Author's response to reviews

Title: "Preventing the preventable through effective surveillance: the case of diphtheria in a rural district of Maharashtra, India."

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Author's response to reviews: see over
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Version: Dated February 22, 2013

Dear Editor(s), and Reviewer’s,

We appreciate the valuable suggestions made and the chance to revise our manuscript. Attached is a point-by-point response to the comments from each of the reviewer’s. We are hopeful that we have responded satisfactorily to all your concerns.

All authors have read, edited and approved the revised paper.

We will appreciate and gladly incorporate further comments if any.

Sincerely,

Revati Phalkey
Reviewer 1 report

Title: "Preventing the preventable through effective surveillance: the case of diphtheria in a rural district of Maharashtra, India."

Version: 5

Date: 18 October 2012

Reviewer: Arun Humne

Reviewer's report: During re-review it finds that the authors have incorporated all the suggested corrections under the defined categories. The article may be considered for publication.

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: 'I declare that I have no competing interests

The authors appreciate the comments of Dr. Humne and are grateful that he accepts the paper for publication.
Reviewer's report

Title: "Preventing the preventable through effective surveillance: the case of diphtheria in a rural district of Maharashtra, India."

Version: 5

Date: 30 October 2012

Reviewer: Thomas Cherian

Reviewer's report:
While the paper has improved after the revisions, unfortunately there are still many remaining errors and inconsistencies in the paper and it is still not suitable for publication.

At the first instance- we would like to thank Dr. Cherian for a thorough and in depth review of our paper. We especially appreciate the opportunity he gave us to clarify our position and to revise the manuscript. We unanimously applaud his precise eye for detail. It has indeed provided us with greater insights and enabled the district level officers to re-think the way disease outbreaks will be investigated in the future. Particularly the Integrated Disease Surveillance System staff and district epidemiologist gained thoughtful insights from the revision exercise of this paper. We would like to express our sincere thanks once again. Below we outline our responses to the concerns raised in this second round of revision.

1. It is very unclear how the patients were identified and how many patients there actually were with confirmed disease. In the results the authors describe 2 initial “index” cases that prompted the household surveys and screening. The results seem to suggest that through the screening process they identified 85 probable cases of which 11 were lab confirmed. The data in Table 1 also suggests the same, wherein the 11 confirmed cases appear from among the 85 probable cases from the household screening. These 11 cases, along with the two index cases that triggered the investigation, would bring the total to 13. But, only 11 are described.

The 11 cases that we describe in the paper include both the death index case and the second index. After the first death case (index1)- village health workers only screened school children (0-6years) and no clinically probable cases were identified. Mass prophylaxis was nonetheless administered to all fever cases in the village at the time. Six weeks later another case (index 2) was diagnosed in the village and that’s when the second round of house to house screening was done. Village workers identified 91 persons with any one of the following symptoms - fever, sore throat, difficulty in swallowing, running nose, cough, tonsillar patch or pseudo-membrane. An all inclusive approach to case classification was taken to reduce the false negatives since the first screening was done by paramedical staff. All identified cases were referred to the sub-center for in-depth clinical examination. On examination by a qualified medical practitioner, 85 patients were requested for swabs and an all inclusive approach was taken to treat them all. The reason why 85 swabs were taken irrespective of the presence of a membrane or not were mainly that the medical college team along with a microbiologist were present and it was logistically easier that all swabs were collected on site rather than refer patients later to the district headquarters which is 45km away. Although wasted resources this decision was taken for damage reduction. Further in-depth clinical examination by an internal medicine expert and a pediatrician from the civil hospital- ten cases were identified with either a clear white patch on one or both tonsils (4 cases) or an adherent pseudo-membrane (6 cases) and these cases were advised admission for further treatment. They were offered transport through the PHC ambulance to the district civil hospital. Of these 10 probable cases (as per WHO definitions) nine were confirmed smear positive and two were culture positive (one case was smear negative but culture positive). The death case was both smear and culture positive and had presented with an advanced pseudo-membrane, giving a total of 10 smear positives and three culture positives in 11 cases. Since we decided to include the death case in the overall analysis- we
had to re-calculate the percentages with eleven as the denominator and this has now been updated at few places in the revised manuscript. However, two of these 10 identified cases chose to transfer to Mumbai for further treatment (whose case papers were later obtained from the Kasturba Hospital for infectious diseases). Thus only eight were treated at the civil hospital. We apologize for the error and the lack of clarity at the first instance.

