Q fever: still a mysterious disease

Sir,
In the concluding paragraph of his editorial,1 Dr Raoult makes a statement about the dangers of false-positive PCR assays arising from DNA contamination during the detection of *Coxiella burnetii*. The caution references a study2 from our Q fever Research Group. The general reader is likely to conclude that the artifacts mentioned by Raoult invalidate our observations. We urge the reader to study the actualities of our report before deciding whether Raoult’s comments have any validity for our paper.

In relation to long-term carriage of *C. burnetii*, we make two main points. First, there is ample evidence from the 1940s onwards, based on the isolation of the organism from humans and animals, that *C. burnetii* may persist in the host after an initial infection. Persistence of infection is necessary for recrudescence: e.g. some years later as Q-fever endocarditis or in late pregnancy after an infection up to 3 years previously.3 Harris *et al.* addressed the question of *how often* infection persists and *where* in the body; the report did *not* claim that persistence is the sole and sufficient cause for the post-Q-fever fatigue syndrome (QFS = ‘asthenia Q fever’) in French patients. It is necessary to follow patients systematically for more than two years after the initial acute infection. We agree (and have reported earlier) that a substantial proportion of primary acute Q fever patients have similar symptoms to QFS—essentially a downsized version of the acute phase symptoms without the fever—for 6 to 9 months after the acute attack, and then recover. It is the small proportion, some 8–10%, who exhibit similar symptoms but do not reach immune or other homeostasis after one year or longer that constitute the serious social and medical problem. They are the proper group for comparative studies.

Finally, in turn, we caution Dr Raoult that PCR detection of small numbers of *C. burnetii* in the presence of highly inhibitory human DNA is considerably more difficult than the simple examination of endocarditis vegetations or placenta which have large target numbers. Despite its theoretical sensitivity, the IS1111a PCR gives variable results with the tissue samples. Currently, we find the nested PCR with a target in the *com1* gene described by Zhang *et al.*6 and used by Kato *et al.*7 for blood or serum appears to offer a way round the inhibition problem with tissue extracts. Sequencing...
of amplicon is mandatory for final verification of the presence of \textit{C. burnetii} genomic sequences.

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References


Sir,

We were interested to read the editorial by Raoult\textsuperscript{1} relating to our papers on chronic fatigue following Q fever. In the editorial, he suggested that the reported percentage of fatigue amongst controls in the Wildman et al. study\textsuperscript{2} was high in contrast to studies from England, which he cited as showing a fatigue prevalence of 9.9–11.7\%. It is unclear where the figures of 9.9–11.7\% come from, as the paper referenced is entirely devoted to peer review.\textsuperscript{3} It is important to emphasize that a thorough understanding of the difficulties of fatigue definition was fundamental to the design of the Wildman paper, and that in fact the levels of fatigue found in the controls was exactly what would be expected in controls drawn from a UK general practice population. It is the use of well-defined instruments with large normal population reference data that makes the Wildman study of particular utility in gaining insight into patterns of fatigue following Q fever. Our study used the International Chronic Fatigue Syndrome study group’s 1994 Centre for Disease Control definition,\textsuperscript{4} operationalized with identical instruments to those used by Wessely. Wessely’s primary care study is pivotal in any study of fatigue, because it provides the largest survey of fatigue prevalence in the ‘normal’ UK general practice population.\textsuperscript{5} This well-validated operationalization of the CDC definition of fatigue allows patients to be classified into three levels of increasing severity of fatigue: (i) fatigue, (ii) idiopathic chronic fatigue, and (iii) chronic fatigue syndrome. Wessely found the prevalence of fatigue to be 38\% (95\%CI 37.2–38.7) using questionnaires returned by post by individuals identified from a UK general practice population. This corresponds very well with the prevalence of fatigue of 36.3\% (95\%CI 25.8–47.8\%) in controls returning the identical questionnaire in our study. Wessely found ‘idiopathic chronic fatigue’ in 18.3\% (95\%CI 17.7–18.9\%) of his normal general practice population, in comparison to 15\% (95\%CI 8.0–24.7\%) in the Wildman controls.

Painstaking attention to the quantification of fatigue using well-defined fatigue instruments is essential in any studies of this nature, and we were scrupulous in this regard. The editorial by Raoult did not cite the large Wessely series, but instead describes Raoult’s experience of finding a prevalence of undefined asthenia of 5–10\% in patients 6 months after Q fever onset, and asks why this 5–10\% differs from the findings in the UK study. It is quite clear from the extensive literature on the difficulties in the measurement of fatigue that lack of explicit measurement instruments will make comparison of fatigue between studies impossible. In 1994, the Centre for Disease Control recommended that painstaking care should be taken in defining and measuring fatigue.\textsuperscript{4} If workers are to make progress in the understanding of fatigue following Q fever, it is crucial as a first step that standard instruments are used. Our study applied these principles to the investigation of fatigue following Q fever, and the Wessely instruments used have performed exactly as expected in the controls, suggesting that they have utility in tackling this area. The Wessely instruments do have the potential to identify differences in fatigue between Q exposed individuals and controls; however, the methodological problems inherent in following up patients exposed to salient febrile illness are apparent. Our study makes it clear that the Wessely instruments would allow an important next step in understanding the prevalence of fatigue following Q fever to be made, if a large simultaneous questionnaire and serology study were carried out.
where respondents are blinded to their serology results until after the Wessely questionnaires are completed.

We reiterate that the increased fatigue scores in the Q exposed cohort have been measured with instruments that were standardized and well-validated, permitting other workers the possibility of replication in a way that will allow meaningful comparisons to be made. However, we readily acknowledge that the study design has the consequence that it is not possible to determine whether the elevated fatigue scores are due to bias, confounding, or the effects of persistent antigen.

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References


