Author's response to reviews

Title: A guidance for contact tracing of plane passengers with the Viral Haemorrhagic Fevers Lassa, Ebola or Marburg Results of an European expert consultation

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Author's response to reviews: see over
Feedback on the comments received on the article: “A guidance for contact tracing of plane passengers with Lassa, Ebola or Marburg Viral Haemorrhagic Fevers, Results of an European expert consultation”

Reviewer 1:
1. Background
I suggest providing the figures to support the statement that travel from and to Africa has increased substantially. Although the numbers of travelers have increased, I doubt that this contributes to the risk of acquiring VHF. One does not simply get infected with one of the viruses causing VHF during a touristic stay in an endemic country. It is the increased risk of significant exposure (medics and paramedics working in hospitals, adventurous destinations with possible exposure to bats, etc) that contributed to importation of cases with VHF in Europe and the US.

- The increase of tourists traveling to Africa has been added.
- Statistics of number of medical helpers and adventurous tourists in Africa are not available, therefore I could reference this suspicion, but I tried to include it in the text as such.

Move the information about the RAGIDA project to the Methods section
- The overall RAGIDA project is the background of our expert consultation. It was not part of our own work. Therefore I believe that the background is the best place to mention it.

2. Methods
This article would benefit from a more systematic description of the methodology. I suggest to present shortly the RAGIDA project followed a step-by-step description of the literature searches, selection of the evidence, composition of the panel and consensus procedure.

- The literature review was done in RAGIDA part 1 and is described there. I clarified that in the article. The members of the panel are mentioned in the acknowledgments.
- The systematic review covered over 3,700 peer-reviewed articles and grey literature for the following diseases: tuberculosis, influenza, severe acute respiratory syndrome (SARS), invasive meningococcal disease, measles, rubella, diphtheria, Ebola and Marburg haemorrhagic fevers, Lassa fever, smallpox and anthrax. In addition, general guidelines on risk assessment and management from international aviation boards and national and international public health agencies were systematically searched. Experts were interviewed on case-based events by standardised questionnaires. Disease-specific guidance documents on tuberculosis, SARS, meningococcal infections, measles, rubella, Ebola and Marburg haemorrhagic fevers, Lassa fever, smallpox and anthrax were the result of consultations of disease-specific expert panels (cut and paste from Eurosurveillance article)

3. Results
In the section over “Guidance” I would like to read something about the dilemmas in reaching consensus. For instance: what is a symptomatic case? The authors refer to symptomatic cases as an important condition to consider contact tracing, to which I completely agree. But, in the very early stages symptoms can be very aspecific. How to deal with this problem in practice?

- I added in the discussion, that also non-specific symptoms should be considered.

Reviewer 2
Major revisions:
1. Title – should specify that this is a European review and that it focuses only on 3 of the many viral hemorrhagic fevers. Suggest "A guidance for…with certain
Viral hemorrhagic fevers; Results of a European expert consultation

- The title is changed

2. Abstract – needs review by an editor or native English speaker. For example, in the results section – “plus if” is unclear. Do the authors mean “and” or “or”? Conclusion – last sentence appears to contradict all that precedes it. If all should be decided on a case-by-case basis what is the value of this guidance? What is “all relevant information”? Something besides the information included in the algorithm?

- It is meant, that the document is just guidance and cannot consider all possible factors/contexts, therefore the final decision on the scope of contact tracing will always remain with the respective responsible nationals/officials, who can decide to vary from the guidance. I tried to change the wording to make it better understandable.

3. Background – this is lightly referenced for such a guidance document. Why was there no review of other hemorrhagic fever transmission (South American arenaviruses, CCHF, and importantly dengue)? What about the experience with other airline transmission events? The experience with SARS, influenza, TB, and others is relevant. SARS especially had many many flights with passengers infected that resulted in no apparent transmission. A conclusion similar to this one would have been logical on this basis, except for the one flight from Hong Kong to Beijing on which for some reason there was abundant transmission, to more than 20 other passengers and crew, resulting in 5 deaths. Such an experience highlights the need for humility and caution in drawing conclusions about minimal risk based on very limited exposure events.

- I agree. The other diseases are covered by other expert groups within the RAGIDA project and reported there.

- Members of the ECDC Advisory Forum (representatives of national health institutes of the EU MS) agreed on the following priority diseases for the RAGIS+DA project: TB, SARS, meningococcal disease, measles, rubella, diphtheria, Ebola haemorrhagic fever, Marburg hemorrhagic fever, Lassa fever, smallpox, and anthrax......

