PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Who is at risk of occupational Q fever: new insights from a multi-profession cross-sectional study
AUTHORS	Groten, Tanja; Kuenzer, Karola; Moog, Udo; Hermann, Beate; Maier, Katrin; Boden, Katharina

VERSION 1 – REVIEW

REVIEWER	Peter Massey Program Manager Health Protection Hunter New England Population Health, NSW Australia
REVIEW RETURNED	08-Apr-2019

GENERAL COMMENTS	The multi professional serosurvey described in this report is interesting and worthwhile. The study covers a relatively small number of participants but does point to issues for further work. The references are not complete and seem to be older references that need to be updated. In the Introduction references are needed at Page 4 lines 9, 13, 20, 29,32, 46. Page 4 Line 50, the study does not assess risk but is a descriptive study of the seroprevalence of Q fever in some occupational groups. The methods do not describe how data on length of exposure were collected. Were participants in the occupation for 1 day, 1 year, 10 years, 50 years? Length of time in the occupation is going to explain some of the exposures. The control group is not described. The 92 blood donors were they from rural areas, different occupations, different age groups? Table 1- suggest to use proportions instead of percentages when there are small numbers in the groups. The number positive is not otherwise displayed. The Discussion infers some issues that are not supported by the data. Examples, Page 7 Line 60 strains from cattle are as infective , and Page 8 Line 3 animal husbandry is not an issue that comes from the data. Page 8 Line 15, 'value' is seroprevalence The important limitation of self selection at professional events will lead to higher prevalence rates. Did other studies use the same technique? How many people were at the events, what proportion were tested?

REVIEWER	Dr S B Barbuddhe ICAR-National Research Centre on Meat, Hyderabad, India
REVIEW RETURNED	26-Apr-2019

GENERAL COMMENTS	Who is at risk of occupational Q fever: new insights from a multiprofessional cross sectional study by Tanja Groten and others The authors investigated the question, who was at risk of occupational Q fever, by determining the seroprevalence of C. burnetii antibodies in multiprofessional occupational groups. The samples size (n=250) is reliable. High seroprevalences were observed in individuals with frequent animal contact (64-77%). Overall this is a good small study. The manuscript needs to be checked for usage of language. Specific comment Abattoir associated personnel as occupational group are at a greater risk of acquiring Coxiella burnetii infection. Though this group was not included in this study, authors may mention about the group in Discussion for wider readership. Minor comments Page 2, line 45 and page 5, Lines 14-15: union of midwifes : union of midwives..... Page 5, Line 10, ...veterinaries at a number: Veterinarians at a number ..... Page 6, line 168: contract but still significant greater than .....contact but still significantly greater than.....

REVIEWER	Marit de Lange National Institute for Public Health and the Environment (RIVM), the Netherlands
REVIEW RETURNED	02-May-2019

GENERAL COMMENTS	1. The study objectives in the abstract and in the introduction are not similar. Next, seroprevalences are not unknown in most investigated risk groups, see the following articles: - Schimmer B, Schotten N, van Engelen E, Hautvast JL, Schneeberger PM, van Duijnhoven YT. Coxiella burnetii seroprevalence and risk for humans on dairy cattle farms, the Netherlands, 2010-2011. Emerg Infect Dis. 2014;20(3):417-25. - De Lange MM, Schimmer B, Vellema P, Hautvast JL, Schneeberger PM, Van Duijnhoven YT. Coxiella burnetii seroprevalence and risk factors in sheep farmers and farm residents in The Netherlands. Epidemiol Infect. 2014 Jun;142(6):1231-44. - de Rooij MM, Schimmer B, Versteeg B, Schneeberger P, Berends BR, Heederik D, van der Hoek W, Wouters IM. Risk factors of Coxiella burnetii (Q fever) seropositivity in veterinary medicine students. PLoS One. 2012;7(2):e32108. The only new research question of this study is the seroprevalence of obstetricians. I would advise to focus more on this topic. 2. In my opinion, the abstract is not well balanced. The objectives are too long, and the rest of the abstract is too short.

