Self-reported sick leave and long-term health symptoms of Q-fever patients

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Introduction

Q-fever is a worldwide zoonotic disease caused by Coxiella burnetii, an obligate intracellular bacterium. In The Netherlands, Q-fever was uncommon before 2007 with 10–20 notified cases annually. Since 2007 and up to December 2010, more than 4000 cases were notified in four outbreaks implicating dairy goats as the source. Approximately 80% of the notified Q-fever patients reside in Noord-Brabant, the province with the highest dairy goat density in The Netherlands.

Coxiella burnetii is common in a wide range of wild and domestic animals but only small ruminants, in particular sheep and goats, are associated with large human outbreaks. Infected animals excrete billions of bacteria in birth products and to a lesser extent in faeces, urine and milk. Human infection occurs mainly after inhaling dust particles contaminated with C. burnetii.

In susceptible individuals, infection develops after a mean incubation period of 21 days. In general, 60% of the infected Q-fever patients are asymptomatic, whereas 20% of the patients develop mild symptoms. Another 20%, however, present with more severe symptoms ranging from high fever, severe headache, night sweating, nausea, diarrhoea, pneumonia, hepatitis, pericarditis, myocarditis and neurological symptoms.

Chronic Q-fever may develop in up to 5% of acute cases due to a reactivation of Coxiella. A follow-up of 686 Dutch acute Q-fever patients from 2007 to 2008 finds that 1.6% converted to chronic Q-fever. A feared presentation of chronic Q-fever is endocarditis that may take 10–15 years to develop. Pregnant women and people with heart valve disorders, vascular prosthesis or impaired immunity have a higher risk to develop a chronic infection.

Q-fever patients may develop Q-fever fatigue syndrome (QFS), a debilitating fatigue out of proportion with exertion that may last up to 10 years. Post-infection fatigue is not unique for Q-fever. It may also occur after other infectious diseases such as Lyme disease, Epstein–Barr virus infection, legionnaires disease and other pneumonias.

Anecdotal information suggests that patients from the 2007 cohort had a more severe course of illness compared with those from the 2008 outbreak and were longer absent from work. However, evidence on the recovery of patients from the Dutch 2007 and 2008 cohorts is lacking. This study aims to fill that gap. The first objective is to assess the duration of sick leave after an episode of acute Q-fever—in 2007 or 2008—and the long-term self-reported symptoms and associated risk factors. The second objective is to assess differences between the two cohorts for the duration of self-reported sick leave and the occurrence and frequency of long-term health symptom.

Methods

Study design and population

The population for this cohort study consisted of 898 patients notified in 2007 and 2008 to the Municipal Health Services ‘Hart voor Brabant’ and ‘Brabant Zuid-Oost’. Due to incomplete data or an unknown month of onset of illness, 28 patients were excluded (figure 1). The remaining 870 Q-fever patients fitted the Dutch notification criteria; a laboratory confirmation of Q-fever and clinical presentation with fever, pneumonia or hepatitis.

Data collection

In February 2009, all patients received a study information fold-
er including a participation request and consent form by post (figure 1). Patients could state their willingness to take part in any of a
number of studies under the so-called Q Quest-1 project, by signing and returning the consent form. Participating patients received a questionnaire—by postal mail—focusing on demographic characteristics, medical history, smoking behaviour, current Q-fever-related physical symptoms and employment-related items, such as duration of sick leave following acute Q-fever, resumption and current ability to work (employed, self-employed, volunteer work, household work). During a pre-test, the completion of the questionnaire took 20–30 min.

All patients from the 2007 cohort received the questionnaire in February 2009 (13–26 months after onset of Q-fever illness). Patients notified in 2008 were mailed a questionnaire 1 year after the month of onset of illness. Patients from both cohorts received two reminders after 3 and 6 weeks. We obtained data on non-responders regarding gender, age, year of onset of disease and hospitalization from the notification data of the Municipal Health Services.

Data analysis

Questionnaires were double scanned and data were cleaned. Statistical analysis was done using SPSS 16 for windows. We used the Mantel–Haensel \( x^2 \) test and Fisher’s exact test to compare proportions. \( P \)-values are based on two-tailed tests with a \( P < 0.05 \) defined as significant. The notification data of the Municipal Health Services were used to compare responders and non-responders for age, gender, year of onset of illness and hospitalization.

