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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Version: 4 Date: 28 September 2012

Author's response to reviews: see over
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's report
Title: "Preventing the preventable through effective surveillance: the case of diphtheria in a rural district of Maharashtra, India."
Version: 3 Date: 12 July 2012
Reviewer: Arun Humne

Reviewer's report:

Major Compulsory Revisions
1. There are discrepancies in the number of positive cases and attack rate reported in Table 1. For example, correct number of total positive cases in the age group 6-10 years should be 2 (1 male + 1 female positive case) instead of 1. Similarly correct attack rate for this age group should be 0.9 instead of 0.4.
*The table 1 has been replaced and the attack rates re-calculated as per your comments. Thank you very much for the comment.*

2. (n) should be inserted below the column headings in Table 1 so that denominators for calculating percent attack rates among male, female and total population are self-evident; for example Males (n), Females (n) and total population (n).
*Thank you for the comment. (n) has been added to the revised table as per your recommendation.*

3. In the abstract, justify in the background why Dhule district has been specifically chosen for the study purpose.
*Thank you for your valuable comment. We have added “Dhule a predominantly rural district in Northern Maharashtra has reported low vaccination coverage's consistently but has recently developed awareness to recognize outbreaks in time through its syndromic surveillance system.” to the background section in the abstract of the revised manuscript.*

4. The results section mainly includes only the coincidental findings or findings on secondary outcomes. It would have been more relevant if the findings specifically related to the assessment and response to the outbreak of diphtheria instituted by the District Surveillance Team had been mentioned first in the results section and later on discussed in discussion section as this appeared to be the primary objective of the study.
*Thank you for the comment. We have added the following text summarizing the findings to the results section (Page 10) “A short questionnaire was designed and all concerned health staff from the PHC and subcenters were trained in screening and data collection for the house to house survey and the medical camp. All households in the village were covered by three teams and all 2100 individuals in the village at time of outbreak were screened. Positive cases and their contacts were continuously tracked. Additionally other health conditions were attended to during the survey and attempts were made to obtain verbal vaccination history or cards during the visits” and to the first paragraph in the discussion section “The outbreak provides a realistic view of how the district authorities detected and reacted to the event. Although the first response mounted was fairly reasonable the incident raises several concerns regarding the epidemiology of diphtheria itself in the district. It also alerts us to the issues and next steps in preventing recurrence” in the revised manuscript.*

5. As per results presented in Table 1 the total population denominator was
3,359 i.e. total population of the village. Further, it has also been stated on page no. 9 that the screened population in two waves was 560+2100 = 2,660. This discrepancy in denominator needs clarification.

Although the official population of the village was 3359, the people who were actually living in the village and were available during the screening procedures were 2100. Secondly, following the first death case the district authorities only screened the school children and the contact cases of the students in the primary school (560) people. However, during the second wave all residents of the village irrespective of their age and exposure status were screened. Therefore, there is a discrepancy in the numbers. We have clarified this on page 10 in the revised manuscript.

6. Page 10 – Bacteriology section – clarity is needed in calculation of percentages like \(81.8\% \frac{9}{11} + 27.2\% \frac{3}{11} = 109\%\)? It is not clear whether the numerator used is 2 or 3 for culture? Should the case which was both smear and culture-positive be included twice i.e. both in smear positive and culture positivity rates?

Thank you for the comment. Ten cases were smear positives and 3 were culture positives. One case the smear was negative but the culture was positive, therefore we have calculated the positivity rates separately for smear and culture in the revised manuscript. The numerator however, for the culture cases positives as pointed by you is three of the 11 cases (27.2%). We have changed this accordingly in the revised manuscript.

Minor Essential Revisions
1. What is the Research Question …is not clear.

Thank you for the comment. We have refined the objectives of the study and elaborated on the main research question which was to describe the outbreak occurrence and the response mounted to it in paragraph 2 page 7 of the revised manuscript. The paper also aims to discuss the epidemiological reasons for the persistence of the disease in the region and to pave the path for the future discussions. The authors realize that the investigation is rather basic and descriptive and does not take traditional approaches to describe the outbreak investigation because all the cases were detected and admitted on the same day- so it was not possible to track an epidemiological curve or describe onset and conclusion of the event. Nonetheless we wish to bring up relevant issues to the table so that future outbreaks are prevented and watched for in a timely manner in the predominantly rural and tribal district of Dhule.