- We already included for the Marburg and Ebola information about transmission in other settings to advice the guidance. The expert group based their guidance on the existing evidence for the three VHF. If an event will occur in future, that provides new evidence the guidance needs to be reviewed.

4. Results – were the 9 incidents of Lassa only those with importation to Europe? Were there other incidents for passengers traveling elsewhere?

- One Incident was on a flight via Europe to America, this is mentioned in the text. No other events could be found in the literature review.

5. Results – Marburg – citing the WHO fact sheet as an information source is particularly weak. Is there no original source material on which that fact sheet was based?

- The fact sheet of WHO is not citing other sources. But I add another support of the information by Bausch et al.

6. Discussion, paragraph 3 – need more guidance on the restriction to follow laboratory confirmation. What if this will take many days or is not possible? What minimum delay should be tolerated in making a trace-back decision?

- This is covered both in the algorithm and in the text in Discussion. The expert group considered a laboratory confirmation as important to advice on starting a trace back in light of the lack of evidence found for transmission and the huge work load related with a trace back. However, if a laboratory confirmation is delayed or not possible, it is
7. Algorithm – The requirement for “body fluid” exposure seems critical and likely to exclude most potential flight circumstances, unless sweat is included as a body fluid. If so, then it would seem that any touching of the patient would qualify, and would require much more extensive trace-back since it would be difficult to know without interviews who might have touched the ill person. Should specify in the box and text whether sweat is intended to be included.

- *Only for Lassa sweat is excluded, this is why for Lassa contact to other body fluids is necessary, for Ebola and Marburg the contamination of sweat cannot be excluded and therefore not explicit contact to body fluids are necessary This is already explained in the table in the section “effective exposure”.*

Reviewer 3:
Major Compulsory Revisions
1. Discussion, 1st paragraph: The statement I object most strongly to is the statement “no treatment is available for Marburg and Ebola infections”. This is wrong. Marburg and Ebola patients who accept hospital care systematically receive supportive and symptomatic treatment, which alleviates their suffering and may improve their chances for survival. In the only filovirus outbreak where patients received intensive care to the standards of industrialised countries (Marburg HF 1967 in Germany and Yugoslavia), case fatality was much lower than in African filovirus outbreaks (20% vs. 50-90%) – this may have had several reasons, but we can in no way rule out that better, more intensive care improves the patient’s chances for survival. The reason why I object strongly to this statement is that it has caused a lot of damage in the field, because it has undermined the willingness of cases and their relatives to accept hospitalisation and isolation. We should avoid propagating the demonising myth that there is no treatment or cure for Ebola and Marburg HF. It is, however, true that there is no antiviral or causal treatment for EHF/MHF. This is in itself not so unusual – there are many diseases for which causal treatment is not available or not used (e.g. dengue, cholera), and where supportive treatment makes has a considerable on the outcome. For Lassa fever, not only treatment exists, but it includes an antiviral drug, ribavirin. Thus, for Ebola, Marburg and Lassa alike, the “reasons of starting a contact tracing should be to raise awareness and prevent onward transmission” and to initiate optimum care as early as possible.

- *Thank you for pointing that out. I clarified this in the article.*

2. Referencing should be reviewed, as on many occasions, references do not point to the original research papers but to articles citing such research (and occasionally, not even that). For example: in table 1, one reference for the statement “Ebola virus has also been detected in sweat” is the Bausch et al. paper on “Risk factors for Marburg HF”, in which no information on whether or not Ebola virus is contained in sweat can be found. In another example, the statement “nonhuman primates and bats are recognised sources of infection” is referenced by reports on the importation of Marburg cases to the Netherlands and the US, which have, understandably, not added any new information on the sources of primary transmission of Marburg virus. This is not considered good practice, since it risks perpetuating errors in the literature if the first paper cited the original paper wrongly. I am under the impression that citing secondary literature has occurred on many occasions, so please review thoroughly. By the way: a helpful document to locate original research papers is Kuhn’s book “Filoviruses. A compendium of 40 years of epidemiological, clinical, and laboratory studies”.

- *I am sorry, I mixed the two Bausch citations. It is corrected now.*
I reviewed the references and tried to refer to the original papers.

3. Table 1: Ebola: “Evidence indicates to bats as one of the reservoir of Ebola [35]. Also contact with primates has been reported in Ebola cases [36, 37].”

