Author’s response to reviews

Title: Localizing chronic Q fever: a challenging query

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Author’s response to reviews: see over
Dear editor,

We thank the reviewers for their comments on our manuscript entitled “Localizing chronic Q fever: a challenging query”. Incorporating their suggestions significantly improved the manuscript. Please find enclosed our revised manuscript. Hopefully, you consider our revised manuscript suitable for publication in BMC Infectious Diseases.

Reviewer #1: Minor text related items;
1. p.14 first paragraph, line 14 first word "ileac" referring to the iliac bone of the pelvis should be spelt "iliac".

Response: This has been changed in the revised manuscript; “os ileum” has been changed to “iliac bone” (p.15, line 4 and 5).

2. Page 8 second paragraph "present >3 months after acute infection in combination with (1) (worsening of) valvular defects not meeting the modified Duke criteria OR (2) a known aneurysm and/or vascular or cardiac valve” – I should like the authors to tidy up the text. "1. (worsening of) ..." I think they could write this in a sentence without brackets.

Response: The text has been adjusted and tidied up (p. 8, line 15-20). Specific symptoms have been deleted, as they are already mentioned in the background section. Bottom line of the criteria is to include all patients with a valvular defect who do not meet the modified Duke criteria. Therefore, it is irrelevant if the valvular defect has worsened, because patients would still be classified as probable chronic Q fever. As a result, we have eliminated “(worsening of)”, in accordance with the Dutch consensus on chronic Q fever, reference 15 in the manuscript (p. 8, line 15).

Reviewer #1: More important items for author attention;

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Table 3: Screening CT Aneurysm 2, Suggestive of infected aneurysm 0, Fluid collection/abscess 1
I would have thought that fluid collection/abscess (the third heading) was essentially the same as "Suggestive of infected aneurysm". Perhaps the authors could consider this.

Response: We thank the reviewer for this comment. Criteria used for the definition “suggestive of infected aneurysm” were initially: infiltration of adipose tissue, local lymphadenopathy and non-specific findings. We agree with the reviewer that fluid collection and/or abscesses suggest an infected aneurysm. Therefore, we decided to combine these two rows in table 3 (p. 36).

Reviewer #2: Major compulsory revisions;

1) Methods: Study design and patients. Patients were recruited based on PCR >1 month / serology >3 months after the acute episode – but large numbers of patients did not have symptomatic acute Q fever. How was the timing of onset of acute Q fever determined in patients without a symptomatic episode? This point also related to Table 1 in the calculation of time from episode of acute Q fever.

Response: The mean interval between acute Q fever to analysis for chronic Q fever was only calculated for those patients who experienced a symptomatic episode of acute Q fever. For some patients without a symptomatic episode it was indeed challenging to determine whether there was evidence for chronic infection or not. For this purpose the Dutch guideline was followed. Decision making is described below. Patients without symptomatic acute Q fever infection were included if anti-phase I IgG remained >1024 over the course of >3 months or if there was positive serum PCR over the course of >1 month. This was added to the Methods section, subheading ‘Study design and patients’ (p. 7, lines 8-10).

- In the “possible chronic Q fever” group, all patients have experienced symptomatic acute infection before analysis for chronic Q fever was commenced (table 1), so here it was no issue. In the absence of risk factors or proof of active infection, in all of these patients a “watch and see” policy was carried out. None of these patients were treated. In 8 out of 20 patients, the anti-phase I IgG titre decreased to <1024, with an average of 7.5 ± 5.1 months. The remaining 12 patients still had an anti-phase I IgG >1024 by time of analysis.
- In the “probable chronic Q fever” group, 2 patients (14%) did not experience symptomatic acute infection. In one patient persistently high anti-phase I IgG (>1024) titers were measured during >5 months. This patient was treated for Q fever endocarditis (possible IE according to modified Duke criteria) because of these persistently high titers and predisposing valvulopathies. In the second patient persistently high anti-phase I IgG were measured over the course of >9 months. Probable Q fever was considered because of an anti-phase I IgG titer >1024 combined with predisposing valvulopathies. This patient did not receive treatment because of severe co-morbidity.
- In the “proven chronic Q fever” group all patients had a proven site of infection and/or positive serum PCR. There were 5 patients with unknown localization: all of these were considered ‘proven’ because of positive serum PCR. 3 out of these 5 patients did not have symptomatic acute infection. In patient no. 1 positive serum PCR was measured 5 and 6 months after the start of symptoms of chronic infection. In patient no 2 and 3 there were positive serum PCR results over the course of >3 months, and anti-phase I IgG titer >1024 for more than 9 months in both patients.
2) Methods: Imaging studies. It would be helpful to have more information on how the PET/CT scans were reviewed and classified as “helpful”. Was a single radiologist responsible for this at each centre? Were the original reports used for this study or were images specifically re-reviewed as part of this work? If the latter was the reviewer blinded to the other clinical data? What cut-off of metabolic activity was taken to be indicative of a site of infection?

