Author's response to reviews

Title: The health status of Q-fever patients after long-term follow-up.

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Author's response to reviews: see over
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Version: 1 Date: 21 February 2011

Author’s response to reviews: see over
The BioMed Central Editorial Team

ref: MS: 17068896284856263

21 February 2011

Dear Ms Rhona Morris

Thank you for reviewing our manuscript MS: 17068896284856263

The health status of Q-fever patients after long-term follow-up. We addressed all reviewers comments and have adapted the manuscript accordingly. The manuscript has also been edited by a native English speaker.

We hope that you will find the adapted manuscript suitable for publication in your journal,

Sincerely yours,

Gabriëlla Morroy
Comments of reviewer 1: Jean Paul Stahl

General comments:

1) The summary has 321 words, that is more than the “classical” authorization of 250, but I had no information about this abstract length for BMC.

We followed the instructions for authors that the abstract should not exceed 350 words.

2) Verbs used to relate outbreaks should be, in my sense, the past.
   a. For example “...60% are asymptomatic » (in the introduction) should be «.... Were asymptomatic », and so on, if, as I understand, it refers to the Netherlands recent outbreaks. If it refers to general observations about Q-fever, the present is correct.

   As the whole second paragraph refers to general observations on Q fever we maintained the present tense.

   b. In the discussion, it is the same. Verbs relating the study should be used in the past tense: “General quality of life (44•9%) and fatigue (43•5%) are severely affected in our study subjects » should be “…were severely…”, in order to make clearly the difference between literature and the study.
In response to your valid observation we have adjusted all verbs in
the manuscript -in phrases relating to our study- to the past tense.

c. Authors should clarify better, in the introduction, what is related
to the literature, and what is the objective of their study. I
understand that literature describes some clinical presentations, and
authors of this paper wanted to verify, using their large cohort, if it
is correlated to their own data.

We trust that with the adjustment of the right tense the distinction
between literature and the own study becomes clear.

We made the text more explicit by adding the following phrase in
the introduction:

"In order to asses the long-term health status of Dutch Q-fever
patients we started this study."

4) Authors did not give information about the patients’ serological
tests. It is said that chronic Q-fever is correlated to phase I
antigens. Do authors have data leading to conclusions about it? It
could be interesting to confirm, or not, it, if possible. Anyway, even
if these data are lacking, it is interesting to discuss it.
In order to clarify our inclusion criteria better we added the requested information to the manuscript under the heading; Study design and population. We also added reference 13. See also the Associate Editor’s comments

“Patients were diagnosed by 3 different laboratories. At the beginning of the outbreak in 2007 the laboratory test most frequently used was the CFT (complement fixation test). A seroconversion or a fourfold increase in titre, between two subsequent tests with a minimum time interval of two to four weeks, was considered positive. Later during the outbreak one laboratory used the IFA (Immuno Fluorescence Assay). This latter test distinguished between phase I en II IgM and IgG [13].”

Furthermore we added under limitations;

“As not all patients in our study were serologically followed up we were unable to establish if and who developed chronic Q fever.”

See also our answer under your next question.
5) Authors do not report endocarditis cases, which are reported in literature as frequent presentations of chronic Q-fever. Could they comment?

In our study we are unable to report endocarditis as one of the presentations of chronic Q fever. To clarify this we have added the following text under the heading study limitations.

“In at least 1.6% of the Q-fever patients in the Dutch 2007-2008 cohorts, the condition became chronic (van der Hoek et al, submitted for publication). For our study population this could potentially mean eight or nine patients with chronic Q-fever. As not all patients in our study were followed up serologically we were unable to establish if and who developed chronic Q-fever or any of its presentations such as endocarditis.”
Comments of reviewer 2: Christian J Hoebe

Major compulsory revisions

1. There should be more clearly in the manuscript why the authors chose the group division in two categories of below and over 50 years of age beforehand. I doubt whether this is the appropriate design. In a patient reference study bias can be introduced by the wrong reference group.

   *We chose our method to be as strict and transparent as possible. In order to explain our choice in study design we have added the following explanation on the use of categories below and above 50 years in the text of the article in the paragraph; methodological considerations and study limitations.*

   "Normative data of healthy subjects and those with COPD were only available for patients over 50 years of age. This was unfortunate as 46.2 % of Q-fever patients were younger than 50. As we chose our method to be as strict and transparent as possible, we presented data for patients over and under 50 separately."