Marburg: “The reservoir of Marburg is not known, nonhuman primates and bats are recognised sources of infection”. I do not understand why the authors treat Ebola and Marburg differently with respect to the reservoir to be known or unknown, since for both diseases filovirus has been found in wild bats, which is a strong indication for bats being the reservoir (for Marburg: Towner JS et al, 2009. Isolation of genetically diverse Marburg viruses from Egyptian fruit bats. PLoS Pathog 5: e1000536.) Nonhuman primates, however, are considered widely to be accidental hosts for both filoviruses, given the very high case-fatality of Ebola and Marburg infection in non-human primates.

- I added this citation and rewrote the paragraph.

4. Table 1: Ebola: “Also contact with primates has been reported in Ebola cases [36, 37].” The list of species who have reportedly been sources of primary includes cephalophus antelopes (Formenty P et al, 2003. L’épidémie de fièvre hémorragique à virus Ebola en Republique du Congo, 2003: une nouvelle stratégie? Med Trop (Mars) 63: 291–295.).

The list of species associated with human Ebola cases has been updated.

5. Table 1: Ebola: “Big outbreaks have been reported in hospital settings.” Again, it is unclear why Ebola is being treated differently from Marburg: in both major African Marburg outbreaks, transmission has occurred in hospital settings to patients and staff, and in Uige/Angola, nosocomial amplification can even be considered as major driving force of the outbreak. Considerable outbreaks in hospital settings have also occurred for Lassa fever. It is misleading to mention nosocomial transmission/amplification for Ebola only. By the way: “Big” should probably read “Large” – to be discussed with a native English speaker.

- Hospital outbreaks have been added to the other VHF as well with a reference.

- Minor Essential Revisions

1. The paper is well written, but could still profit from careful editing by a native speaker. At times, the syntax is unnecessarily complicated, and there are a few errors as well. Examples: “Often this public pressure influences the decision on public health measures, such as passenger trace back more than the existing evidence” (insert comma after “back”); “evidence for disease transmission but also wider aspect including disease severity…” (replace aspect by aspects); “the severity was not considered as a criteria” (replace criteria by criterion); “However, the airline should be contacted to enquire whether crew members remembered or recorded any incidents on board which might have resulted in potential exposures to crew or passengers and the availability of the passenger manifest while awaiting the laboratory result.” – does this mean that crew members and passengers involved in such incidents should be contacted and their availability for further investigation assured?

- Suggestions were included

- It was suggested by the expert group to start investigating special events during a flight with the crew, while waiting for the results of the test.

2. Results, Literature review, EHF, 1st paragraph: personal communication by whom?

- Has been deleted

3. Results, Literature review, EHF, 2nd paragraph: “risk of transmission may increase with transition to later stages of the disease” not only because of rising
virus titres, but because of increased virus shedding: patients with fever, 
headache and muscle ache excrete less body fluid and do so more controllably 
than patients with vomiting and diarrhoea.

- Added in the text.

4. Abstract: Instead of “resulting in very little evidence of transmission of VHF 
during air travel”, write “so that no evidence of transmission of VHF during air 
travel exists to date.” Instead of “Little evidence has been found for the 
transmission of VHF in airplanes” write “No evidence has been found …” 
Transmission may have occurred, but evidence does not exist (as opposed to 
little evidence exists).

- Added in the text.

- Discretionary Revisions

1. Title: since this paper deals with Lassa fever, Ebola and Marburg 
haemorrhagic fever and not with the many other types of HF, the title should be 
more specific.

- Title adjusted

2. Disease caused by Lassa virus is usually called Lassa fever, not Lassa 
haemorrhagic fever. The authors should adhere to this convention since 
deviating from it might lead to the misunderstanding that their paper deals with 
haemorrhagic cases of Lassa fever only – and I don’t think that was the authors’ 
intention.

- Corrected in the text, when Lassa was mentioned.

3. Background, 2nd paragraph: I suggest to add “and has led to secondary 
transmission in the country of destination only once” so that the complete 
sentence reads: “Although the air transportation of a passenger suffering from a 
VHF is rare and has led to secondary transmission in the country of destination 
only once, the severe potential outcome of the disease and the public perception 
of its infectiousness result in high public attention, sometimes even panic.” This 
gives a more accurate idea of the risks involved. The addition refers to the 
exportation of Ebola HF from Gabon to South Africa, a possible reference would 
be “Ebola haemorrhagic fever - A summary of the outbreak in Gabon. Wkly 
Epidemiol Rec 72: 7-8.”