Multivariate logistic regression was used to model the relationship between outcome (sick leave >1 month or presence of symptoms) and the independent variables age, gender, hospitalization, underlying diseases and year of onset of illness. Multivariate logistic regression was used to model the relationship between the determinants year of onset of illness and hospitalization with the outcomes presence of symptoms (fatigue) and long-term sick leave. For the potential confounders, age, gender, smoking and co-morbidity, we used the same model.

Results

Patient participation

The overall response rate was 63.9% (figure 1). The mean time between the day of onset of illness and receiving the questionnaire was 19.5 months (SD 2.3) for patients of the 2007 cohort and 12.1 months (SD 0.5) for patients of the 2008 cohort. We were informed that five patients died, but had no information on the cause of death.

The response rate of men was lower than that of women as was that of younger (<30 years of age) compared with older patients (>30 years of age). There were no differences between responders and non-responders for year of onset of illness and hospitalization (see Supplementary table S1 for details).

Characteristics of the study population

The study population (table 1) of the 2007 and 2008 cohorts was similar with respect to gender, age group, smoking behaviour and underlying diseases. The hospitalization rate of patients of the 2007 cohort, however, was significantly higher [relative risk (RR) 2.50, 95% CI 1.68–3.01; \( P < 0.001 \)] than that of the 2008 cohort. Patients from the 2007 cohort were more often depressed (OR 1.88, 95% CI 1.10–3.34; \( P = 0.044 \)) than patients from the 2008 cohort.

Sick leave

Prior to the Q-fever infection 62% of the study population was gainfully employed. During the episode of acute fever, 91.3% of these patients reported sick for work (figure 2). Overall, 132 (39.6%) of the study subjects who worked prior to the infection were longer than 1 month (long-term sick leave) absent from work following an acute Q-fever infection. See Supplementary table S2 for sick leave of the gainfully employed, volunteers and those who do household work.

Hospitalization, smoking and underlying heart disease were independent predictors for long-term sick leave (table 2). Gender, age, year of onset of illness, underlying lung disease, depression or level of education were not significantly related to long-term sick leave (table 2).

Self-reported symptoms

Almost 40% of the patients reported at least one current health complaint at the time of follow-up that they perceived to be Q-fever-related (Supplementary table S3). The most frequently reported symptoms were: fatigue, 19.8%; difficulty concentrating, 9.5%; muscle pain, 9.0%; and night-time sweating, 7.9%. Women (OR 1.84, 95% CI 1.27–2.67; \( P = 0.001 \)) were more likely to report symptoms than men. For fatigue, this was 25.1% of women vs. 16.2% among men.

The 2007 and 2008 cohorts were similar in number, type and frequency of reported symptoms (Supplementary table S3). Multivariate logistic regression showed that year of onset of illness was not significantly related to the reporting of a health complaint, when controlling for differences in age, smoking, underlying heart/lung disease and depression. Women and patients that had been hospitalized or suffered depression were more likely to report fatigue at the time of follow-up (table 2).

Long-term sick leave, resumption of work or daily activities in relation to perceived Q-fever-related health symptoms

Study subjects \((N=132, 39.6\%)\) that were longer than 1 month (long-term sick leave) absent from work following an acute Q-fever infection showed more fatigue at 12–26 months after initial illness than patients with a shorter absence.

Of the patients that resumed work, 9.3% reported that they were unable to function at pre Q-fever levels at the time they completed the questionnaire, due to perceived Q-fever-related health symptoms, mainly fatigue and concentration problems. Almost one-third of the patients (29.0% of the 2007 cohort and 33.1% of the 2008 cohort), reported that they had not fully resumed their daily activities at 12–26 months.
after onset of illness. Stated reasons were fatigue (80.8%) and respiratory problems (4.9%).

Discussion

We analysed data from notifications and questionnaires of 556 Q-fever patients notified in 2007 and 2008 in The Netherlands. Our most important findings were that after an episode of acute Q-fever, two out of five patients were over a month absent from work. We found that hospitalization in the acute phase, underlying heart disease and smoking behaviour were independent predictors for sick leave exceeding a month. Almost, 1 in 10 patients were unable to function at pre Q-fever infection level at the time of the questionnaire mainly due to fatigue and concentration problems. Two out of five patients reported Q-fever-related symptoms and one-third indicated that they had not resumed their daily activities to the pre Q-fever infection level.

