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Severely impaired health status of non-notified Q fever patients leads to an underestimation of the true burden of disease

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SUMMARY

Q fever patients are often reported to experience a long-term impaired health status, including fatigue, which can persist for many years. During the large Q fever epidemic in The Netherlands, many patients with a laboratory-confirmed *Coxiella burnetii* infection were not notified as acute Q fever because they did not fulfil the clinical criteria of the acute Q fever case definition (fever, pneumonia and/or hepatitis). Our study assessed and compared the long-term health status of notified and non-notified Q fever patients at 4 years after onset of illness, using the Nijmegen Clinical Screening Instrument (NCSI). The study included 448 notified and 193 non-notified Q fever patients. The most severely affected subdomain in both patient groups was 'Fatigue' (50·5% of the notified and 54·6% of the non-notified patients had severe fatigue). Long-term health status did not differ significantly between the notified and non-notified patient groups, and patients scored worse on all subdomains compared to a healthy reference group. Our findings suggest that the magnitude of the 2007–2009 Q fever outbreak in The Netherlands was underestimated when only notified patients according to the European Union case definition are considered.

Key words: *Coxiella burnetii*, fatigue, health status, Q fever, quality of life.

INTRODUCTION

Q fever is a zoonosis caused by the intracellular bacterium *Coxiella burnetii*. Several studies have shown that many patients suffer from a severely impaired health status, including persistent fatigue, after acute Q fever [1–9]. These symptoms have been reported for as long as 10 years after onset of illness [3], but follow-up of health status for >2 years has so far only occurred in a relatively small number of patients (around $\leqslant$100 cases) [1, 3]. The current study is part of a cohort study on the long-term health status of Q fever patients [10].

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Q fever is a notifiable infectious disease within the European Union (EU). The main reasons for an infectious disease being notifiable are source identification and the possible implementation of control measures to protect public health. The current EU harmonized case definition for Q fever was introduced in 2008. Besides laboratory and epidemiological criteria, this case definition includes a clinical presentation with fever, pneumonia and/or hepatitis [11]. Therefore, not everyone with a laboratory diagnosis of an acute *C. burnetii* infection is notified to a national institute of public health, since some of the patients do not fulfil the clinical criteria.

The large outbreak of Q fever in The Netherlands, with a total of 3522 notified patients over the period 2007–2009 [12], offers a unique opportunity to study long-term health status in a large group of Q fever patients. We were interested in long-term health status of patients with an acute *C. burnetii* infection that were not notified based on the clinical criteria. Therefore, we conducted the present study in which we compared the long-term health status of notified acute Q fever patients and of patients who had serological evidence of an acute *C. burnetii* infection, but who were not notified because they had a clinical presentation other than fever, pneumonia or hepatitis (referred to in this paper as non-notified Q fever patients). This is important to help assess the true burden of disease due to a Q fever outbreak.

MATERIALS AND METHODS

The design used in this study was a cross-sectional study of Q fever patients 4 years after diagnosis, taking place from 2011 to 2013. This study was approved by the Medical Ethical Committee Brabant (METC Brabant, number NL35654·028·11).

Study population

Within this study, we grouped patients according to the current EU case definition for Q fever, which was introduced in July 2008 and revised in August 2012, although the criteria did not change in 2012 [13]. The current EU case definition is presented in Table 1.

We refer to patients who fulfil the EU case definition as 'notified Q fever patients', *vs.* 'non-notified Q fever patients', who fulfilled the laboratory criteria but not the clinical criteria. The epidemiological criteria are not considered relevant in The Netherlands, since most of the country is potentially at risk for infection due to intensive animal husbandry (roughly 4 million cows, 1 million sheep, 400000 goats in 2013 [14]). Figure 1 shows the classification of the two study groups.

Table 1. *European Union case definition since 2008 (revised in 2012)*

Criteria	Definition
Laboratory	• Isolation of *Coxiella burnetii* from a clinical specimen • Detection of *C. burnetii* nucleic acid in a clinical specimen • *C. burnetii* specific antibody response (IgG or IgM phase II)
Clinical	• Fever • Pneumonia • Hepatitis
Epidemiological	• Exposure to a common source • Animal to human transmission

All patients included in the present study were at least 18 years of age, had a laboratory diagnosis of an acute *C. burnetii* infection and were reported by the Laboratory of Medical Microbiology to the local Municipal Health Service (MHS). In addition, general practitioners (GPs) or consulting physicians who requested the laboratory test were informed of the laboratory results and provided patients with adequate treatment. The standard treatment used by GPs for patients with a *C. burnetii* infection in The Netherlands is 2–3 weeks of antibiotics, and the most commonly used antibiotic is doxycycline (in 2007 and 2008, doxycycline was the first prescribed antibiotic for 62·1% of Q fever patients) [12, 15]. Following a standard protocol, all reported patients were contacted by an expert (a physician or nurse) from the local MHS about their clinical symptoms during the acute phase of their illness, and only patients who reported fever, pneumonia and/or hepatitis were notified.

