. Reference 24 is in Chinese so I am unable to ascertain if it verifies these claims. I am unable to find any other English references to poor performance of Chinese measles vaccines, including regarding the Beijing 55 strain.”

Response: We have corrected the statement and references in p13 line 9-11.

Comment: “on p.14 lines 4-5 the authors suggest that Beijing could refer to the "current" US recommendations or Japan's strategies for adult immunization". Reference 26 refers to the 1998 US guidelines (2013 is current) - nevertheless, neither recommend anything more innovative than ensuring all adults have two lifetime doses of measles containing vaccine.”

Response: We have updated the literature in p13 line 13-15.
Comment: “The reference for cases with pneumonia having a longer infectious period is a South African autopsy study. I cannot find any evidence there about transmissibility - certainly much of the pneumonia associated with measles is due to secondary viral or bacterial infection, and I cannot find any reference that pneumonia indicates prolonged transmissibility of measles. If the authors have such references I would be grateful to be directed to them. Further, just because measles virus can still be detected by PCR a couple of weeks after rash onset does not mean that it is viable or infectious. Nevertheless apparently this in the Beijing measles surveillance guidelines which I do not wish to question, however international readers should be able to review the evidence base for this guidance, which is not possible as the guidelines are in Chinese. Depending on how this is resolved, there may need to be subsequent corrections to p.6 lines 14-15 as according to most international guidelines the source patient would not be considered infectious on March 7 & 8.”

Response: We have corrected the infectious period of measles according to international guidelines in p 7 line 8, and deleted the discussion on infectious period.

Comment: “p. 2 line 15 - do you mean after "rash" onset? p. 2 line 15 - reported to whom? the NNDRS? the local CDC?”

Response: We have corrected the statement in p2 line 15-16.

Comment: “p.2 line 22 - do you mean "emphasizes the difficulty"? p.4 line 12 - "in Beijing in recent years" p.6 line 14 - "before he went to hospital"”

Response: All sentences have been corrected in p 2 line 19, p 4 line 5, and p 7 line 7-8, respectively.

Comment: “p.6 line 15 & 16 - specify company A and describe his work area. p. 6 line 18 - specify company A”

Response: The descriptions on company A and department A have been supplemented in p 6 line 9-11 and p 6 line11-12.

Comment: “p. 7 line 22 - is it correct to say "each have separate dedicated entrances"? p.8 line 6: you state here that 30 were migrants, however in Table 1 it gives 30 not migrants - which is correct?

Response: All sentences have been corrected in p 6 line 13, p 19-20 table 1, respectively.

Comment: p.8 lines 8-10 - this meaning of this sentence "The proportion of cases...."is not clear - can it be omitted? ”
Response: This sentence has been deleted.

Comment: “p.8 lines 11-12 this sentence is not clear. Are you referring to just cases, or to all workers in the building? Do you mean that workers without documented measles vaccinated were recalled for vaccination? or that the vaccination status of cases was obtained either through reviewing documentation or recall? ”

Response: The sentence has been corrected in P 7 line 19.

Comment: “p.8 line 12 - "Nine cases (20.9%) had received measles vaccine;"

P.8 line 13-14 - is this information about hospital attendance and travel provided to demonstrate there could be other sources of infection for some cases? If so, introduce the sentence to orient the reader: "Some cases may have contracted measles infection elsewhere...."

p. 8 line 16: reported to whom? the NNDRS? the local CDC?"

Response: These sentences have been corrected in p7 line 20, p 8 line 5, p 8 line 8, respectively.

Comment: “p.8 lines 17-18 - Do you mean that 17.4% of cases who visited a hospital were not reported, compared to 55.8% of those who received primary health care only? If so, please restructure the sentence to improve clarity. ”

Response: This sentence has been corrected in p 8 line 7-9.

Comment: “p. 11 lines 6-7: were any cases identified in the residential communities? If so please provide details, if not, please state that none were found there. ”

Response: This sentence has been corrected in p 10 line 5-6.

Comment: “p.12 line 2: building should be plural (buildings)

p.12 line 6: "on" should be "one""

Response: These sentences have been corrected in p 11 line 5 and p 11 line 9, respectively.

Comment: “p. 12 line 9: "will be emphasized" doesn't make sense. Maybe just "will be challenging for measles elimination..." ”

Response: This sentence has been deleted.

Comment: “p.13 line 1: do you mean "vaccinated in the early stage of the expanded.."? ”

Response: Yes, but this sentence has been deleted.
Comment: “P.13 lines 13-15: do you mean: ‘Delayed recognition of measles cases could have meant that the optimal time for controlling spread was missed, leading to an even larger outbreak’?”

Response: This sentence has been corrected in p 12 line 22.

Comment: “p.14 lines 1-2: without more background about how the measles vaccine is offered to adults, and who should be vaccinated, it is hard to know whether its a matter of acceptability, or other factors leading to low uptake of apparent recommendations for adults. I think to include this point more information is needed to support the contention, or other factors discussed. ”

Response: This sentence has been deleted.