2. The healthy control group is rather small with only 65 individuals - all over 50 years of age. The control group should be enlarged
with more individuals of similar age groups as the q-fever group - thereby diminishing bias.

We appreciate the reviewer’s point. Ideally a norm group is as large as possible. In order to clarify that we used this rather small group we added the following text under the heading methodological consideration and study limitations.

“The healthy control group was rather small with 65 individuals - all over 50 years of age. However, the number of controls provided sufficient power for us to show a large and clear difference between the groups.”

b. Why chosen for the COPD group as control?
This choice does as you point out, need some clarification. We added the following text under the heading methodological considerations and study limitations.

“The municipal health service regularly received Q-fever patient reports of continuing respiratory complaints. We therefore looked for a norm group with a known respiratory component that we could compare these Q-fever patients with.”
When we compared data from Q-fever patients with the NCSI norm group of COPD patients it should be realized that this is a specific subgroup of COPD patients with a severely impaired health status in multiple sub-domains. We made the choice to use this COPD norm group as we wished to compare the long-term health status of Q-fever patients (who often suffered a pneumonia initially) with another group of patients with a known impaired health status.

3. Why did the authors chose the NCSI for health status assessment?

In order to clarify our choice to the reader we adjusted the following text under methodological considerations and limitations into:

“The advantage of the NCSI it that provides a detailed assessment of many domains of health status covering symptoms, functional impairment and quality of life.”

Under the same heading we also added;

“The NCSI provides more and specific information on sub-domains than some of the other instruments such as the SF-36.”
Furthermore, the availability of datasets of both a COPD, and a healthy norm group for the NCSI, enabled us to compare the health status of Q-fever patients with these two groups. Such a comparison provides useful information for GPs and medical specialists in their understanding of Q-fever patients.”

b. how many scales were evaluated for this goal?

The NCSI contains 8 sub-domains, each expressed as a single score on its own scale. Thus eight different scales were used.

We added an extra table – table 1- see the table following question 4a.

4. a. The explanation of the sub-domains of the NCSI need more clarification because these remain vague: are these symptoms? how severe? Abnormal health status? subjective symptoms? subjective impairment? impaired physical function? physical pain? Impaired emotional role? impaired social function?

In order to clarify what the domains and subdomains stand for and how they are measured we included table 1. in the method
Table 1: Definitions and instruments of the sub-domains of health status measured by the Nijmegen Clinical Screening Instrument

<table>
<thead>
<tr>
<th>Domain</th>
<th>sub-domain</th>
<th>Definition</th>
<th>Instruments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Symptoms</strong></td>
<td>Subjective symptoms</td>
<td>The patient’s overall burden of pulmonary symptoms</td>
<td>PARS-D Global Dyspnea Activity, Global Dyspnea Burden (15)</td>
</tr>
<tr>
<td></td>
<td>Dyspnoea emotions</td>
<td>The level of frustration and anxiety a person experiences when dyspnoeic</td>
<td>DEQ Frustration, Anxiety (15)</td>
</tr>
<tr>
<td></td>
<td>Fatigue</td>
<td>The level of experienced fatigue</td>
<td>CIS Subjective fatigue (16)</td>
</tr>
<tr>
<td><strong>Functional impairment</strong></td>
<td>Behavioural impairment</td>
<td>The extent to which a person cannot perform specific and concrete activities as a result of having the disease</td>
<td>SIP Home Management, Ambulation (17)</td>
</tr>
<tr>
<td></td>
<td>Subjective impairment</td>
<td>The experienced degree of impairment in general and in social functioning</td>
<td>QoLRiQ General Activities (18)</td>
</tr>
<tr>
<td><strong>Quality of Life</strong></td>
<td>General Quality of Life</td>
<td>Mood and the satisfaction of a person with his/her life as a whole</td>
<td>BDI Primary Care (19) Satisfaction With Life Scale (20)</td>
</tr>
<tr>
<td></td>
<td>Health-related Quality of Life</td>
<td>Satisfaction related to physiological functioning and the future</td>
<td>Satisfaction Physiological Functioning, Satisfaction Future (15)</td>
</tr>
<tr>
<td></td>
<td>Satisfaction relations</td>
<td>Satisfaction with the (absent) relationships with spouse and others</td>
<td>Satisfaction spouse, Satisfaction social (15)</td>
</tr>
</tbody>
</table>

*PARS-D: Physical Activity Rating Scale-Dyspnea; DEQ: Dyspnea Emotions Questionnaire; CIS: Checklist Individual Strength; SIP: Sickness Impact Profile; QoLRiQ: Quality of Life for Respiratory Illness Questionnaire; BDI: Beck Depression Inventory*
b. What was the time-scale.. did q-fever patients suffer from fatigue mainly the First year? how many improved?