Symptoms of all patients, reported during the acute phase of Q fever at the MHS, were checked to classify all patients in the correct study groups according to the EU definition, since the case definition used by the MHS before July 2008 was based on 'matching clinical symptoms' instead of 'fever, pneumonia and/or hepatitis'. Due to this check, ten patients originally qualified as notified patients were considered as non-notified patients in the analysis. The current Dutch case definition contains one additional criterion

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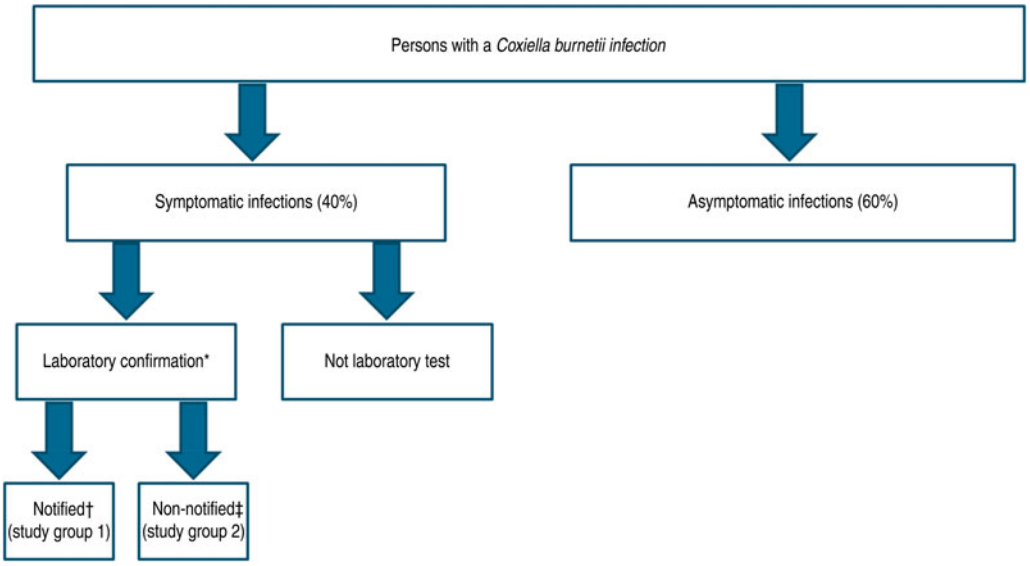

Fig. 1. Classification of the study groups in relation to all individuals with a *Coxiella burnetii* infection. * All patients were tested for Q fever in the laboratory after a request by their general practitioner or consultant physician. † Notified patients fulfil the EU case definition for Q fever (fever, pneumonia and/or hepatitis). ‡ Non-notified patients do not fulfil the clinical case definition because they had no fever, pneumonia and/or hepatitis.

compared to the EU case definition, namely an onset of illness within 90 days before diagnosis [12]. This was added in 2008 to identify only recent infections [16]. In our study, non-notified patients are only qualified as such because they do not fulfil the clinical criteria and not because their onset of illness was >90 days before diagnosis.

Notified Q fever patients (study group 1, Fig. 1)

This group consisted of those patients that fulfilled the EU case definition for Q fever [11]. All patients had an onset of illness in 2007 or 2008 and gave consent in the study by Morroy *et al.* [7] to be included in further research studies ($n = 562$).

Non-notified Q fever patients (study group 2, Fig. 1)

Patients who fulfilled the laboratory criteria, but not the clinical criteria (fever, pneumonia and/or hepatitis) were eligible for this study group ($n = 278$). All patients had a positive laboratory test for Q fever in 2008 or 2009. The most frequently reported symptoms during the acute phase of Q fever in this group were muscular pain, headache, malaise, fatigue, coughing and sweating. For 33 patients, no symptoms were reported. These patients were not excluded from the study since all of them were seen by a physician, who requested a laboratory test, and contacted by the MHS. Since they did not fulfil the clinical criteria for a case definition, they were considered non-notified.

