Author's response to reviews

Title: Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis

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Version: 2 Date: 3 June 2010

Author's response to reviews: see over
Reviewer’s report

Title: Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis

Version: 1 Date: 8 April 2010

Reviewer: Masayuki Saijo

Reviewer’s report:

Review for the paper entitled “Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis”

Minor Essential Revisions:

The paper describes the efficacy of ribavirin for the treatment of Crimean-Congo hemorrhagic fever. The authors analyzed the efficacy based on the paper published so far in the scientific journals and other form of publications. This paper is well written. The efficacy of ribavirin for the treatment of CCHF is still open question, but is very important issue to be addressed. Therefore, the statement in this paper is very important.

Minor comments

1. Page 2, line 3: “Crimean-Congo Hemorrhagic Fever” should be “Crimean-Congo hemorrhagic fever”. DONE

2. Page 2, line 4 in the Background section: “will help justify ------” should be “will help to justify------”. DONE

3. Page 2, line 2 in the Methods section: “Crimean-Congo Haemorrhagic Fever” should be “Crimean-Congo hemorrhagic fever”. DONE
4. Page 3, line 3 and 4 in the Conclusions section: The terms, “large” and “very”, might be removed. DONE

5. Page 4, line 4-5: “the Dagbe Virus and the Nairobi sheep disease” should be “Dagbe virus and Nairobi sheep disease virus”. DONE

6. Page 4, line 14: “The most important--- --- is most likely” should be “The most important--- --- is likely” DONE

7. Page 5, line 15: “haemorrhage” should be “hemorrhage”. DONE

8. Page 5, line 5 from the last: “reverse transcriptase” should be “reverse transcription”. DONE

9. Page 6, line 1: blood products” should be “blood products administration”. “blood products administration” should be used instead of “blood products” in the entire text. DONE

10. Page 7, line 7: “Children or adults of any age” should be Children and adults of any age”. DONE

11. Page 7, line 8 from the last: “time to recovery of symptoms” might be “time to recovery from symptoms”. DONE

12. Page 7, line 2 from the last: Please clearly mention about “numbers of days from onset of symptoms”. What are the numbers of days from onset to? Outcome measure looked at was to evaluate the effects of Ribavirin according to the number of days from onset of symptoms that the drug was started. The text has now been changed to clarify this.

13. Page 8, Search strategy section: Please mention the website for Medline,
EMBASE, and other databases. Website addresses added for these two databases.

14. Page 9, the last line: Please clearly mention about “numbers of days from onset of symptoms”. What are the numbers of days from onset to?

SEE POINT 12

15. Page 11, line 9: Please make the meaning of the sentence, “antibodies against virus antigens were used in 14 studies”. What were the antibodies against virus antigens used in 14 studies for? This sentence was referring to the use of antigen detection to help with the diagnosis in 12 of the studies, sentence altered to reflect this.

16. 13, line 7 from the last: “Polymerase Chain Reaction” should be “polymerase chain reaction”, or simply “PCR”. DONE

17. Page 19 line 10: “Crimea-Congo Hemorrhagic fever” should be “Crimean-Congo hemorrhagic fever”, or simply be “CCHF”. DONE

18. References: Please follow the guidelines for the reference format, especially in the journal name. DONE according to guidance on the website

19. Please update the citation number 34. DONE

20. Page 29: Figure legend and Table title sections: The figure legends and Table title should be improved in order to make readers easier to understand the figures and table. For example, the X-axis of the Fig 2 should be defined. This has now been done.

21. Table 1, 8th and 9th columns: “The mean Length” should be corrected to “The mean length”. Done
22. Additional 3 file, the last column: “Elisa” should be “ELISA”. What is the “ELISA” for? Is it for antibody-detection or antigen-detection? DONE (mainly antigen detection)

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**Which journal?:** Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

**What next?:** Accept for publication in BMC Medicine after minor essential revisions

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

I declare that I have no competing interests.
Reviewer's report

Title: Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis

Version: 1 Date: 13 April 2010

Reviewer: Helen Maltezou

Reviewer's report:

Minor Essential Revisions

1. Background section, page 5, second paragraph, lines 2-3: “Different domestic and wild animals have been identified as a reservoir for the virus, including cattle, sheep, hedgehogs, mice and dogs”. Please note that the main and widely available reservoirs for CCHF include cattle, sheep, goats, and hares. Other animals may have been found occasionally infected, and their role as reservoirs is not supported or not investigated so far. The wording of this paragraph has been altered to reflect this comment.

2. Background, page 4, second paragraph, lines 4-5: “Numerous species of ticks carry the virus, however only a few of them have been implicated as vectors”. This statement is wrong. There are few other tick species found infected with CCHF, either in nature or under laboratory conditions, however this does not mean that they can serve as vectors. As of today, Hyalomma ticks are the almost exclusive vectors for CCHF. The wording of this paragraph has been altered to reflect this comment.