2. Aims are mentioned at more than one place, but mentioning specific objectives…primary or secondary… would have aptly justified the need and purpose of the study.

Thank you for the comment. We have refined the objectives of the study as proposed by you which reads as “The main objective of the study was to describe the nature of the disease itself and the outbreak in the region, identify the probable causes for the persistence of the disease in the area and to highlight some of the strategies for prevent recurrence of the event” In paragraph 2 page 7 of the revised manuscript.

3. In the methods, elaborating on standard IDSP methodology used for data collection (Syndromic, Presumptive or Confirmative surveillance.) could have been more useful for understanding of readers who do not have detailed knowledge on surveillance techniques used for epidemic investigation under IDSP.
Thank you very much for the comment. We have added a short description of the IDSP to paragraph 1 page 8 in the methodology section of the revised manuscript which reads as “Dhule is one of the 34 districts in Maharashtra that is implementing the Integrated Disease Surveillance Project (IDSP) since 2005. The system uses syndromic, presumptive and lab confirmation approaches to collect data on cases of 21 priority diseases and syndromes through S, P and L reporting formats respectively from identified public and private reporting units on a weekly basis in both urban and rural areas. The main objective of the system is outbreak detection and response.”

4. In data processing and analysis 1 or 2 sentences could be inserted to enhance clarity. For example. Secondary data “regarding outbreak investigation and response was collected from….,” but the clinical data were extracted from the hospital records”. At the end of the paragraph, a sentence “Frequency distributions showing number and percentages were generated for each identified clinical and non-clinical variables” can also be inserted.

Thank you very much for the valuable comment. We have revised the section (paragraph 1, page 9) and it now reads as “Secondary data regarding outbreak detection, investigation and response was collected from the Integrated Disease Surveillance (IDSP) office in Dhule district. Clinical data on identified treatment and outcome variables was extracted from case reports of suspected and confirmed cases from the PHC and the hospital charts and discharge reports of 11 cases by a consultant physician in general medicine (nine cases treated at the medical college (civil) hospital and two cases at the Kasturba Hospital for Infectious Diseases, Mumbai). The data were entered, cleaned and analyzed in Microsoft Excel 2010. Frequency distributions showing number and percentages were generated for each identified clinical and non-clinical variables”

5. Some typos and spelling mistakes need to be rectified in the edited version.
Like Page 6: 1990′s = Nineties
Page 10, add comma after age. Vaccination status: 2nd line DPT 1 and 2, add DPT 2 in place of 2.
Page 12: Para 1, line 8- Vaccine coverage = Vaccination coverage
Page 13: Para 2, line 1 instated = instituted; para 3, line 3 levels of antitoxin = level of antibodies
Page 14: first line: in India = India; 2nd line: plays = play. Para 1, line 3: School entry leaving= School leaving
Page 16, 2nd line: sulpha ethax azol = sulpha methaxazol

Thank you very much for bringing these to our notice. We apologize for the oversight. All of the points have been addressed in the revised manuscript and changed as per your suggestions.

Discretionary Revisions
1. Page 7– Study area may be mentioned as Peshte village in place of Peshte.

Thank you for the comment we have altered the text in the revised manuscript accordingly.

2. Page 9, last para, line 2- death case = index death case

Thank you for the comment. We have altered the text in the revised manuscript accordingly.
3. There is some lack of coherence in discussion of the study findings…for example paragraphs on age shift, then immunization and again ending paragraph on age shift?…these could be rearranged in proper order. For example; Page 13, para 2 discussion regarding age shift would be more appropriate if shifted to page 12 after para 2.

Thank you for the valuable comment. We have shifted the paragraph to Page 12 as suggested by you.

4. Page 17, para 2 – Surveillance is the key - First two sentences are totally uncalled for.

Thank you for the suggestion. We have deleted the first sentence and moved the second one to a later position in the revised manuscript.

5. Limitations of secondary data analyses could have been specifically highlighted in the context of generalizing this study’s findings to the other district populations which are similar or not similar to Dhule district.

Thank you for the comment. We do completely agree that the findings are specific to the population, but are also of the opinion that there are some lessons that can be learnt from our experience. We propose the sentence “Although the use of secondary data and especially from an outbreak of this size does not allow generalizations to other areas or populations, there are some issues that could be common and help discretionary collateral learning” and have added it to the limitations section of the revised manuscript.