Response: FDG-PET/CT scans were performed according to international guidelines, using integrated PET/CT scanners (Biograph™; Siemens, Knoxville, TN, USA or Gemini™, Philips, Eindhoven, the Netherlands). FDG-PET/CT scans were all performed in regular patient care, therefore primarily reviewed by specialized nuclear radiologists from the department of Nuclear Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, and the Canisius Wilhelmina Hospital, Nijmegen, the Netherlands. These nuclear radiologists have extensive experience in the evaluation of FDG-PET/CT scans for infection. Based on these original reports, the primary investigator classified the FDG-PET/CT scans as helpful, if findings described in the initial report enabled localization of infection. Diagnosis of infection depends on several factors. First, with the exception of a few organs (brain, heart, kidneys, bladder and sometimes intestines), the physiological uptake of $^{18}$F-FDG is low and clearance from non-target tissue is fast [1]. In general, a more intense uptake compared to the mediastinal blood stream is considered pathological. Second, places with high FDG-uptake will be correlated with the CT scan, giving guidance to localization and providing extra information on possible infection. The anatomical site of FDG-uptake plays an important role. For example, the linear mildly to moderately increased uptake around vascular grafts seems to attributable to a chronic aseptic inflammation in the synthetic graft material [2]. Finally, as in the context of oncology, FDG-PET is generally assessed using visual criteria. It is unclear how far semi-quantitative measurements can contribute to the assessment, partly because of the variability in the methodology used [3, 4]. Higher metabolic activity than physiological uptake in surrounding tissue in tissues with normally low physiological uptake was considered to be indicative of infection. In addition, irregular/localized FDG-uptake in tissues with normally homogenous uptake was considered indicative of infection. This has been added to the section Methods, subheading ‘Imaging studies’ (p. 9, line 15-22).

3) Result: Proven Chronic Q-Fever Paragraphs 2+3. What percentage of PET+VE lesions were confirmed via PCR/Tissue. Of sites where tissue/fluid was PCR positive (paragraph 2 of this section) what percentage of these lesions were also PET positive.

Response: 6 patients had positive fluid/tissue PCR. 4 out of 6 were analyzed by FDG-PET/CT, all of which showed FDG-positive lesions. The other 2 were already found to have definite IE according to the modified Duke criteria and (unfortunately) no FDG-PET/CT was performed. In these 2 patients, PCR was positive on infected cardiac valves that were replaced by surgery. It would indeed be interesting to know if these 2 patients with Q fever endocarditis would also have FDG-positive lesions at FDG-PET/CT. This has been added to the section Results, subheading ‘Proven chronic Q fever’ (p. 12, lines 3-6). Conversely, we found FDG-positive lesions in 10 patients (with proven chronic Q fever). In 4 out of these 10 patients positive lesions were confirmed via PCR/tissue. In all of these 4 patients FDG-PET/CT was conducted prior to PCR. In the remaining patients, surgery was not indicated and/or the lesions were very difficult to reach so tissue PCR could not be performed. This has been added to the section Results, subheading ‘Proven chronic Q fever’ (p. 12, lines 17-20).
4) Results: Proven Chronic Q-Fever Paragraph 4. How was death from chronic Q-fever defined and what was the presumed mechanism of death? It would be of interest (although not essential for the manuscript) to know if post-mortems were performed in these cases and if material was PCR positive/showed histological evidence of ongoing Q-Fever.

Response: Death from chronic Q fever was defined as death as a result of active chronic infection. One patient died at 11 months following cardiac valve replacement due to progressive heart failure, probably as a result of artificial valve dysfunction due to chronic Q fever. PCR on valve tissue was positive. The second patient died in the perioperative period (in the first month) due to bleeding following acute aneurysm repair for a symptomatic aneurysm. PCR on aneurysm tissue was positive for Q fever. The third patient died in the perioperative period (in the first month) due to SIRS following acute cardiac valve replacement for severe Q fever endocarditis, with tissue PCR being positive. Unfortunately, no post-mortems were performed in these cases. However, in all cases there were positive PCR results on tissue (cardiac valve in 2 patients, mycotic aneurysm in 1 patient). This has been added to the section Results, subheading ‘Proven chronic Q fever’ (p. 13, lines 17-24).

5) Results/Discussion: The authors rightly comment that many patients did not undergo a full diagnostic workup. Did you find evidence that once a localization was established further tests were not have been carried out?

Response: 16 of 18 patients with proven chronic Q fever did undergo a full diagnostic work-up. In the 2 remaining patients there was definite IE according to the modified Duke criteria and no AUS, CT and/or PET-CT was carried out. It is possible that these 2 patients had 2 sites of infection.

6) Results and Discussion (para 4 in particular). The relatively low sensitivity of PET (33-75%) for IE has been noted in other settings (refs below). A reliance on PET+VE as proof of localization may have reduced yield especially given the relatively low rates of TEE in the study group and lack of tissue samples. Do the authors consider that many patients may have had two sites of infection — valve + graft/aneurysm — which may have been missed due to reliance of PET and lack of TEE? (Kouijzer IJE et al. The value of 18F-FDG PET/CT in diagnosing infectious endocarditis. European Journal of Nuclear Medicine and Molecular Imaging March 2013, Saby L et al . Positron Emission Tomography/Computed Tomography for Diagnosis of Prosthetic Valve Endocarditis: Increased Valvular 18F-Fluorodeoxyglucose Uptake as a Novel Major Criterion. J Am Coll Cardiol. 2013 Apr 10. pii: S0735-1097(13)01411-3. doi: 10.1016/j.jacc.2013.01.092).