- Added in the text.

Reviewer 4:
I do not believe that the paper in the current version is suitable for publication on an peer- 
reviewed international journal as it is in the present form. 
My belief is due to:
1. The paper does not represent an original unpublished research/data. It is in fact an extract 
from guidelines which was already published by ECDC on 2009 (revised in 2011) and 

- We made it clear in the cover letter and the background, that the guidance was 
published in an ECDC Report. However, this is not a peer reviewed publication. It is 
very difficult to find the report in the web, and therefore the aim of the article is to 
“advise a wider scientific and public health community and other relevant 
stakeholders on the decision to implement a passenger trace back and indicate the 
scale of the response.”

- The editorial team had earlier suggested to change the article to the type 
“correspondence” (“An article that may not cover ‘standard research’ but that is of 
general interest to the broad readership of BMC Public Health”), I believe that is in 
line with the suggestions of the reviewer.
2. The paper does not meet the standard criteria for “systematic review” or “guidelines” reporting; to be worthy of being published in a peer-reviewed paper, the report would need to at least a more formal description of methods for systematic review; I do suggest to apply “PRISMA-statement”, as also suggested by BMC-Public health editorial policy see at http://www.biomedcentral.com/bmcpublichealth/about;

- The type “correspondence” should be in line with the suggestions of the reviewer.

3. At least a more formal description of methods for systematic review; I do suggest to apply “PRISMA-statement”, as also suggested by BMC-Public health editorial policy see at http://www.biomedcentral.com/bmcpublichealth/about; The type “correspondence” should be in line with the suggestions of the reviewer.

4. At best a transparent description of guidance production; this include the list of expert involved and the way they used to reach consensus for each specific issue (in this case authors might have a look to EQUATOR-statement).

- The experts are listed at the end of the article and the method is described.

In my opinion the author could decide to either to write an editorial/letter to explain the relevance of the RAGIDA’s work (in this case the paper should focus on the most relevant aspect of RAGIDA network) or to produce a formal systematic review/guideline (in this case expand methods and results in order to meet at least PRISMA statement’s requirement). I report below my remark in details by section (please consider all remarks as “major”)

- The type “correspondence” should be in line with the suggestions of the reviewer.

Background

- Second paragraph :“In 2010, 5.04 billion passengers arrived and departed from 1318 airports worldwide, nearly half of them on international flights [1].” Please provide updated figures for 2011.

- The data for 2011 have not been published yet. ACI announced publication for August 2012.

- Second paragraph: “Although the air transportation of a passenger suffering from a VHF is rare, the severe potential outcome of the disease and the public perception of its infectiousness result in high public attention, sometimes even panic. Often this public pressure influences the decision on public health measures, such as passenger trace back more than the existing evidence.” To my knowledge, in EU there was no major event of VHF transmission due to air transport, nor did events of “panic” occur in EU due to fear of VHF outbreak. In fact, in my opinion, there is not a strong perception of the potential risk of VHF in public opinion. Please remove the statement or provide evidence for it.

- Media attention can be quite high, but panic is too much, that is right, I deleted the part of the sentence.

- Second paragraph: “Absence of guidance documents to help the decision on necessity and scale of the trace back contributed to this variation.” Actually full RAGIDA guidelines has published this since 2009 by the ECDC. This guideline are periodically updated, open access and contain the same data here reported. To me there is no reason to duplicate publication of a short extract of them on a peer-reviewed journal.

- See above: the guidance is wider accessible if available through literature search and pubmed.

- Third paragraph: “This article will report on the recommendations of the expert panel on the VHFs Lassa, Ebola and Marburg hemorrhagic fevers in order to advise the wider scientific and public health community and other relevant stakeholders on the decision to implement a passenger trace back and indicate the scale of the response.” (see above)  

- See above

Methods

I believe that author should decided either they are going to publish an original paper or an editorial/letter about their work in RAGIDA network. In case they are going to publish an original paper please:
1. Describe systematic review procedure, this should include research strategy and the way of literature analysis. For a detailed description of systematic review reporting please (see general issue above).
   - *The literature review was based on the work of RAGIDA I, and described there and published in the Eurosurveillance article*

2. Describe the way the expert reach consensus and provide a list of all participants with their position. This will make the report more transparent.
   - *I added in the methods, that the participants are listed at the end in the acknowledgments.*

In case the authors are going to publish an editorial/letter about the relevance of RAGIDA network they needn’t methods and results sections.