	4. I missed several aspects in the methods section: - Who were in the group of office employees? - Why was the data collection of the several groups in different periods? This makes it difficult to compare the groups and a good reason must be given for this. - It has been described in the Discussion section that participants were selected with random sampling. However, it is not described in the Methods sections how it is performed. - I miss a sample size calculation in the Methods section. 5. Nothing is described if the participants signed a consent form; please add this, as this is important ethical information. 6. Could you add more information on the ELISA test that was used, as it is short described. 8. In the introduction, not many references are used. It is not clear to me what you mean with that the disease is re-emerged. Was Q fever gone for a while in Germany, and is there now an increase? And which outbreaks do you describe in the introduction, when you mention 4000 patients? Is this the Dutch outbreak? This is now not clear to me. 10. The main results were presented clearly. However, I miss the results of the interview about the occupational and the animal contact. Can you add information on this, or otherwise do not mention them in the Methods section. 11. In my opinion, the conclusions are drawn on very small numbers of participants. Therefore, I would be more careful to draw this conclusion. The low seroprevalence in obstetricians should be repeated in a larger group. 12. The limitation are mentioned as bullet points on page 3, but are barely describes in the Discussion section. Please elaborate more on that in the Discussion section. 15. I would advise you to have a native speaker read the manuscript.

VERSION 1 – AUTHOR RESPONSE

1 Reviewer :

• The references in the introduction have been completed.
• We changed: who is at risk of…. to descriptive study of seroprevalence
• collection data on length of exposure: We added the methods and data about the length of exposure (modification in text and addition of figure 1)
• Information about age, sex ratio and region of residence was added for the group of blood donors.
• Table 1: we added the proportion to present the absolute numbers
• We removed issues that are not supported by the data like infectivity of cattle-associated strains and the discussion about animal husbandry.
• Page 8 Line 15: value was replaced by seroprevalence
• Self-selection at professional events: We do not know of a study that covers self-selection at professional events. We added data about proportion tested if available.

2 Reviewer

• We did not include the interesting group of slaughterhouse workers in our study as there is no professional slaughterhouse for sheep in Thueringia. We mentioned this fact in the discussion and added data from the metaanalysis by Woldeyohannes [Woldeyohannes 2018].

• Issues of phrasing were tackled by a native speaker

3 Reviewer
zu 1)
• Revision of the objectives in the abstract in accordance to introduction
• A paragraph about the Dutch seroprevalence studies was added to the discussion.
zu 2)
• We revised the abstract.

zu 4)
• Office employees have been characterized.
• The time line of data collection has been described in more detail in material and method section.
• random sampling has been corrected to non-random sampling
• Sample size calculation was not possible because of the study design and lacking data.

zu 5)
• Done

zu 6)
We added information about the ELISA test in the discussion chapter. For more information see: Frosinski J, Hermann B, Maier K, et al. Enzyme-linked immunosorbent assays in seroprevalence studies of Q fever: the need for cut-off adaptation and the consequences for prevalence data. Epidemiol Infect 2016;144(6):1148-52.

zu 8 & 10)
• Done

zu 11)
• We recommended further testing on a larger group and modified the conclusions.

zu 12)
• Limitations elaborated in the discussion

zu 15)
• Done

VERSION 2 – REVIEW

REVIEWER	Marit de Lange National Institute for Public Health and the Environment, the Netherlands
REVIEW RETURNED	18-Jun-2019

GENERAL COMMENTS	A few mentioned points are addressed in the new version. However, nothing has been changed to the comment on some crucial points in my point of view. Here again the points that in my view should be explained / adjusted and additionally a few extra points based on the resubmitted manuscript: • The study objectives in the abstract and in the introduction are not similar and should be the same in both.

	• Why was the data collection of the several groups in different periods? This makes it difficult to compare the groups and a good reason must be given for this. Please give an explanation why the data collection was performed in different periods. • I miss a sample size calculation in the Methods section. Please add this. • Nothing is described if the participants signed a consent form; please add this to the Methods section, as this is important ethical information. • Please add to the Results section what the profession was of the people in control group (92 blood donors). They might also had contact with animals, so please add this if this was the case. • In table 1 the 'Time of exposition* (range)' is added, which is good, but is this in years? Please add this. • In my opinion, the conclusions are drawn on very small numbers of participants. Therefore, I would be more careful to draw this conclusion. The low seroprevalence in obstetricians should be repeated in a larger group. • The limitation are mentioned as bullet points on page 3, but are barely describes in the Discussion section. Please elaborate more on that in the Discussion section. • In the Discussion section you mentioned that the IFAT is the reference test for Q fever. Why did not you used this test? Please add this consideration. • I would advise you to have a native speaker read the manuscript.

VERSION 2 – AUTHOR RESPONSE

Regarding the reviewer 3 comments on the test system used we would like to state that we are well aware, that the reviewer used the IFAT in her epidemiological studies on seroprevalence in sheep farmers and farm residents in the Netherlands. However, we think that the test systems we are using are at least equally reliable.