Data collection

Notified Q fever patients from 2007 and 2008 were contacted in 2011 and 2012, respectively (about 4 years after their onset of illness). Non-notified Q fever patients were contacted about 4 years after their positive laboratory result. To obtain a large enough sample size, we also contacted non-notified patients with a positive laboratory test in 2009.

All patients received an information letter, a consent form and a questionnaire by post. Patients were asked to return the signed consent form and the questionnaire simultaneously, or only the consent form, stating that they did not want to participate. Patients who did not respond received a reminder 4 weeks later by post. Patients who returned an incomplete questionnaire were contacted by telephone, post or email by a member of the research team.

Questionnaire

The questionnaires included the Nijmegen Clinical Screening Instrument (NCSI) [17], which consists of eight subdomains and was developed at the Department of Medical Psychology at Radboud university medical center. It provides normative data

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indicating normal functioning, mild problems or severe problems for each subdomain, based on the sum score of the individual questions of the subdomain. The thresholds for mild problems and severe problems were based on scores of healthy participants and chronic obstructive pulmonary disease patients, respectively [17]. To compare the health status scores of the patients, the above-mentioned reference group of healthy participants [17] was expanded to match the Q fever patients for age and gender. They were recruited via local newspapers in the city of Nijmegen area and asked to visit Radboud university medical center, University Center for Chronic Diseases Dekkerswald, where they completed an electronic questionnaire, including the NCSI. The lung function of the healthy reference group was tested, so that individuals with an undiagnosed underlying respiratory illness could be excluded. The healthy references were not serologically tested for Q fever, so it is possible that individuals are included who previously had a Q fever infection.

Information on individual characteristics of patients was also collected, namely: socio-demographic information (gender, age, educational level) and medical background information (comorbidity, any additional treatment for long-lasting effects of Q fever).

Data analysis

Differences in baseline characteristics between the patient groups were tested with Pearson χ^2 tests and independent-samples t tests. The proportion of severely affected patients was calculated for each NCSI subdomain for both study groups and compared to the healthy reference group. Differences in subdomain scores between the notified and non-notified Q fever patients were analysed using a multivariate model for each subdomain, with correction for relevant confounding characteristics. Data were analysed using SPSS for Windows v. 20 software (SPSS Inc., USA). A P value <0·05 was considered statistically significant, based on two-sided tests.

RESULTS

We received 448 questionnaires from notified Q fever patients (80% response) and 193 questionnaires from non-notified Q fever patients (69% response). There were statistically significant differences in mean age (54·4 *vs.* 51·8 years) and gender (57·6% *vs.* 69·3% male) between participants and non-participants, respectively, for the notified patients, and in mean age (50·2 *vs.* 43·2 years) for the non-notified patients (data not shown).

The baseline characteristics of the participating groups of notified and non-notified Q fever patients are presented in Table 2. Notified patients were significantly older and more often male than non-notified patients. There were no significant differences in educational level and comorbidity between the two groups. The groups contained similar proportions of patients that followed an additional treatment for long-lasting health effects of Q fever, except for additional treatment with antibiotics, which seemed to be slightly higher in the notified group.

Health status of a large proportion of the patients (both notified and non-notified Q fever patients) was severely affected at 4 years after onset of illness as measured by the NCSI, ranging from 14·1% for the subdomain Subjective Impairment to 54·6% for the subdomain Fatigue (Table 3). In both study groups, the subdomains Fatigue and General Quality of Life were the most severely affected. On all subdomains, the proportion of severely affected patients was higher compared to the healthy reference group.

Health status scores between notified and non-notified Q fever patients after 4 years were compared. There were no significant differences in subdomain scores between the groups after correcting for differences in gender and age (Table 4).

DISCUSSION

This is the largest study to date in which health status of Q fever patients ($n = 448$ notified patients) was assessed as long as 4 years after the acute episode, and the first study in which health status of notified and non-notified Q fever patients has been compared. A large proportion of notified and non-notified patients still suffer from a severely affected health status at about 4 years after infection, mainly for the subdomains Fatigue (50·5% and 54·6%, respectively) and General Quality of Life (42·3% and 44·4%, respectively). There were no significant differences in mean scores on any of the health status subdomains between these two groups.

