Author's response to reviews

Title: Outbreak of viral hemorrhagic fever caused by dengue virus type 3 in Al-Mukalla, Yemen

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Version: 2 Date: 5 February 2013

Author's response to reviews: see over
6 February 2013

The Editor, BMC Infectious Diseases

Re: Manuscript ID: 1698722919783709

Article Title: Outbreak of viral hemorrhagic fever caused by dengue virus type 3 in Al-Mukalla, Yemen.

Dear the Editor

Thank you very much for giving us the opportunity to revise the above mentioned manuscript.

The reviewers' comments were valuable indeed and were carefully followed to revise this manuscript. Please, find attached the revised version of the manuscript with the changes made tracked. The following are the authors’ responses and the changes made point by point according to the comments of the two reviewers.

We hope the revised manuscript satisfies your expectation to be published in the Journal of Infection.

Thank you

Corresponding author

Tariq A. Madani

Reviewer: Paolo Ravanini
MINOR ESSENTIAL REVISIONS:

1. Methods, Laboratory confirmation:

In the last sentence, the authors write that the samples were tested with RT-PCR for ALKV, RVFV, CHIKV and YFV. The cited article (Drosten et al) describes a method to test for several haemorrhagic fevers, but it doesn’t include ALKV and CHIKV. The authors should indicate how they performed the RT-PCR for ALKV and CHIKV (method used or cited reference).

Response:

In response to this comment, two new references were cited to describe how ALKV (reference 7) and CHIKV (a new reference numbered 15) were performed. As a result of inserting the new reference (numbered 15), the original references number 15 to 20 were renumbered 16 to 21.

2. Discussion, second paragraph:

It is acceptable to write that the presence of IgG positive specimens in more than half of the acute patients (within 7 days after the onset of illness) can suggest a previous exposure to other DENV serotypes, but the authors should emphasize that this doesn’t rule out completely the possibility that these positivities are due to the appearing of a low IgG titre at the end of the first week of illness. To clarify this aspect, it is interesting to know if there are data about the titre of these positivities and the days elapsed after the onset of illness (how many of these positive acute samples were collected in the first few days after the onset).

Response:
The following sentence was added to the end of the 2nd paragraph of the Discussion "It should be noted that some of the IgG positive results of the 181 patients with acute dengue might have represented early development of IgG response at the end of the first week of acute dengue infection rather than previous exposure to another dengue serotype."

Unfortunately, data about the titer of IgG positive serologies and the days elapsed after the onset of illness is not available.

DISCRETIONARY REVISIONS:

1. Methods, The Outbreak Region:

This part includes some unnecessary information about the geographical region, which could be replaced by a map figure to shorten the text.

Response:

We preferred to describe the geography and weather in text rather than a map to be able to emphasize details pertinent to dengue fever which is known to be endemic in certain pockets in tropical and subtropical countries where the number of cases of dengue fever correlate with weather conditions, including minimum and maximum temperature, wind velocity, humidity and rainfall.

2. Discussion:

The authors could say if they have in mind to sequence in the near future the two positive samples (or the amplicons) to obtain further phylogenetic and epidemiological information about the virus.
Response:

The following sentences were added to the end of the first paragraph under the Discussion section: "DENV-3 was confirmed to be the cause of the dengue outbreak described herein. Sequencing of the two positive samples, intended to be performed by the authors in the near future, will provide phylogenetic and epidemiological information about the virus."

MINOR ISSUES NOT FOR PUBLICATION:

1. Methods, The Outbreak Region:

The area of the city of Al-Mukalla should be indicated as square km, not simply km.

Response:

Km was corrected to Km²

2. Methods, Laboratory confirmation:

It is not perfectly clear in the text the use of the different primers. The problem can be solved changing this part of the second sentence: “... 1 mM of the 5’ primer D1, D2 and 3’ primer TS1, ...” should be modified to “ ... 1 mM of the 5’ primer D1 and 3’ primers D2 and TS1, ...” (according to the work by Lanciotti, the D2 primer is a downstream primer, as primers TS1-4 are, while the primer D1 is the unique upstream primer)

Response:

Corrected as suggested
Reviewer: Matthias Niedrig

The manuscript from Madani et al. describes a DEN 3 outbreak in Yemen in 2010. Since information on such outbreaks in this region are rather rare this report is interesting for some readers. As the information provided by the article are rather limited a short communication or note should be considered as more appropriate if supported by the journal.

Response:

BMC Infectious Diseases does not consider short report

However the manuscript could be improved by some changes.

The information of Tab. 1 is presented in the text. Therefore tab. 1 could be deleted.

Response:

Table 1 was omitted as suggested by the reviewer from the first paragraph of the Results section; and tables 2-4 were re-numbered 1-3. At the end of the first paragraph of the Results section the sentence "No other hemorrhagic fever viruses RNA were detected" was replaced with "RT-PCR of the 222 human specimens was negative for ALKV, RVFV, CHIKV, and YFV RNA."

Discussion

Sentences with rather common information with no direct impact on this finding should be deleted.

for example: "Previous exposure of a person to a DENV..." " Dengue virus genome, which is 11 kilobase.."
Response:

The following sentence was removed from paragraph 2 of the Discussion as suggested by the reviewer: "Previous exposure of a person to a DENV serotype increases the risk of complications with subsequent exposures to other dengue serotypes, a phenomenon known as Antibody-Dependent Enhancement or Immune Enhancement Syndrome."

The next sentence was rewritten as follows: "In this study, more than half (55.2%) of the patients with acute dengue had serological evidence (positive for DENV IgG) of previous exposure to this virus suggesting that more than one serotype are circulating in the region, thus increasing the risk of complicated dengue through a phenomenon known as antibody-dependent enhancement or immune enhancement syndrome."

The following sentence and reference 21 were removed from paragraph 3 of the Discussion section as suggested by the reviewer: "The structure of DENV has direct influence on the methods used for its early diagnosis. Dengue virus genome, which is 11 kilobase (kb), single stranded, positive-sense RNA molecule, codes for three structural proteins designated C (core), M (membrane), and E (envelope) proteins; and seven non-structural (NS) proteins designated NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5. Accordingly reference number 21 was deleted.

Conclusions

limitations should be replaced by proper

.... proper storage and transportation conditions for specimens are missing.

Response:
This was revised as recommended. The statement now reads as follows "It is important to use both IgM and NS1-antigen tests to confirm acute dengue particularly under the adverse field conditions, where proper storage and transportation of specimens are missing, which substantially reduce the sensitivity of RT-PCR for detecting DENV RNA."