Work and sick leave

To our knowledge, this is the first time that data on Q-fever and sick leave following a Q-fever outbreak are presented. We are therefore unable to compare the results with other studies on Q-fever patients. We do, however, know that in The Netherlands the average duration of sick leave per employee was 6.3 days in 2008. One in three Dutch patients with sick leave have a cold or flu-like symptoms, but are rarely longer than 1 week absent from work. In a large cross-sectional study, 16% of the Dutch employees reported >9 days sick leave per year. In our study, 57% of Q-fever patients reported >9 days sick leave per year.

Patients that reported persisting fatigue at 12–26 months, were also significantly more often long-term absent from work due to sick leave following the acute infection. Our findings are in line with a study from Huibers et al. that showed that persisting fatigue has a strong correlation with sickness absence exceeding 42 days.

Symptoms

One to 2 years after acute Q-fever, two-thirds of the patients still reported symptoms that they attributed to Q-fever. Cohorts did not differ in the overall reported symptoms and specific symptoms. We had expected to find a difference in symptoms between the cohorts as clinicians often reported that patients of the 2007 cohort had more serious illness. Due to methodological reasons (see under ‘Methodological considerations and study limitations’ section), we are unable to assess if the 2007 cohort initially had more symptoms during the convalescence period and partially recovered or that the level of persistent symptoms was similar for both cohorts.

Hatchette and Hayes reported 51% of the Q-fever patients with persistent symptoms 26 months after the acute Q-fever episode. Ayres et al. studied a cohort of 71 Q-fever patients and found that 5 years after the initial infection up to 68% of study subjects presented with symptoms. Our findings are in line with these two studies. It may be questioned whether long-term persistence of symptoms is unique for Q-fever. In a study of patients with community-acquired pneumonia (of varying degrees of severity), a full recovery was reported after 6–18 months. Persistence of symptoms was mostly attributed to morbidity that existed before the pneumonia episode. In our study, patients with pre-existent heart or lung disease had similar outcomes for persisting symptoms than those without pre-existent disease.
Fatigue

In the present study, 19.8% of the Q-fever patients report fatigue 12–26 months after the onset of illness, without a significant difference between both cohorts. Although patients from the 2007 cohort were more often hospitalized and our study shows that hospitalization in the past—due to Q-fever—is significantly related to fatigue 12–26 months later, it appeared that the year of onset of illness did not influence long-term fatigue.

In another study,23 on these same patients, we found that when using a validated instrument, the NCSCI (Nijmegen Clinical Screening Instrument)24,25 up to 43.5% of the patients stated fatigue. Other studies also report much higher rates of 52%26 undue tiredness after 1 year, 51% up to 5 years later,14 or even 64% 10 years after Q-fever infections.13 We therefore suspect that the outcome is related to the way the information on fatigue is gathered.

Our finding that patients who reported fatigue had been more often hospitalized is in line with Hickie et al.27 who report that the key risk factor for post-infective fatigue syndromes is the severity of the acute illness. In their study, they found no age, sex-related or psychological risk factors. We found, however, that women and patients with depression reported more fatigue. Depression has two components:28 a somatic factor often expressed as fatigue and a depression factor. The dominating factor may determine the diagnosis. In our study, we could not make a distinction between the two as we did not ask additional questions. Different co-morbidities—including chronic fatigue—associated with depression can be explained by (neuro) inflammatory and oxidative and nitrosative stress pathways.29 Unexplained fatigue and depression might act as independent risk factors of each other.30 The question is whether the explainable fatigue caused by Q-fever might be a pre-cursor to depression.

Women also reported other symptoms significantly more often. This does not necessarily mean that women have more symptoms, as woman are known to present symptoms more often.31

We did not medically examine patients and could not establish whether the fatigue fulfilled the diagnostic criteria of the chronic fatigue syndrome (CFS).32,33 Nor did we have information on the duration, the severity of the fatigue, the presence of tender lymph nodes or possible other causes.

