Author’s response to reviews

Title: Necrotizing Fasciitis following measles vaccine administration: A case report

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Author’s response to reviews:

World Health Organization
Ondo State Field Office
Akure, Ondo State, Nigeria

6 February 2019.

The Editor-In-Chief,
BMC Infection Disease

Dear Sir,

Re: Covering Letter for Revised Article being submitted for Publication
This is to confirm that a revision has been made in line with the guidelines given by the reviewers for our article titled "Necrotizing Fasciitis following measles vaccine administration: A case report". Changes made are highlighted in the text of the manuscripts as directed.

A table showing the query by the reviewers and how we have dealt with the query, including the changes in the manuscripts is provided below.

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Karina Top (Reviewer 1):

1. This manuscript reports a concerning case report of necrotizing fasciitis following measles vaccine that was attributed to bacterial contamination resulting from improper vaccine handling practices (use of vaccine reconstituted >6 hours prior). A second child (of 3 in total) receiving the same vaccine on the same day developed an abscess at the site. The investigation and causality assessment is briefly described. No information on the outcome of either child is presented.

A key takeaway that deserves greater emphasis is that infectious complications following immunization should prompt investigation and follow up of other patients vaccinated in the same clinic (as was done). The manuscript would be strengthened by condensing (or removing) the general descriptions of NF and AEFIs, and expanding on the details of the ensuing investigation and causality assessment process. Further details on the clinical presentation of the child with abscess (if available) would be helpful.

The manuscript contains numerous typographical and grammatical errors, and would benefit from careful review by a colleague with strong writing skills in English.

-We sincerely appreciate the reviewer for the positive comments made about our article and the article has been reviewed in line with these comments.

The outcome of the case and other children have been included as suggested. Line 70-71, 81-88

The general description of AEFI have been removed as suggested and the aspect of causality assessment expanded based on data available during the investigation. Line 74-102

The available details of the second child with abscess have been included. The child had with very mild clinical presentation. Line 82-84

Tis has been done with comments of other colleagues addressed likewise.

2. Major comments
Abstract:

1. Line 28-30: "The incidence of cases of AEFI is very significant" - This implies that vaccines are unsafe and could unnecessarily alarm healthcare providers and the public while providing fuel for anti-vaccination advocates. Please reword to clarify the main point which seems to be that AEFIs are usually mild and serious adverse events are rare.

2. Lines 52-54: "...which could have been caused by incorrect use of...measles vaccine": This conclusion is not supported by the information in the case presentation which does not mention the investigation into the cause of the necrotizing fasciitis, such information would be important to include in the abstract.

Comments have been removed as suggested by the first reviewer

Thank you for your suggestion we have included the statement on causality assessment in the abstract to justify the conclusion (Line 21-23)

3. Background

1. Lines: 42-55: The definition of what an AEFI is, the differential diagnosis for what can cause an AEFI, and description of mild AEFIs could be condensed significantly since many of the details are not relevant to this case.

Case presentation

1. Line 42: Were cultures taken of blood or tissue to identify the causative organism? If so, please provide results.

2. Was any follow up information available on the child's outcome?

Causality assessment

1. Lines 12-16: was the measles vaccine dispensed and reconstituted in a multi-dose vial or single dose? Was there residual reconstituted vaccine available for culture? Was the diluent cultured for bacteria? If so, what were the results?

2. Lines 12-13: What framework was used for assessing causality (e.g., WHO algorithm)?
3. Lines 15-16: Please indicate how long the vaccine had been reconstituted at the time each of the three children was vaccinated, if known. How was the reconstituted vaccine stored between patients?

We have totally removed this section has suggested as we have realized it is not relevant to the write up.

Blood was taken for culture by the attending physician in the local hospital where the case was initially managed before referral to a teaching hospital but this was not properly handled by the lab officials with contaminated culture plate resulting from the test (Line 102-105). Follow up information have now been included as this was not available at the initial stage of writing this draft (73-75).

Thank you for this comment. Measles vaccine in Nigeria is reconstituted in Multi-dose vial however, empty vial of the measles vaccine used was already discarded as at the time of visit to the hospital for investigation has culture was not done (Line 100-103). Also, WHO AEFI causality assessment methodology was used. (Line 80)

This have been included (Line 95-97)

L Discussion

1. Lines 49-50: Was Staphylococcus aureus isolated from the diluent/vaccine or from either child? If so, this should be stated in the causality assessment or case presentation sections not the discussion. If S. aureus is the presumed (but not proven) cause then this should be stated.

2. Instead of focusing on NF in general (e.g., risk factors, presentation), consider discussing the range of complications that can result from vaccines contaminated with bacteria, how frequent such cases are, etc.

This statement have been rephrased as suggested (Line 123)

This was well highlighted in Line 111-122

5. Minor comments

1. Please insert page numbers.
2. Background, Lines 28-32: "Vaccination of children at 9 months for routine immunization... however, in some occasion, cases of adverse events..." - This sentence is repetitive, unclear and overly complex. It needs to be reworded split into at least 2 sentences.

Suggestion has been noted and correction have been done (Line 43-44)

Nigel W Crawford (Reviewer 2):

1. Abstract line 1: Background (sp)- would remove the comment around incidence and generic AEFI.

This is a case report that reports a serious AEFI. It does not provide incidence data and the focus should be on appropriate management - as detailed on this case.

This was sighted by the 1st reviewer and section on AEFI have been totally removed from the write up. Also, in Nigeria, there is no data showing the incidence or trend of AEFI cases over the years hence we might not be able to provide the data as suggested.

2. Regarding the case details: more clinical information is required:

Clinical signs (HR, RR, BP)

This have been included Line 58-60

3. Investigations: Blood culture, blood tests (FBC etc. if available)

Where any swabs taken in theatre

Blood was taken for culture by the attending physician in the local hospital where the case was initially managed before referral to a teaching hospital but this was not properly handled by the lab officials with contaminated culture plate resulting from the test (Line 102-105).

4. Discussion:

Investigation: Was it a multi-dose measles vaccine vial?

Did they test any of the vials for contamination?
Also need to consider alternative pathogens (e.g. Invasive group A strep) review medical management (e.g. clindamycin) additional reference: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4286984/ 

Thank you for this comment. Measles vaccine in Nigeria is reconstituted in Multi-dose vial however, empty vial of the measles vaccine used was already discarded as at the time of visit to the hospital for investigation has culture was not done (Line 100-103)

Reference 12: WHO causality assessment a real strength of the paper, need to give the direct link http://www.who.int/vaccine_safety/publications/gvs_aefi/en/

Done

If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage The manuscript was given to several medical colleagues to review the and all suggestion and correction made have been effected. Although we did not engage the any Research Editing Service for this exercise but if the editor-in-chief is not still satisfied and still insist then we will.

Yours sincerely,

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