Comment: “p.14 line 13: missing "of" between Isolation and fever ”

Response: This sentence has been corrected in p 12 line 18.

Comment: “p.15 lines 10-11: The phrase "especially pubic traffics" is not clear, similarly "by exposure made in public contact".

p.15 line 17: do you mean " avidity"?

p.15 line 21 - as for p.13 lines 13-15, "Early recognition of cases is the key to controlling an outbreak" (by the time you have an epidemic it is by definition already an outbreak) ”

Response: These sentences have been deleted.

Comment: “p.16 lines 9-10: do you mean "emphasizes the difficulty of measles eradication in crowded cities"?”

Response: This sentence has been corrected in p 14 line 2.

Comment: “Table 1: no need to include vaccination by end of outbreak in the table. Simply state in the text that four individuals who received measles vaccine as part of the response went on to develop measles infection - two of whom had no prior doses and two had an unknown vaccination history.”

Response: We have corrected table 1 and the sentence in p 7 line 22- p 8 line 1.

Comment: “p.24 line 1: I think you mean "cases who didn't go to hospital are unknown"?

Figure 1: please correct typo in legend "other companies"

Response: They were corrected in p 20 line 3 and figure 1.
Response to Reviewer 2:

Comment: “Table 1: it is very confusing; it doesn't report the numbers mentioned in the text. Tables should be clear so the reader can easily find correspondence with the text. For a better understanding the Table 1 could be splitted in two tables. Please control the number of migrants.”

Response: We have modified the description of the data in p 7 line 16-18 and corrected the number of migrants in table 1.

Comment: “Table 2: as mentioned before, the number of RT-PCR positive samples doesn't correspond with the text.”

Response: We have corrected the data in p 8 line 12.

Comment: “Table 3: it reports data about receipt of MCR that are not mentioned in the text. Please explain.”

Response: We have deleted the data about receipt of MCR from table 3 on the advice of Dr. Sheppeard.

Comment: “Figure 1: according to the figure, the last measles case is on March 30 but in the text is reported March 28.”

Response: March 28 in Figure 1 is the date of rash. I have changed the abscissa of figure 1 from date of rash to date of onset.

Comment: “The authors identify genotype H1 as responsible for the outbreak but didn't report any data about the sequences identified. Phylogenetic analysis would be desirable.”

Response: We have already reduced the description on laboratory results on the advice of Dr. Sheppeard, so I will not add any more information about H1.

Comment: “ABSTRACT Line 13 : except for its commercial center…”

Response: This sentence has been corrected in p 2 line 13.

Comment: “Line 16 : Sera collected at 0-3 days….”

Response: The sentence has been deleted.

Comment: “BACKGROUND Line 16 : " incidence has reduced from 210,6 per million in 2005 to 58,1 per million". please specify When.”

Response: The sentence has been corrected in p 3 line 15.
Comment: “Page 4 line 3: The authors should better clarify this sentence "..it is very common that residents’ workplaces and residence are not in the same district".”

Response: This sentence has been deleted.

Comment: “LABORATORY TESTING Line 14: 5 days from rash

RESULTS Line 14: it has more sense: However he continued going to work at his company's office not only before his hospitalization, but also after March 7 and 8.”

Response: These sentences have been corrected in p 5 line 7 and p 7 line 7-8.

Comment: “Page 7 line 2-3: the cases are confirmed”

Response: The sentence has been deleted.

Comment: “CHARACTERISTIC OF MEASLES CASES Page 8 line 6: after (Table 1). They resided…. who are they? 43 people?”

Response: The sentence has been corrected p 7 line 16.

Comment: “specify the authors say that 30 (69,8%) were migrants, but in tab. 1 under migrant column there are yes 13 (30.2%) and no 30 (69,8%). these numbers don't fit with the text.”

Response: We have corrected the data in table 1.

Comment: “LABORATORY RESULTS page 8 line 21: or 4-28 days after rash onset… line 22: "thirty-four of 42 cases (81,0%) were RT-PCR positive", but in tab. 2 there are 35 RT-PCR positive and 8 RT-PCR negative, total 43 and not 42? Line 22: within 5 days from rash.”

Response: 42 of 43 throat swabs were obtained within 5 days from rash onset, and the rest was obtained after 5 days.

Comment: “Page 9 line 7: in sera”

Response: The table 2 and notes (in sera) have been deleted.

Comment: “Page 11 line 1: "Active searching and case management" is a title, should be in bold. Page 11 line 8: Post-exposure vaccination (the same in bold) and should recall Table 3. Page 11 line 15: Other (in bold)"

Response: We have changed the format in p 9 line 10, p 10 line 7, p 10 line 18.

Comment: “DISCUSSION Page 13 line 8: the authors should explain which type of is used for vaccination campaign.”
Response: The measles vaccine is combined measles and rubella vaccine, we have added in p 10 line 10-11.