Reviewer's report

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

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Reviewer: Thomas Cherian

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The lack of adequate surveillance capacity is a serious impediment to disease control efforts in many developing countries, including India. The lack of epidemiological data makes it difficult to establish appropriate policies and strategies. Therefore, the authors efforts to use the existing integrated disease surveillance project to detect and investigate an outbreak of diphtheria and to analyze and draw inferences from data generated is commendable. However, the paper has several deficiencies, as described in the comments below, which if addressed could significantly enhance its value of the paper and set an example of how national HMIS and integrated disease surveillance projects could be used to generate valuable epidemiological information to guide national or subnational policies and practice. The report of the outbreak, as currently presented in this manuscript, is incomplete and the validity of the findings is difficult to judge.

Major compulsory revisions

1. The paper provides no description of the integrated disease surveillance system/project in India. A short description of the surveillance project is essential for international readers of this article to be able to fully understand and interpret the data.

2. While the paper reports on bacteriological findings, there is no description of bacteriological methods in the paper. In the absence of these, it is difficult to decide on the validity of the bacteriological findings. The authors should include a description of the bacteriological methods, including staining technique, culture media and methods, and antimicrobial susceptibility testing methods. It would also be useful to mention the internal quality assurance procedures in the laboratory and whether the laboratory participates in any external quality assurance programme.

3. It would be better if the authors describe the methods used for the outbreak investigation in the methods section. The results section refers to house to house surveys, but provides no further details on the survey methodology. The authors should provide details on the methods for selection of the population for the house-to-house surveys (how were the number of households selected for the surveys and who in each house-hold was screened?), the methods and instruments used for screening the target populations (questionnaires etc.), the
level of training of the persons conducting the screening, and the method for collection and transport of the throat swabs in the second survey.

4. Under the methods section (para 3, subtitled “case definitions”), the authors provide definition for probable and confirmed cases, but they report out only suspect cases detected in the house-to-house surveys (Results, para 2). What was the definition of a “suspect case”? In the results section, the symptoms of probable and suspect cases seem to overlap.

5. The authors state that swabs were collected for bacterial culture from 85 cases during the house to house surveys (Results, para 2). Yet, they provide results only for the 11 hospitalized cases, 9 of whom were confirmed. Therefore, there were a total of 96 cases, 9 of whom were confirmed and 87 were probable or suspect (as stated earlier, it is not clear if the definitions were the same of different for suspect and probable cases). No further details of the suspect cases identified in the house-to-house survey, including age distribution, are provided. This is an incomplete description of the outbreak and in estimating the attack rates, the authors use a mix of confirmed and probable cases while leaving out other suspect or probable cases.

6. In table 2, the authors provide annual estimates of the DTP3 coverage in India and cite different figures from WHO and UNICEF. Since 2000, WHO and UNICEF have been jointly estimating the coverage and the estimates are identical (http://apps.who.int/immunization_monitoring/en/globalsummary/countryprofileresult.cfm). The estimates as reported in the paper are incorrect. The authors should correct the information in the table from data available on this site. They may also update their estimate for 2010.

7. Since the outbreak seems to be limited to one village of 3359 persons and since household surveys were conducted, were not immunization coverage data from the village collected, through review of the immunization registers, child health cards or parental recall? The authors merely state that vaccination history was not available in the majority of the cases, but make no mention of what they did to obtain the vaccination history. All health centres maintain immunization registers. Were attempts made to review these registers? It seems a shame that an outbreak investigation was carried out without better documentation of the local immunization coverage data and dependence on estimates of national and state level coverage and district surveys that are several years old.

Minor essential revisions

1. The authors state that “there is no standard vaccination schedule for diphtheria and the choice depends on the sero-epidemiology and endemicity of disease in each country” (Background, para 2). This is not strictly true. While there may be some variation in the schedule used for the primary series, all schedules deliver a primary series consisting of three doses that start at a minimum age of 6 weeks with a minimum interval of 4 weeks between doses. The choice of the schedule is not solely dependent on the epidemiology of diphtheria but also of the other
diseases in the combination vaccines that contain diphtheria toxoid. The timing and number of booster doses does, however, vary between countries and is, as the authors point out, dictated by local epidemiological data. This sentence may be corrected to reflect these points.

2. In stating that India accounted for 74% of reported cases of diphtheria (background, para 3), it should also be recognized that this is partly accounted for by the disproportionate size of the Indian birth cohort and influenced by variable reporting efficiency of diphtheria cases between countries.

3. It is unclear what a “geographically localized major outbreak” means. Did the authors also make efforts to determine whether there were reports of diphtheria in other villages in the district or in adjacent districts?

4. The authors only refer to ethical approvals obtained from universities in Delhi and Germany (Methods, para 5, subtitled “ethics approval). Was any effort made to obtain ethics approval at the local (district or state) level? Were the village leaders consulted and did they give consent for the surveys? Was informed consent sought for collecting throat swabs from suspect cases?

5. The dose and route of administration of anti-diphtheria serum (ADS) should be mentioned (Results, para 1). The authors also mention that in 54% of cases the ADS was administered for 3 days (Results, para 8, subtitled “treatment”). The recommendation for administration of ADS is as a single dose, preferably intravenously. Why was ADS given over 3 days and what was the route of administration?

6. Under treatment (Results, para 8, subtitled “treatment”), the authors state that chemoprophylaxis with administered as per guidelines. Was it treatment of prophylaxis that was provided? The dosage of antibiotics (given in mg or units/kg in case of children) and the duration of treatment should be reported.

7. What were the ages of the culture confirmed cases. In the tables the authors provide the age break-down of all the hospitalized cases, but not the confirmed cases. The age distribution of the suspect cases during the survey are also not provided.

8. The coverage thresholds required for herd protection to eliminate disease are not necessarily the same as those that will result in a shift in the age, and could in fact be lower (Discussion, subtitle “the age of paranoia”, para 2).

9. While the authors have pointed out to the need for booster doses (Discussion, para 2 under the subtitle “the booster dilemma”), they have not provided sufficient evidence for their recommendation on adult boosters every 10 years. Such recommendation will require better data and consideration of the programmatic feasibility of administering such doses at scale and the cost-effectiveness of such a strategy vis-a-vis other pressing health priorities. They could instead call for more frequent and more rigorous outbreak investigation and sero-surveys to determine the need, timing and number of booster doses.
10. The authors point out that the one death was due to respiratory obstruction and since it occurred early in the course of hospitalization and would, therefore, not have been influenced by the administration of ADS. Hence, the last paragraph in discussion, under the subtitle “immunized or not- does it really matter?”) should be rephrased accordingly.

11. There are several limitations to the study as outlined in the comments above, which may be used to improve the section of the manuscript subtitled “limitations of the study”.

12. Lastly, in their “conclusions”, the authors refer to the “faltering vaccination programmes”, though their own data in Table 2 show increasing coverage in Maharashtra. As noted above, the evidence provided in this manuscript does not justify their conclusions about the need for adult boosters.

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

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

I declare I have no competing interests