6. Some conclusions are not based on the study findings. There is a tendency to generalize the findings totally out of the box. For example, conclusions A) “Faltering …revitalized” is not at all based on this study findings and B) “Introducing adolescent…on others” is altogether based on findings of the other study.

Thank you very much for pointing these rather broad generalizations we took the liberty to make. We have modified them to look more like suggestions rather than lessons drawn from our study as per your recommendation. The sentences have been changed and now read as “The vaccination programs need to be assessed for efficiency and revitalized to prevent future outbreaks.” and “Introducing adolescent and adult immunization at ten year intervals should be considered as the next step to a long term strategy for the future” in the revised manuscript. We do realize that this may be stretching the conclusions a bit far- but in our opinion these issues are more important to break the cycle of diphtheria in the district. Having a large vulnerable adult population will create future risks for major epidemics like the ones in Eastern Europe. We strongly think that adult vaccination should be offered as a choice to the population even if not implemented as a mandatory strategy.

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.
Reviewer's report:
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 author’s 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.

Thank you very much for appreciating the relevance of our study and providing valuable comments in improving the manuscript and the opportunity to revise it!

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.

   Thank you for the comment. We have added the following text to paragraph 1 page 8, to support your suggestions “Dhule is one of the 34 districts in Maharashtra that is implementing the Integrated Disease Surveillance Project (IDSP) since 2005. The system uses syndromic, presumptive and lab confirmation approaches to collect data on cases of 21 priority diseases and syndromes through S, P and L reporting formats respectively from identified public and private reporting units on a weekly basis in both urban and rural areas. The main objective of the system is outbreak detection and response.”

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.

   Thank you very much for your comment. We have added the following details to the bacteriology section on page 11 of the revised manuscript “Staining techniques included Gram’s staining followed by Albert’s staining. Culture included inoculation using streaking on blood agar medium and blood potassium tellurite agar was used as the selective medium. Antimicrobial susceptibility was tested using Kirby-Bauer (disc diffusion method) with American Type Culture Collection (ATCC) strains of gram positive and gram negative organisms as controls”. All sample collection and laboratory testing was done by qualified technicians and microbiologists and staff of the Government Medical College (GMC), Dhule. The GMC lab is also a Referral
Lab under the IDSP. Internal quality assurance was done using known ATCC strains of gram positive and gram negative organisms. The lab also participates in external quality assurance program for TB, malaria and HIV under national disease control programs.

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.

Thank you for your valuable input. In the first wave of the outbreak only the school children aged 0-6 years were screened. However, in the second wave of the outbreak the screening was extended to all individuals living in the village. The selection of households was also a 100%. We have added the following text to paragraph 10 of the revised manuscript to address your concern: “A short questionnaire was designed and all concerned health staff from the PHC and subcenters were trained in screening and data collection for the house to house survey and the medical camp. All households in the village were covered by three teams and all 2100 individuals in the village at time of outbreak were screened. Positive cases and their contacts were continuously tracked. Additionally other health conditions were attended to during the survey and attempts were made to obtain verbal vaccination history or cards during the visits.”

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.

Thank you very much for the very relevant concern and valuable insight. We have deleted the word “suspected” with relation to cases from the manuscript as it may convey unintentionally that the cases were classified as suspected. We used the WHO standards for diphtheria surveillance which classifies case as:


- **Suspected**: Not applicable
- **Probable**: A case that meets the clinical description of laryngitis or pharyngitis or tonsillitis, and an adherent membrane of the tonsils, pharynx and/or nose.
- **Confirmed**: A probable case which is laboratory confirmed or linked epidemiologically to a laboratory confirmed case (isolation of Corynebacterium diphtheriae from a clinical specimen, or fourfold or greater rise in serum antibody (but only if both serum samples were obtained before the administration of diphtheria toxoid or antitoxin)). Persons with positive C. diphtheriae cultures and not meeting the clinical description (i.e. asymptomatic carriers) should not be reported probable or confirmed diphtheria cases.

We have revised the revised manuscript to reflect the definitions and case classifications accordingly.
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.