2. Later in the paper the authors say that 45% of the cases consulted a private doctor before they came to hospital. This suggests that the 11 cases they are referring to were picked up in a hospital and not through the household screening. All put together, it is unclear how many cases there were and where and how they were detected.

Thank you for the comment. We do recognize the lack of clarity in this as well. As a knee-jerk reaction, after the second confirmed case (and a death earlier at the civil hospital) people sought care at the private sector for a second opinion. However, since the government offered transport to and fro from the district civil hospital and provided free of cost care (including the stay of the relative) the patients finally chose to be admitted at the civil hospital. This is why we mention that 45% of the cases had also sought opinion at a private clinic before being admitted to the civil hospital. We have revised this in the new manuscript.

3. Case definitions: The authors state that they used the WHO case definitions and that a probable case was defined as “a person having acute pharyngitis or laryngitis with or without a tonsillar patch or a pseudomembrane”. However, the WHO surveillance standards that they cite define a probable case as: “an illness characterised by laryngitis or pharyngitis or tonsillitis, and an adherent membrane of the tonsils, pharynx and/or nose” (http://www.who.int/immunization_monitoring/diseases/diphtheria_surveillance/en/index.html)

Thank you for this very important comment. We also admit that we did use the term “suspected cases” for the initial screening done by the village health workers who were instructed to identify any cases of tonsillitis, pharyngitis, fever, sore throat, pain in swallowing, etc. with or without a tonsillar patch or a well-defined membrane for a broader all-inclusive approach and to minimize false negatives. So they were asked to identify any symptoms and therefore 91 cases were identified by them. But when referring back to the WHO standards- only the ten cases that were clinically confirmed by a qualified internist or a pediatrician to have a tonsillar patch or a membrane qualify as probable cases. This has been revised accordingly in the manuscript. All of these ten probable cases were later confirmed either with a smear or a culture positive. This exercise of revising the manuscript has served as a very important lesson for the rapid response team at the district level to understand the intricacies of an epidemiologically sound investigation and the practical difficulties in doing it. We would like to sincerely thank Dr. Cherian for his comments. This was a first-time research exercise for majority of the district surveillance cell and the PHC staff which made it even more interesting and facilitated capacity building.

4. Furthermore, it unclear how many of the cases actually had a tonsillar patch or a pseudo membrane. In the abstract and on page 18, they state that only two cases (18.1%) had a pseudo membrane and 36.3% had a tonsillar patch. On the other hand, on page 12, they state that 60% had a tonsillar patch. As we outline it in point 1- there were 7 cases of the 11 (64%) with a well formed membrane (6 of 10 and the death case) and 4 cases (4 of 11 = 36%) with a white tonsillar patch. All values have been corrected in the revised manuscript including the Figure. We do apologize for these errors and also their oversight in the first revision.

5. If only 2 cases had a pseudo membrane and it is not known whether the C diphtheriae isolated were toxigenic, then perhaps then we may have only two valid cases of diphtheria. If these were the two index cases, then all their comments about age shift and need for boosters are not substantiated with any data.
Thank you for the comment. We do note the concern but would like to reiterate that we have 11 cases which had either a tonsillar patch or a well formed pseudo-membrane along with either a smear or a culture positive result. Therefore our fear of a probable age shift although not grounded in statistically strong evidence given the sample size- is nonetheless in our opinion relevant. We would also like to support our observation with the data from the Integrated Disease Surveillance System which shows that from the period January 2011 to the occurrence of the death case- six clinically and lab confirmed cases have been reported from the district as shown in table below. Although preliminary - the data does show that the age of disease occurrence is indeed advancing.