Cohort comparison

Patients from the 2007 cohort received the questionnaire later (13–26 months after the acute episode) than those of the 2008 cohort (12 months). Therefore, data from the two cohorts are not entirely comparable as we are unable to assess the initial level of symptoms of the 2007 cohort.

The hospitalization rate was much higher for the 2007 cohort (43.8%) than for the 2008 cohort (19.5%). This shows that our study population is in this respect a good representation of the notified Q-fever patients as mandatory notification data show that the hospitalization rate for our area was 43.7% in 2007 and 16.3% in 2008. This is much higher than the rate of 2–3% reported in literature.34 The high percentage of hospitalized patients in 2007 was largely influenced by active case finding in a retrospective survey among hospitalized cases.35 Both patients and clinicians recognized and diagnosed Q-fever more readily in 2008, when it had become apparent that this previously uncommon disease presented more often in the area. Only the very ill patients might have been recognized and diagnosed by clinicians in 2007.

Although hospitalized patients reported more long-term fatigue and sick leave, we did not find an independent significant relation between cohort and reported fatigue or sick leave.

Methodological considerations and study limitations

A limitation of this study is that we lacked a control group. The reason was that this study was designed as a cost of illness study rather than an aetiological study.

One of the complexities of this study is that we were dealing with many confounders such as age, gender and co-morbidity; for example, heart disease, depression and health symptoms such as fatigue. Our determinants of interest were, however, hospitalization and the year of onset of illness.

The response rate was significantly higher for woman and patients older than 30 years this is in line with survey response rates in the Netherlands.36 Due to this selection bias, the percentage of fatigue found in this study might be slightly higher than that in the total Q-fever population.

Table 2: Multivariate logistic regression analysis of risk factors for long-term sick leave (exceeding 1 month) in 334 paid workers following acute Q-fever and self-reported long-term fatigue measured at 12–26 months after the onset of illness

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Long-term sick leave, N = 132</th>
<th>Long-term fatigue, N = 110</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI) P-value</td>
<td>OR (95% CI) P-value</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1.39 (0.83–2.35) 0.213</td>
<td>1.77 (1.14–2.75) 0.012</td>
</tr>
<tr>
<td>Male (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agea</td>
<td>1.01 (0.99–1.03) 0.890</td>
<td>1.01 (0.99–1.03) 0.213</td>
</tr>
<tr>
<td>Hospitalizationb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.99 (2.15–7.43) 0.000</td>
<td>1.95 (1.19–3.19) 0.008</td>
</tr>
<tr>
<td>No (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007</td>
<td>1.18 (0.60–2.33) 0.626</td>
<td>1.23 (0.71–2.15) 0.461</td>
</tr>
<tr>
<td>2008 (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1.69 (1.01–2.84) 0.046</td>
<td>1.29 (0.79–2.10) 0.299</td>
</tr>
<tr>
<td>No (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying Heart disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.51 (1.27–16.09) 0.020</td>
<td>1.66 (0.79–3.49) 0.182</td>
</tr>
<tr>
<td>No (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Underlying Lung disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>2.78 (0.93–8.34) 0.068</td>
<td>1.61 (0.77–3.33) 0.204</td>
</tr>
<tr>
<td>No (ref.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.98 (0.23–4.26) 0.976</td>
<td>2.53 (1.11–5.76) 0.027</td>
</tr>
<tr>
<td>No (ref.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a: Age has been modelled as a continuous variable
b: Hospitalization during the acute phase of illness
Access to pre-Q-fever health status and sick leave data would have been ideal but these data were unavailable. Therefore, we can not proof if all reported sick leave and health symptoms are completely related to Q-fever.

In the absence of other data, our data give a valuable insight into sick leave and symptoms related to Q-fever. One could question whether these symptoms were caused by Q-fever because symptoms of Q-fever may not be very specific. By asking per symptom whether the symptom was present, we might have prompted patients which could have led to over reporting. The same could have applied to co-morbidity.

Although we asked questions on past or initial symptoms, we only analysed current symptoms thereby omitting problems with recall bias.

For sick leave, we cannot exclude recall bias as we asked patients to recall their sick leave up to 26 months after an episode of acute Q-fever. Many patients were, however, very precise and even stated dates of sick leave. Although we asked patients about productivity loss at work, we did not use a validated instrument and can therefore not directly compare our findings with other studies.