Studies that assessed health status of large groups of notified Q fever patients at 12 or 12–26 months after onset of illness also found that the subdomains Fatigue (60·2% and 43·5%) and General Quality of Life (50·0% and 44·9%) were the most severely affected [7, 8], similar to the results in our study. When comparing the proportions of severely affected

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Table 2. *Baseline characteristics of notified and non-notified Q fever patients*

Variable	Notified Q fever patients ($n = 448$)	Non-notified Q fever patients ($n = 193$)	Difference* *P* value
Male sex, %	57·6	45·1	0·004
Age (years), mean (±S.D.)	54·4 (12·4)	50·2 (15·3)	<0·001
Educational level†, %			0·883
Low	47·8	49·1	
Middle	28·9	29·6	
High	23·2	21·3	
Comorbidity‡, %	51·1	52·6	0·731
Additional treatment for Q fever§, %			
Psychological guidance	4·5	5·8	
Cognitive Behavioural Therapy	3·4	4·8	
Graded Exercise Therapy	4·5	5·8	
Additional treatment with antibiotics	11·0	6·3	
Other	7·1	5·8	

* For age, the difference between the groups was tested using an independent-samples *t* test. For the other characteristics, Pearson's χ^2 test was used. We did not test the difference for the characteristic 'Additional treatment for Q fever'.
† Educational level for notified Q fever patients was available for patients that participated in a study by Morroy *et al.* (n = 370) [7]. For the non-notified Q fever patients, this question was included only in the 2013 questionnaire, i.e. patients with a laboratory confirmation in 2009 ($n = 169$).
‡ Comorbidity can be either a serious medical event or medical intervention in the past 5 years (e.g. cancer, heart attack, pacemaker), or a chronic illness (e.g. rheumatoid arthritis, ulcerative colitis, diabetes); $n = 446$ for the notified group and $n = 192$ for the non-notified group.
§ Additional treatment for long-lasting health effects of Q fever (e.g. fatigue). This information was self-reported by the patients; $n = 446$ for the notified group and $n = 189$ for the non-notified group.

Table 3. *Proportion of severely impaired patients within each NCSI subdomain in the groups of notified and non-notified Q fever patients at 4 years after onset of illness/diagnosis, and individuals in a healthy reference group*

NCSI subdomain	Healthy reference group, % ($n = 121$)	Notified Q fever patients, % ($n = 448$)	Non-notified Q fever patients, % ($n = 193$)
Subjective Pulmonary Symptoms	0·8	26·6	25·5
Dyspnoea Emotions	1·7	30·8	31·9
Fatigue	2·5	50·5	54·6
Behavioural Impairment	0·8	15·2	15·7
Subjective Impairment	0·0	17·7	14·1
General Quality of Life	19·8	42·3	44·4
Health-related Quality of Life	2·5	27·4	21·4
Satisfaction Relations	10·7	18·3	19·3

NCSI, Nijmegen Clinical Screening Instrument.

patients on these subdomains to our own study results (50·5% and 42·3% of severely affected notified patients for Fatigue and General Quality of Life, respectively), it appears there is little improvement in health status between 1 and 4 years after onset of illness. These results are especially marked considering that there is a large overlap in patients that participated in our study and the study by Morroy *et al.* [7], which suggests that these outcomes cannot be explained by differences between study cohorts. Studies that assessed health status at 5 and 10 years after the acute phase of Q fever in relatively small patients groups ($n = 71$ and 108, respectively) also found higher fatigue levels in cases than in controls [1, 3].

The results of the present study imply that long-term health status is not determined by the symptoms

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Table 4. *Linear regression models presenting the NCSI scores for each subdomain at about 4 years after diagnosis for notified and non-notified Q fever patients, corrected for gender and age. Non-notified Q fever patients are the reference group. A lower score indicates better health*

Subdomain	Min-max (Δ)	Notified Q fever patients		Non-notified Q fever patients		Difference between groups corrected for confounders	
		Mean (s.d.)	*n*	Mean (s.d.)	*n*	(95% CI)	*P* value
Subjective Pulmonary Symptoms	2–20 (18)	6·1 (4·9)	447	6·1 (4·9)	192	0·0 (−0·8 to 0·9)	0·964
Dyspnoea Emotions	6–22 (16)	8·6 (3·4)	445	8·6 (3·4)	191	0·1 (−0·5 to 0·7)	0·759
Fatigue	8–56 (48)	33·5 (14·9)	440	33·4 (13·8)	185	1·2 (−1·3 to 3·7)	0·362
Behavioural Impairment	0–78 (78)	7·8 (11·3)	447	7·9 (11·9)	191	−0·6 (−2·6 to 1·3)	0·523
Subjective Impairment	4–28 (24)	7·7 (4·9)	446	7·3 (4·7)	192	0·2 (−0·6 to 1·1)	0·559
General Quality of Life	1–76 (75)	15·5 (13·8)	442	15·6 (14·1)	187	0·4 (−2·0 to 2·8)	0·744
Health-related Quality of Life	2–10 (8)	4·2 (2·0)	445	4·0 (1·9)	192	0·2 (−0·2 to 0·5)	0·323
Satisfaction Relations	2–10 (8)	3·1 (1·5)	443	3·2 (1·7)	192	0·0 (−0·3 to 0·2)	0·739