Thank you very much for your comment. We have revised the manuscript to clearly define probable and confirmed cases in definitions section of page 8 in the revised manuscript. When the individuals were identified from the house to house visits, the primary health care workers were instructed to identify “suspected cases” (for ease of their understanding) and referring the individuals to the paediatrician and internal medicine consultants who were conducting detailed clinical examination. However, since this can mislead the readers we have now deleted the word “suspected” from the manuscript. Eighty Five of these individuals after detailed clinical examination by a qualified medical personal qualified as probable cases and therefore their throat swabs were taken. Of these ten were swab positive and 3 were culture positives. One case was smear negative but culture positive and therefore 11 confirmed cases were admitted and treated with IV antibiotics and ADS. This explanation and clarification of probable and confirmed cases and their definitions have been added to the bacteriology section of the revised manuscript. We have also added the age and gender distribution of the 85 probable cases to the Table 1 in the revised manuscript and re-calculated the attack rates. We also added the median age and range of the lab confirmed cases to age and gender section on page 12 of the revised manuscript.

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.

Thank you very much for the comment. We did use this website to update the table and the revised table 2 is as under and had been added to the revised manuscript.

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</table>

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.

Thank you for your very valid comment. We did make an attempt to review the immunization registers (R-16) at the PHC which were unfortunately available only for the last two years and were largely incomplete. The District Health officer, District Surveillance officer, Taluka Health officer and the Medical Officer at the Pashte PHC all admitted informally that the vaccine coverage was around 40% in the district which was also the case in the village. However, documentation to support this was unavailable. A cold chain audit was summoned to in November 2011 to assess the actual situation by UNICEF which was later abandoned. We also tried to look at the immunization diaries of the subcenter and PHC staff as they make a note of the vaccines used. However, the records were unreliable and incomplete. Secondly, the age group affected was 5 years to 15 years which would mean that their vaccination history was not possible to obtain in the local system due to poor documentation. Additionally after the outbreak was over when the authors went to collect data individually to the positive cases parental recall was sought and even attempted on the second day, but was very poor. Third, we attempted to get the vaccine coverage data from the National Rural Health Mission (NRHM) Reproductive and Child Health II (RCH II) databases. However, these monitor targets given to each block based on estimated birth cohort. All blocks presented over estimates of targets met making these data useless for our study. This was the only reason why we relied on state and national data only to give an estimate that although progress has been made, sub-optimal success was observed in Dhule district. We have added the following sentence to the vaccination status section on page 12 of the revised manuscript to address your very valid concern “Attempts made to obtain vaccination coverage estimates for the village through the registers at the PHC, vaccination diaries of the subcenter and PHC staff and the National Rural Health Mission (NRHM) Reproductive and Child Health II (RCH II) databases were in vain due to incomplete documentation and monitoring of targets instead of actual number of children vaccinated. Secondly parental recall and vaccination cards were sought during two separate visits but were also very poor.”

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.

Thank you very much for your comment. We have modified the sentence in the background section para 2 in the revised manuscript to read as “There is no standard vaccination schedule...}
for diphtheria although all schedules deliver a primary series consisting of three doses starting
at a minimum age of six weeks with a minimum interval of 4 weeks between doses. The choice for
the timing and number of boosters depends on the other diseases in the combination vaccines
used in respective Expanded Programs for Immunization (EPI) and mainly on the sero-
epidemiology and endemicity of the disease in each country.”

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.
Thank you very much for your comment. The sentence in para 3 has been modified to read as
“Although 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, the disease
remains largely neglected and widely prevalent with periodic outbreaks from over 12 states in
the country” in the revised manuscript.

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?
Yes. The neighbouring district Nashik has a long standing history of diphtheria outbreaks in the
last several years especially in Malegaon (as mentioned in the manuscript). Most patients come
to Dhule civil hospital for treatment as it is about 45 mins on bus to reach. We carefully
examined the records of the Dhule civil hospital for addresses of the patients and noted that this
was the first and the largest outbreak of diphtheria geographically located in Dhule district,
which was also the cause of concern for the District Health Officer and why we investigated this
outbreak.

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?
Thank you for your comment. Yes we did obtain necessary permissions and approvals at the
district level and since the District Health Officer and the District Surveillance Officer were
actively participating in the study the cooperation from all health and non-health staff was
easier. Although no written ethical permissions were taken since we had already obtained
ministry and ethical clearances elsewhere, informed verbal consent was sought at every level
including the village leaders, gram panchayat members and the cases from which swabs were
collected. The village leaders were at the forefront in obtaining the village maps, GIS mappings
and making sure that all households and individuals in the village were covered. We have added
the following sentence “Additionally relevant permissions and consent was obtained from the
District Health Officer, the Gram Panchayat members and the village leaders. Informed verbal
consent was obtained from all individuals from whom swabs were collected.” to the ethics
approval section of the revised manuscript.