*In order to explain the our finding we added the following text under the heading discussion 3rd paragraph;*

"*Unfortunately we were unable to establish if Q fever patients mainly suffered fatigue the first year and later recovered as we only had contact with patients once. The fact that we found no differences between patients of the 2007 and 2008 cohorts is suggestive of persisting complaints."


c. I miss the details of the assessment of health status -while this was the main aim of the study.

*We hope that the alterations we made under method see also question 4a. clarifies this issue.*

5.Limitations of the study should be addressed in the discussion and also the implications for GP's and other MD's should be clarified more clearly.

*In reaction to questions of reviewers we stated the following limitations in the chapter limitations and methodological considerations:*
“The healthy control group was rather small with 65 individuals all over 50 years of age. However, the number of controls provided sufficient power for us to show a large and clear difference between the groups.

Normative data of healthy subjects and those with COPD were only available for patients over 50 years of age. This was unfortunate as 46.2% of Q-fever patients were younger than 50. As we chose our method to be as strict and transparent as possible, we presented data for patients over and under 50 separately.

In at least 1.6% of the Q-fever patients in the Dutch 2007-2008 cohorts, the condition became chronic (van der Hoek et al, submitted for publication). For our study population this could potentially mean eight or nine patients with chronic Q-fever. As not all patients in our study were followed up serologically we were unable to establish if and who developed chronic Q-fever or any of its presentations such as endocarditis.”

We added the following text as the last phrase of the subheading implications.
“Knowledge of these detrimental long-term outcomes should help MDs to be more supportive to these patients and refer promptly and adequately to specialist care.”

**Minor essential revisons**

6. the abstract is misleading - the number of 515 used questionnaires (study population 57%) should be included in the abstract as should the numbers of the control groups. Which is in itself a fair and substantial study population.

*We added the numbers of patients under methods:*

*The NCSI scores of Q-fever patients older than 50 years (N=277) were compared with patients younger than 50 years (N= 238) and with norm data from healthy individuals (N=65) and patients with chronic obstructive pulmonary disease (N=128).*

*And we changed the first line of the results in the abstract to:*

“The response rate was 65.7% but due to exclusion criteria 515 patients were included in this study.”

7. the punctuation is rather sloppy and should be improved in the whole manuscript.
The punctuation has been adjusted and is hopefully meets the editors’ standards.

8. the number of decimals used in results should be synchronized - rather one decimal than two.
All decimals used in the results were reduced to one decimal.

Discretionary revisions

9. Figure 1 can be deleted when explanation in the text is clear.
With the additions we made to our manuscript it has already become quite long. We would like to avoid adding more text. We would therefore prefer to keep figure 1. If required, we could remove the figure.

Associate Editor's comments:

In addition to the comments from reviewers, the authors should indicate which tests were used to confirm cases of Q fever included (serology; which technique and which positivity criteria; was the test done in one or several labs ?).
Thank you for pointing this out. In order to clarify our inclusion criteria better we added the requested information to the manuscript under the heading Study design and population;

"Patients were diagnosed by 3 different laboratories. At the beginning of the outbreak in 2007 the laboratory test most frequently used was the CFT (complement fixation test). A seroconversion or a fourfold increase in titre, between two subsequent tests with a minimum time interval of two to four weeks, was considered positive. Later during the outbreak one laboratory used the IFA (Immuno Fluorescence Assay). This latter test distinguished between phase I en II IgM and IgG [13].”

Editorial Requests:

1. Further consideration of your manuscript is conditional on improvement of the English used. Please ensure particular attention is paid to the abstract. You should have a native English speaking colleague help you with this, if possible, or use a commercial copyediting service. Examples are those provided by the Manuscript Presentation Service (www.biomedes.co.uk), International Science Editing (http://www.internationalscienceediting.com/) and English Manager Science Editing (http://www.sciencemanager.com/).
BioMed Central has no first-hand experience of these companies and can take no responsibility for the quality of their service.

The article has been edited by a native English speaker.

2. Please can you include all of the author's email addresses on the title page for your manuscript.

All the author's email addresses have been added to the title page.