3. Background, page 4, second paragraph, line 5: “The most important tick vector
is most likely the *Hyalomma* spp”. This statement is correct, based on studies on competence and not only on geographic suggestions. OK

4. Background, page 5, first paragraph, last line: Published mortality rates range from 5-50%, and not from 30-50%. Please use [ref 9] for epidemiology only, and add another reference for clinical manifestations [e.g. Ergonul, Lancet Infectious Diseases 2006, or Vorou et al, Current Opinion in Infectious Diseases 2007], since these are the more recent review articles on CCHF. Ergonul article used as a reference for clinical manifestations.

5. Background, page 6, second paragraph, 1st line: please use the article by Maltezou et al (Eurosurveillance;2010; March 11 issue) for this comment.

This reference has been added.

Major Essential Revisions

Search strategy; Page 8, first paragraph: which words were used for this search? Please include them here. *There search terminology was extensive, for searches of the relevant databases. This is provided in an appendix to the article, and unfortunately could not be presented as part of the article due to the extensive space this would take up. We hope this is acceptable to the editors.*

7. Page 9, second paragraph, line 1: Why the cut-off of 0.10 was chosen as statistically significant? Typically, in statistical analyses a p-value of 0.05 or less is considered statistically significant.

*KSW: For the meta-analysis the p-value is of 0.05. The p-value of 0.10 was used to test heterogeneity. This is justified because we intend to evaluate the evidence of NO HETEROGENITY. Please see section 9.5.2 of the Cochrane*
Handbook as quoted, “Care must be taken in the interpretation of the chi-squared test, since it has low power in the (common) situation of a meta-analysis when studies have small sample size or are few in number. This means that while a statistically significant result may indicate a problem with heterogeneity, a non-significant result must not be taken as evidence of no heterogeneity. This is also why a P value of 0.10, rather than the conventional level of 0.05, is sometimes used to determine statistical significance. A further problem with the test, which seldom occurs in Cochrane reviews, is that when there are many studies in a meta-analysis, the test has high power to detect a small amount of heterogeneity that may be clinically unimportant”.

8. The authors do not mention anything about prognostic factors in the meta-analysis, described by Swaenpoel in 1980 and recently by Ergonul. Such factors include platelet count, white blood cell counts, INR, gastrointestinal hemorrhage, etc. This is very important, since prognostic factors influence the outcome of CCHF cases, and thus should be taken under consideration in a meta-analysis for ribavirin efficacy.

Agree that this is an important point that affects the outcome in these patients. Unfortunately, there was not enough data in many of the reviewed trials to be able to review and compare severity of disease with treatment and outcome. A paragraph in the discussion, under limitations of the study, has been added to address this issue.

9. Page 15, section: prophylactic use of ribavirin in health-care workers: in this study by Ergonul et al, do the authors report anything about ribavirin prophylaxis? As far as I know, the authors tested the personnel for antibodies against CCHF after the main CCHF epidemic in a hospital in Turkey.
Agree, no one in this study was given prophylactic ribavirin, but the study highlights spread of infection and highlights the possible need to consider prophylaxis in outbreak situations, and the need for research into this. The heading for this section has therefore been altered to take this into account (Antibody responses following exposure to CCHF virus).

**Which journal?:** Not appropriate for BMC Medicine: an article of only archival interest, but might be suited to BMC Infectious Diseases

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests.

**REVIEWER 3 COMMENTS AND RESPONSE**

**Reviewer's report**

**Title:** Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis

**Version:** 1  **Date:** 30 April 2010

**Reviewer:** Girdhar Agarwal

**Reviewer’s report:**

Review of the article “Ribavirin for Crimean-Congo hemorrhagic fever: systematic
In this paper, a systematic review of observational and experimental studies is done to appraise and summarize the evidence about benefits and harms of ribavirin for treating CCHF in humans. The summary estimates are presented using meta-analytical tools. My specific comments are as follows:

1. The studies included are mostly from a particular region (Pakistan, Iran and Turkey). I am sceptical about the external validity of the results. These are the countries where this disease occurs, and we agree there are issues on the reliability and validity of the results, mainly because of the high risk of bias due to these being observational studies. We discuss this carefully.

2. Out of selected 21 studies, only two were RCTs. In my view, there will be problem in combining the results of randomized controlled trials and analytical non-randomized studies. As observed by the authors, the observational data are of very low quality. The combined estimate will too imprecise to draw any worthwhile conclusion.

We provided data separately for observational and RCTs. The only RCT added to the meta-analysis was published very recently as there was a certain impression – corroborated in many of the narrative reviews in the field – that it was unethical to perform RCTs on this population. They also found it unethical not to use ribavirin, based on observational studies and case series. We tried to go one step further and compare the results of RCTs and observational studies,
and the results were provided separately for these two study designs. Hopefully this will help engage the clinical community working in this area-to simply reject all their studies and not attempt to draw out research findings would be counterproductive.

3. GRADE method is for the quality assessment of the studies. It is not for finding the “summary estimates” of the studies (Data collection and assessment section, p.9).

the sentence should be “risk of bias was assessed using the GRADE methodology [28]” in order to reflect this comment. This is now done.

4. The steps used for systematic reviews are well-followed. Others aspects of meta-analysis are also mostly observed.

5. In my view, the paper should be shortened, for example, there is no need of funnel plot. Agree, therefore funnel plot and the discussion about it has been removed.

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

What next?: Accept for publication in BMC Medicine after minor essential revisions

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