Results
   - *Correct, as the article wanted to report of the outcome of the expert meeting.*
   - *This was a consensus document – so should not be changed....*

2. Being this the result of a systematic review the overall number of publications retrieved and the selection process should have been shortly described. I suggest to produce a flow-chart to describe the search and selection process.
   - *The literature review was based on the work of RAGIDA I, and described there.*

Guidance
1. Being this a guidance for diseases specific intervention to be implemented in the real life a clear case definition should be explicitly reported. I would eliminate table 1 and report proper case definition and proper case-contact definition instead. In particular author could consider to depict specific scenario. In fact, as reported by the WHO, and proved elsewhere (New Microbiol. 2009 Oct;32(4):359-67), case definition for VHF have low sensitivity and specificity and they may need to be adapted for different specific scenario.
   - *The expert group decided that including one clear case definition was not possible, to account for the difference in the national existing case definitions.*

2. There is no mention of the use of molecular technology for case identification. Nevertheless the paper addresses specifically only 3 VHF pathogens.
   - *To allow the different diagnostic standards to be used in the different countries, a specific description of laboratory technology for diagnostic was not included.*

3. There is no mention on how the case-contact tracing should be performed.
   - *This is just a guidance on the decision on implementing a contact tracing for VHF. Contact tracing itself is described somewhere else and not specific for VHF.*

Discussion
- First paragraph “But other facts have to be considered as well, such as: no treatment is available for Marburg and Ebola infections; hence reasons of starting a contact tracing should be to raise awareness and prevent onward transmission.” This is an arguable statement. In fact, even though no standard treatment for Ebola and Marburg is available by now, relevant experimental experience has been recently published (BMC Medicine 2012, 10:31). In addition if a standard effective treatment were available, given the severity of VHF by Ebola and Marburg the contact tracing would be even more urgent for
preventing the contact to became case and eventually die and/or produce additional cases.

- The respective paragraph is revised taking this and the comments of reviewer 3 into consideration.

- Second paragraph “In the absence of specific incidents involving body fluids, the use of a toilet by the index case is not considered as a risk and therefore would not be considered in the contact tracing.” I’m not sure that the common use of toilet represent a negligible risk. First of all, you should assess if “specific incidents involving body fluids”, such a vomit episode, happened or not, and you should ask to the patient about it. This indication should be added in your paper as part of the decisional process. Moreover, you do not give any indications on actions to be done if the incident with body fluids happened. In this case, do you trace all passengers? Furthermore, even in absence of this specific accidents, during a not accurate use of the toilet you can contaminate your hands with urine or faeces, and after contaminate common surfaces, especially in a airplane toilet where the spaces are very limited. The common use of the toilet is in my opinion more significant than being seated a +1/-1 seat. I perfectly understand that this makes the contact tracing more complex, but I think that, if you really believe that the common use of toilet is not at-risk, you should better motivate/explain this.

- The expert group discussed this issue and came up with the presented conclusion.

- Third paragraph “We recommend trace back to be initiated following laboratory confirmation of the diagnosis. However, the airline should be contacted to enquire whether crew members remembered or recorded any incidents on board which might have resulted in potential exposures to crew or passengers and the availability of the passenger manifest while awaiting the laboratory result. This will facilitate prompt actions should VHF be confirmed. If a diagnosis cannot be laboratory confirmed in a timely manner, contact tracing should be considered if evidence is strongly suggesting VHF as the likely cause of disease in the index case.” This should have been reported in details in the guidance section (see also guidance remark 2 and 3) as all the above are recommendation and not the discussion of results. In addition first statement is in contrast with the recommendation reported in the table which suggest to start contact-case tracing also for probable case (see first line in the table). I suggest to the author to consider to include a specific sub-section for action to be taken in guidance section. In particular this sub section should include laboratory diagnostic and advice on how the case contact tracing is to be done.

- See above: This is just a guidance on the decision on implementing a contact tracing for VHF. Contact tracing itself is described somewhere else and not specific for VHF.

- The issue with timely confirmation is not possible is mentioned in the algorithm and in the discussion part.

Duplicate publication

- We made clear in our cover letter and in the introduction that this article is reporting of the guidance that has been produced by the expert group and published in an ECDC report. As the type has been changed to “correspondence” it might be better acceptable for the reviewer to have it published in BMC Public Health to make it available to a wide scientific audience.