Data on sick leave were only available for responders. This might have biased the results on sick leave. Although we are not sure about that, we do have some indications about the validity of our findings. The strongest indication is that the hospitalization rate, one of the most important determinants of the duration of sick leave, was similar for responders and non-responders.

Conclusions

The negative impact of Q-fever on productivity and perceived health status is considerable, especially when taking the high incidence in certain communities into account. Hospitalization, as an indicator of severity of the acute illness, turned out to be a strong independent predictor for long-term sick leave and persistent fatigue in Q-fever patients.

This study demonstrates the considerable burden of disease from Q-fever for individual patients, families and society.

Supplementary Data

Supplementary Data are available at EURPUB online.

Acknowledgements

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Conflicts of interest: None declared.

Key points

- One year after an episode of acute Q-fever, 40% of the patients still report Q-fever-related symptoms.
- More than 30% of our study population report that they have not resumed their daily activities to the pre Q-fever infection levels.

References

2 Centre for Infectious Disease Control Netherlands. Available at: http://www.rivm.nl/cib/themas/Q-koots/index.jsp (11 February 2010, date last accessed).
Hepatitis C virus seroprevalence in The Netherlands

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A population-based anti-hepatitis C virus (HCV) prevalence is important for surveillance purposes and it provides an insight into the burden of disease. In The Netherlands, a recent HCV seroprevalence estimate is not available. This national population-based cross-sectional serosurvey (PIENTER-2) resulted in a weighted national HCV seroprevalence of 0.30% (95% confidence interval 0.05–0.55%). About 70% of the HCV positive individuals found were born in an HCV-endemic country.

Introduction

The estimated hepatitis C virus (HCV) prevalence in Europe ranges from 0.1% to 6.0%, with the highest prevalence (≥2%) in Southern and Eastern Europe.1 Knowledge of the HCV prevalence in the general population of The Netherlands is limited. A Dutch cross-sectional serosurvey in 1995–96 (the PIENTER-1 study) estimated a national HCV seroprevalence of 0.1% [95% confidence interval (CI) 0.01–0.02%].2 However, groups with higher risk profiles, such as individuals originating from HCV endemic regions, were underrepresented in this study, which resulted in a possible underestimation of HCV prevalence. In 1997, the Dutch Health Council estimated a HCV seroprevalence for the general Dutch population of 0.1–0.4% (www.gezondheidsraad.nl). Furthermore, three seroprevalence studies were performed in urban areas in The Netherlands and these prevalences ranged from 0.2% to 1.1%.3–5 Two of these studies oversampled individuals with a non-Western nationality and resulted in higher HCV seroprevalence than those estimated for the general Dutch population.5,5 In addition, an overall HCV prevalence of 0.4% was modelled in The Netherlands including (suboptimal) data from risk groups.

This current study (PIENTER-2) is an update of the previous national population-based survey (PIENTER-1).6 Individuals with non-Dutch nationalities were better represented in PIENTER-2, so that an improved and more recent estimation of the national HCV seroprevalence could be made.

Methods

Between 2006 and 2007, cross-sectional serum samples and questionnaires from the Dutch population aged 0–79 years, selected from municipal registers, were collected. The questionnaire covered demographic data, vaccination history, activities possibly related to infectious diseases and information related to sexually transmitted diseases (this latter was only asked of individuals aged ≥15 years). In total, 19,781 individuals were invited, including an oversampling of the largest migrant groups in The Netherlands. The study design is described more in detail elsewhere.6

Laboratory methods

The presence of HCV-antibodies was determined using a micro particle enzyme immuno assay (MEIA; Abbott Laboratories, North Chicago, IL, USA) with immunoblot confirmation (INNO-LIA HCV score; Innogenetics, Belgium). The anti-HCV confirmed positive samples were tested for the presence of HCV RNA.2 HCV genotypes 1–4 were detected by sequencing a 436-nt fragment of the NS5B region.2 Viral load was determined using a published quantitative HCV PCR method.8

Statistical analyses

For estimation of the HCV seroprevalence in PIENTER-2, we weighted by gender, age and ethnicity to account for deviations of the sample