NCSI, Nijmegen Clinical Screening Instrument; CI, confidence Interval.

during the acute phase of the disease. The only difference between the groups was found in the proportion of patients that received additional treatment with antibiotics for long-lasting effects of Q fever, which was higher in the notified group. This might be due to the fact that many notified patients suffered from pneumonia during the acute phase of Q fever and are more susceptible for a relapse of this condition. Our findings suggest that there is no basis to distinguish between patients with fever, pneumonia and/or hepatitis and patients with another clinical presentation in the case definition of Q fever, with respect to the long-term health impact. However, the aim of notifying cases is to identify recent infections and making changes the EU case definition needs careful assessment, as a more sensitive case definition would result in an increase of false positives (old infections, rather than recent infections).

Finally, the fact that our results show that non-notified cases experience a long-term health impact similar to notified cases, indicates that the magnitude of the Q fever epidemic over the period 2007–2009 in The Netherlands might be underestimated if only the 3522 notified cases are taken into account [12]. A study by van der Hoek *et al*. estimated the expected number of *C. burnetii* infections over this period at 44 000, based on data of blood donors [18]. However, since all participants in our study visited their GP or consultant physician due to health problems at the time of the acute infection, we cannot extrapolate our study results to the entire population of individuals with a *C. burnetii* infection, since most of them did not seek medical attention due to mild or no health problems [18–20]. An upcoming population-based surveillance study in The Netherlands ($n = 2163$) might provide more insight into the long-term health impact of individuals infected with *C. burnetii* without being previously diagnosed as such.

Limitations

For most non-notified Q fever patients, one or more symptoms that could be attributable to Q fever were reported, but for some patients no symptoms were reported at all. The registration system of the MHS was not set up for research purposes. Symptoms of patients that did not have fever, pneumonia and/or hepatitis may not therefore have been systematically registered, and this might explain why some non-notified patients did not report symptoms. However, since all patients were specifically asked whether they suffered from fever, pneumonia and/or hepatitis, we assume that misclassification between the notified and non-notified group was not an important factor.

A minor limitation is that our study lacks a reference group which could provide information on the proportion of individuals with severe Fatigue or a severely affected General Quality of Life in the general population. In the healthy reference group, the proportion of individuals with a severely affected General Quality of Life is already quite high (19·8%). We expect this proportion to be even higher when measured in the general population. A study from 2009 that investigated the prevalence of fatigue

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in a random sample of the population in the city of Nijmegen found that over 30% suffered from chronic fatigue (fatigue present for longer than 6 months) [21]. In a German study, about 30% of individuals from the general population reported moderate fatigue during the last 6 months, while almost 10% of subjects reported substantial fatigue lasting $\geqslant$6 months [22]. These studies imply that baseline fatigue levels are already quite high in the general population and that the high proportion of patients severely affected on the Fatigue subdomain in our study might also include fatigue due to other reasons than Q fever.

Compared to other studies on Q fever by the same author [8, 23], the response rates of these groups of participants are relatively low (94%, compared to 80% and 69% in the present study). This can partly be explained by the fact that these groups only received one reminder by post, while patients in the other studies received several reminders by telephone. Participants differed from non-participants in age and gender (respondents were older and more often female) and this might lead to an overestimation of the impact on health of patients, since women generally report more symptoms than men [24, 25]. We feel that it is not likely that working patients exaggerate their symptoms to participate in a disability programme as this is checked by occupational physicians and leads to a reduced income in The Netherlands.

CONCLUSIONS

This study shows that long-term health status (which includes fatigue and general quality of life) is seriously reduced, both for notified and non-notified Q fever patients at 4 years after their onset of illness. Our findings suggest that the magnitude of the 2007–2009 Q fever outbreak in The Netherlands was underestimated when only notified patients according to the EU case definition are considered.

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DECLARATION OF INTEREST

None.

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