Table: 1 Confirmed cases of diphtheria as reported to the IDSP

<table>
<thead>
<tr>
<th>Gender</th>
<th>Age</th>
<th>Month</th>
<th>PHC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>23</td>
<td>January</td>
<td>Ner</td>
</tr>
<tr>
<td>Male</td>
<td>17</td>
<td>February</td>
<td>Borkhund</td>
</tr>
<tr>
<td>Female</td>
<td>18</td>
<td>March</td>
<td>Nagaon</td>
</tr>
<tr>
<td>Female</td>
<td>22</td>
<td>April</td>
<td>Songir</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>May</td>
<td>Shirud</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>July</td>
<td>Walkheda</td>
</tr>
</tbody>
</table>

6. The data presented in Table 2 is incorrect. What they have presented in the first row of the table are the country official estimates and not the WHO and UNICEF estimates as they claim. It is unclear where the data are in row 2, which is referred to as UNICEF (India) estimate, are from. UNICEF does not publish independent estimates and only publish joint estimates along with WHO. The country profile that provides the coverage estimates for India is attached.

Thank you very much for bringing this to our notice and the file. We have revisited the link you gave us - updated the data for 2011 and also corrected the references. The labels for the respective data have been corrected and we have added DLHS 2 and 3 data for Maharashtra state and Dhule district which is of more relevance to the study. However, if considered necessary we could also remove the table from the manuscript. We will appreciate Dr. Cherian’s opinion on this. The new table is as under:

Table 2: DPT3 coverage estimates for India and Maharashtra state (in %)

<table>
<thead>
<tr>
<th></th>
<th>2004</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
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</thead>
<tbody>
<tr>
<td>Official Government Estimate (India)</td>
<td>87</td>
<td>90</td>
<td>94</td>
<td>98</td>
<td>84</td>
<td>97</td>
<td>90</td>
<td>85</td>
</tr>
<tr>
<td>WHO-UNICEF Joint Estimate (India)</td>
<td>64</td>
<td>67</td>
<td>66</td>
<td>71</td>
<td>72</td>
<td>72</td>
<td>72</td>
<td>72</td>
</tr>
<tr>
<td>DLHS 2 and 3 (Maharashtra)</td>
<td>72</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>79</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>DLHS 2 and 3 (Dhule district)</td>
<td>88</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>45</td>
<td>-</td>
<td>-</td>
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</tr>
</tbody>
</table>

7. In the absence of clarity on the actual number of confirmed cases of diphtheria, the validity of their recommendations and conclusions cannot be determined.

We appreciate and agree to all the doubts you have raised and rightly so- with the inconsistencies in the last version of our paper – it was difficult to determine the validity of our recommendations. However, we hope we have now provided satisfactory responses to them. We would like to bring to your notice that the opportunity to reach out to the research community in the state through this paper is invaluable for us especially because this is the first attempt of its kind from the district government to come out of the closet and to acknowledge that some issues exist that need urgent attention- particularly vaccine coverage. This is also in a way an encouraging example for other districts to report their experiences with outbreaks of endemic and emerging diseases detected through the Integrated Disease Surveillance Project. We are willing to provide any further corrections that may be necessary as we believe that this paper will help us set an example for effective surveillance in the state.
8. The authors also make recommendations that have no bearing on their report of the diphtheria outbreak. For example, on page 16, they refer to the need to switch over from DTwP to DTaP in the district. The rationale for this recommendation is not clear. Recent data from outbreaks of pertussis in the US and other countries suggest waning immunity from DTaP, with outbreaks involving older age groups. This has thrown open the entire debate on the relative benefits of DTwP and DTaP. Such statements, without any valid data backing them up are not acceptable. 

*Thank you for your valuable insight. We have deleted the statement in the revised manuscript accordingly.*