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Moving from Q fever to *C. burnetii* infection

To the Editor

This paper by Van Loenhout *et al.* [1] gives us the opportunity to discuss the accuracy of the EU case definition for notification of Q fever, and more generally the current nomenclature of this infection.

In the EU definition, cases of 'acute Q fever' are defined by the combination of clinical symptoms (fever, pneumonia, hepatitis) and laboratory criteria. As stated by the authors, the major limitation of this classification is that it probably significantly underestimated the number of cases of *Coxiella burnetii* primary infection during The Netherlands epidemic. Interestingly, the use of this definition can be used to compare symptomatic (notified as 'acute Q fever') and asymptomatic or poorly symptomatic (non-notified) *C. burnetii* primary infections. The main significant differences between these two groups are age and sex, with symptomatic patients being significantly older and more often men than asymptomatic or poorly symptomatic patients. This result confirms what has already been described in previous studies: age and sex are the two major determinants of clinical manifestations of *C. burnetii* primary infection, with older men being more frequently symptomatic than young women, pregnant women and children [2–4]. Moreover, the results of Van Loenhout *et al.* confirm that there is no correlation between clinical manifestations of *C. burnetii* primary infection and the long-term consequences of the infection, with no significant difference in long-term health status between notified and non-notified patients [5].

These elements bring new arguments for an updated nosography of *C. burnetii* infection. We consider that the natural history of *C. burnetii* infection is quite close to what is observed in *Mycobacterium tuberculosis* infection (TB), so that the old simplistic classification of 'acute' and 'chronic Q fever' is no longer accurate. In TB, the primary infection can be symptomatic or not. If left untreated, and in the presence of host factors like immunosuppression or age, long-term complications of the infection can occur and affect different organs (Pott's disease, meningitis, miliary, lymphadenitis). Localization of the focus of infection is necessary to determine treatment duration and prognosis. In the case of *C. burnetii*, the primary infection can be symptomatic (currently described as 'acute Q fever') or not, depending on two major determinants: the strain involved [6] and the patient's susceptibilities (age, sex, pregnancy, immunosuppression) [7]. Then, long-term complications can be classified into two main entities: persistent focalized infections and fatigue syndrome (without an identified focus of infection). These complications are not linked to the severity of the primary infection but mainly to host factors. There is no 'chronic Q fever' with multiplying *C. burnetii* without a focus of infection and different focalized persistent infections have different risk factors, prognoses and treatments. *C. burnetii* endocarditis occurs in subjects with pre-existing valvulopathy, and is associated with high IgG anticardiolipin antibody titres during primary infection [8]. Its prognosis has improved thanks to prophylaxis, early diagnosis and treatment [9]. Vascular infections occur in patients with pre-existing aneurysm or vascular grafts, requires surgical treatment and still has a very poor prognosis [10]. Conversely, no death has been reported to date in patients with *C. burnetii* osteoarticular infections [11, 12]. *C.burnetii* infection during pregnancy is frequently asymptomatic but can lead to severe obstetrical complications like fetal death and malformations [13]. Finally, we recently demonstrated that *C. burnetii* persistent lymphadenitis can lead to lymphoma [14].

Regarding fatigue syndrome, a disease without evidence of *C. burnetii* multiplication and not treatable with antibiotics, this paper demonstrates that it is equally frequent after *C. burnetii* symptomatic and asymptomatic primary infections. Recently, another study from The Netherlands on 'Q fever fatigue syndrome' used the definition of the National Dutch consensus guidelines, which is cited as follows: 'a sudden onset of fatigue related to a symptomatic acute Q fever infection' [15]. Given the data from Van Loenhout *et al*. [1], this definition is obviously misleading. Further studies using a definition allowing detection of fatigue syndrome after *C. burnetii* asymptomatic primary infections are necessary to reach a conclusion on the actual occurrence and risk factors of this syndrome.

In conclusion, the work of Van Loenhout *et al.* stresses the need for moving from the old unspecific 'Q fever' nomenclature to more precise definitions of the different forms of *C. burnetii* infection in order to establish efficient public health strategies. In epidemic situations like the one experienced in The Netherlands, detection and follow-up of asymptomatic *C. burnetii* primary infections should be a priority, especially in high-risk patients (valvulopathy, vascular aneurysms or prosthesis, osteoarticular prosthesis, pregnant women) to detect and prevent the development of both focalized persistent infections and fatigue syndrome.

Declaration of Interest

None.

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