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?

_Thank you for bringing this to our notice. The dose of ADS used was 30000 IU administered intravenously. We have this to the para 1 of results in the revised manuscript. “ADS repeated dose over 3 days was done for desensitisation purposes and is clarified accordingly in para 8 of the results section._

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.

_Chemoprophylaxis administered was Azithromycin 10mg/kg body weight for ten days. The dose and duration of chemoprophylaxis for the patients and contacts had been clarified accordingly and the revised text in the manuscript now reads as “ADS was administered to all patients immediately on admission. About 54% of the cases were administered ADS over three days (range one-four days) for purposes of desensitization and dose adjustment. Three children developed mild reactions that included vomiting and puffiness of eyes. ADS was stopped in one child after four test doses. The dose of ADS used was 30000 IU administered intravenously. Mono-therapy with crystalline penicillin (100000IU/kg) and in cases of resistance or intolerance Azithromycin (10mg/kg) was included in the regimen. The duration of antibiotic therapy was ten days in seven cases and seven days in two surviving cases. One case (documented history of primary immunization) was treated with IV antibiotics for 14 days. Only two cases were vaccinated before discharge due to unavailability of the DT vaccine. Chemoprophylaxis with Azithromycin (10mg/Kg body weight) was administered to all contact cases for three to ten days”._

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.

_Thank you very much for the valid comment. We apologize for the non-clarity of case definitions and classifications used in the manuscript. As stated in our response to query 5, 85 probable cases were identified by the medical personnel and swabs were taken. Of these ten cases were smear positives and one case was smear negative but culture positive. Two other cases were culture positives making a total of ten smear and three culture positives and eleven lab confirmed cases. The median age of the ten smear positive cases was 11 years (range 5-15 years) and that of the three culture positive cases was 12 years (range 6-13 years) and has been added to the age and gender distribution section on page 11 of the revised manuscript._

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).

_Thank you for the comment. We have added the following sentence to the age paranoia section of the revised manuscript “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. Age shift has also been documented before mass immunizations were instituted”._
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. 

Thank you very much for the comment. We have modified the sentences in para 2 of discussion in the revised manuscript accordingly and they now read as “The need to revise the UIP is urgent and has been discussed before. Adult boosters at ten year intervals are currently non-existent in the country and should be considered vis-a-vis the resources availability and the urgency. DT booster at school entry and leaving should be considered to cover adolescents. Serological studies for antibody titres in adults and adolescents should be done to identify the need, timing and number of booster doses for the district”.

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.

Thank you for the comment. We have changed the word adequate to previous in the revised manuscript.

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”.

Thank you for all the valuable comments. We have updated the limitations section and it now reads as “We report data for one particular outbreak especially when diphtheria is endemic in the district with sporadic cases reported for several years. Immunization history and vaccination cards were unavailable in majority of cases despite attempts made to recover vaccination cards. Parental recall was also poor. Strain identification and toxigenicity testing was not possible due to sample contamination. Although the use of retrospective secondary data and especially from an outbreak of this size does not allow generalizations to other areas or populations, there are some issues that could be common and help discretionary collateral learning. Better documentation of the onset, progress and control of outbreaks in the district is necessary to allow institutional learning” in the revised manuscript.

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.

Thank you very much for pointing these generalizations to us. We have modified them to look more like suggestions rather than lessons drawn from our study. The sentences have been changed and now read as “The vaccination programs need to be assessed for efficiency and revitalized to prevent future outbreaks.” and “Introducing adolescent and adult immunization at ten year intervals should be considered as the next step to a long term strategy for the future” in the revised manuscript. We do realize that this may be stretching the conclusions a bit far- but in our opinion these issues are more important to break the cycle of diphtheria in the district.
Having such a large vulnerable adult population will create future risks for major epidemics like the ones in Eastern Europe. We strongly think that adult vaccination should be offered as a choice to the affording population even if not as a mandatorily implemented strategy.

**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. Thank you for the comment. We have revised the manuscript for language corrections.

**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.