Also reviewer 3 advises us to have the manuscript read by a native speaker. However, our manuscript was checked and edited before submission by Dr Andrew Davis (as given in the contribution ship statement). Dr. Davis is not only a trained science editor with 30 years experience but also a native speaker of English. We do not believe, therefore, that our text needs additional extensive editing. If Reviewer 3 can point to some specific problems in the English, we will ask Dr. Davis to look at them again.

Please find the detailed response to the reviewer comments below.

Reviewer: A few mentioned points are addressed in the new version. However, nothing has been changed to the comment on some crucial points in my point of view. Here again the points that in my view should be explained / adjusted and additionally a few extra points based on the resubmitted manuscript:

• The study objectives in the abstract and in the introduction are not similar and should be the same in both.

We thank the reviewer for this comment. In the presented paper we pursued two aims. The first was to investigate the seroprevalence in occupational groups with close animal contact using the Panbio-ELISA. In a previous publication we proved the excellence performance of this ELISA being the only one with sufficient sensitivity and specificity to detect previous and past infection and thus total seroprevalence (Frosinski, Boden, 2016). In the light of this previous data of our group the first aim was to obtain reliable data on seroprevalence in such occupational groups. The second aim was, using the same assay, to obtain pilot data on the seroprevalence of obstetricians and midwifes with potential risk of infection during delivery of infected women. This was in our view of special interest in the context of the uncertainty of the real risk during human delivery. We admit that the wording in the abstract and the introduction was not clear enough and we changed the text accordingly.

• Why was the data collection of the several groups in different periods? This makes it difficult to compare the groups and a good reason must be given for this. Please give an explanation why the data collection was performed in different periods.
The reason for the rather long recruitment period was the need of an evaluation of assays for this special purpose (detection of past infection) after we got questionable results with the first used assay. Resampling in an area with a known outbreak six years ago, gave us this opportunity in 2011. The only test with excellent performance for seroprevalence detection were the Panbio-ELISA, as we already published. The samples of the first cohort of shepherds were than retested with the Panbio-ELISA and the study cohort was enlarged. We now consider this issue in the discussion.

• I miss a sample size calculation in the Methods section. Please add this.
Our approach in the presented study was to obtain as much samples as possible covering the different occupational groups. To be able to do a reliable sample size calculation it would have been necessary to know the sample size of all occupational groups evaluated. However, if we would do a post hoc sample size calculation with the occupational groups with known sample size (shepherds and obstetricians/midwifes of the university hospital Jena) with a confidence level of 95% and a margin of error of 10% the ideal sample size for the shepherds would have been 78 (our sample size is 77) and for the obstetricians/midwifes 33 (our sample size is 34). We do not feel confident to include such a post hoc sample size calculation in our method section, however if this would be mandatory for publication we are willing to do so.

• Nothing is described if the participants signed a consent form; please add this to the Methods section, as this is important ethical information.
We feel that we already included this information in the method section. Please find there the following paragraph: “After obtaining written informed consent, we interviewed people in the different occupational groups.” And an ethical vote was obtained (as described in the method section).

• Please add to the Results section what the profession was of the people in control group (92 blood donors). They might also had contact with animals, so please add this if this was the case.
As we used sera of blood donors as our control group and it is not part of the standard protocol to ask blood donors for animal contact and profession we do not have this information. However, to minimize the risk of involving blood donors with professional contact to animals we included only individuals from residential areas free from animal husbandry.

• In table 1 the 'Time of exposition* (range)' is added, which is good, but is this in years? Please add this.
We thank the reviewer for the accurate reading and were happy to add this information.

• In my opinion, the conclusions are drawn on very small numbers of participants. Therefore, I would be more careful to draw this conclusion. The low seroprevalence in obstetricians should be repeated in a larger group.
We totally agree with this concern and therefore one of our conclusions is to repeat the data for obstetricians with a larger sample size in a different area, as already stated in the discussion.

• The limitation are mentioned as bullet points on page 3, but are barely describes in the Discussion section. Please elaborate more on that in the Discussion section.
We thank the reviewer for pointing this out and were happy to change the discussion accordingly.

• In the Discussion section you mentioned that the IFAT is the reference test for Q fever. Why did not you used this test? Please add this consideration.
We are not aware of known and established cut off titre of IFAT for seroprevalence studies as

mentioned by Blaauw et al 2012. Secondly, our aim was to perform and present data obtained by using a test-system suitable for routine automatized testing.

•I would advise you to have a native speaker read the manuscript.
All versions of the manuscript have been read and revised by a native speaker so far.

VERSION 3 – REVIEW

REVIEWER	Marit de Lange National Institute for Public Health and the Environment, the Netherlands.
REVIEW RETURNED	04-Dec-2019

GENERAL COMMENTS	My comments have been processed correctly and the article is now publishable.