Response: Indeed not all patients were subject to a full diagnostic work-up. Therefore, we bear in mind that some patients indeed may have had two sites of infection. However, because of the retrospective character of this study, it was not possible to examine this. By publishing these results we would like to emphasize the need of a full diagnostic work-up. To emphasize our viewpoint, we added this in the manuscript (p. 23, line 4-6).

Reviewer #2: Minor essential revisions;

7) Methods: Study design and patients. Are the authors aware of what percentage of all patients seen with culture-negative endocarditis in their 2 units in the study period underwent testing for Coxiella?
Response: We feel this is an interesting question, but unfortunately the percentage of patients with culture-negative endocarditis that underwent testing for Coxiella burnetii was not registered.

8) Results: Proven Chronic Q-Fever Paragraph 1. No definition is given for valvular dysfunction. What percentage of valvular dysfunction occurred in people with existing valvulopathy.

Response: Valvular dysfunction was defined as the aggravation of pre-existing valvulopathies to ≥ grade 2, the occurrence of new valvulopathies of ≥ grade 2 or signs of artificial valve dysfunction, or evidence of increasing heart failure or the need for acute cardiac valve replacement. This has been added to the section Methods, subheading ‘Clinical data and outcome’ (p. 10, lines 7-10). There were 5 patients with pre-existing valvulopathy. In 2 of these patients valvular dysfunction occurred. In one patient left ventricular function deteriorated due to Q fever endocarditis and recovered during the course or treatment. In the other patient there was new dysfunction of an artificial cardiac valve, as a consequence of Q fever endocarditis. This has been added to the section Results, subheading ‘Proven chronic Q fever’ (p. 11, lines 9-13).

9) Results: Proven Chronic Q-Fever. Of patients with no definite localization and possible IE what percentage had minor criteria on ECHO? What percentage of possible IE patients underwent TEE? Given the reduced yield with TTE vs TEE this may significantly affect patients final classification – this would also have implications in the probable and possible Q-fever groups.

Response: In 4 of 5 patients with no definite localization and possible IE there were minor echocardiographic criteria. In all 5 patients TTE was performed. 2 of 5 TTE’s showed minor criteria. In 4 patients TEE was performed, 3 of which showed minor criteria. This has been added to the section Results, subheading ‘Proven chronic Q fever’ (p. 13, lines 9-12). Of 20 patients with possible IE (all groups), 11 out of 19 patients who underwent TTE had minor criteria by TTE, and 4 out of 7 patients who underwent TEE had minor criteria. This has been added to the section Results, subheading ‘Analysis after adjustments to the modified Duke criteria’ (p. 17, lines 20-22).

10) Discussion Paragraph 1+4: Use of PET scanning is increasing. Have the authors considered that the higher rate of diagnosis of vascular infections may simply reflect you doing more PET than previous studies.

Response: Ever since the beginning of the Q fever outbreak in the Netherlands, FDG-PET/CT scans were performed in patients with a suspicion of chronic Q fever. The Radboud University Nijmegen Medical Centre already had extensive experience in performing FDG-PET/CT scans in e.g. patients with fever of unknown origin, and patients with a suspicion of an infected vascular prosthesis. Therefore, we already applied this diagnostic tool in patients with a suspicion of chronic Q fever before the Dutch consensus on chronic Q fever was introduced. Conform the Dutch consensus on chronic Q fever, it is now advised to perform a FDG-PET/CT scan in all patients with a suspicion on chronic Q fever. In other chronic Q fever series, hardly any vascular infection was seen. If these patients would have had unidentified vascular infection in addition to endocarditis then you would expect to see complications, because even in case of optimal (surgical) treatment 20-25% of patients with vascular chronic Q fever die. It is possible that we found some extra vascular infections because FDG-PET/CT was performed more often, but it is very unlikely that vascular infections would go unnoticed in other series not using FDG-PET/CT, so we believe that the incidence of vascular infections
really is different between the outbreak in the Netherlands and other outbreaks. This has been added to the section Discussion (p. 21, lines 3-8).

Reviewer #2: Minor issues not for publication;
11) Results: Proven Chronic Q Fever: paragraph 4 – “3 of whom have been treated for more/greater than 18 months”

Response: This has been changed in the revised manuscript; “longer than 18 months” has been changed to “are being treated for already more than 18 months” (p. 13, lines 15-16).

Concerning the editorial points the following. Because of individual patient data, table 4 has been removed from the manuscript (p. 11, line 7, and p. 38). Furthermore, the individual patient data in the figure legend for Figure 2 has been adjusted (p. 43, line 1 and 4).

All authors have seen and approved the revised manuscript. We are looking forward to your decision.

Yours sincerely,

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References: