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Serious long-term health consequences of Q-fever and Legionnaires' disease

JORIS A.F. VAN LOENHOUT^A, HEIN H.M.M. VAN TIEL^A, JET VAN DEN HEUVEL^B, JAN H. VERCOULEN^{C, D}, HANS BOR^A, KOOS VAN DER VELDEN^A, W. JOHN PAGET^{A, E}, JEANNINE L.A. HAUTVAST^A

^a Academic Collaborative Centre AMPHI, Department of Primary and Community Care, Radboud University Medical Center, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

^b Department of Infectious Disease Control, Municipal Health Service Hart voor Brabant, 's-Hertogenbosch, The Netherlands

^c Department of Medical Psychology, Radboud University Medical Center, Nijmegen, The Netherlands

^d Department of Pulmonary Diseases, Radboud University Medical Center, Nijmegen, The Netherlands

^e Netherlands Institute for Health Services Research (NIVEL), Utrecht, The Netherlands

SUMMARY

Background: We assessed and compared the long-term health status of Q-fever patients and patients with Legionnaires' disease.

Methods: Q-fever patients and patients with Legionnaires' disease fulfilling the Dutch notification criteria filled out a questionnaire at one year after onset of illness. The proportion of patients with an abnormal score was calculated for 12 health status subdomains and mean scores for the most relevant subdomains were compared between the patient groups.

Results: We included 309 Q-fever patients and 190 patients with Legionnaires' disease in the study. A large proportion of the two patient groups was negatively affected on many of the subdomains, especially 'Fatigue', 'General Quality of Life' and 'Role Physical'. We assessed health status of the patient groups using a multivariate regression analysis and found no significant difference for 'Fatigue' and 'General Quality of Life'. Only for the subdomain 'Role Physical', Q-fever patients scored significantly worse compared to patients with Legionnaires' disease.

Conclusions: Many Q-fever patients and patients with Legionnaires' disease suffer from a severely affected health status on one or more subdomains at one year after onset of illness. We recommend additional support for a large proportion of both patient groups during the first year after onset of illness.

BACKGROUND

Post-infectious chronic fatigue is a syndrome that is frequently reported to develop after an acute infectious illness.¹ It has been described in patients suffering from various infectious diseases, such as infectious mononucleosis, dengue and infections with *Giardia*,^{2, 3, 4 and 5} although other studies have failed to demonstrate its existence.^{6 and 7} The persistence of an impaired health status, including fatigue, of patients after acute Q-fever was recently shown in studies in the Netherlands.^{8 and 9} These results are in line with previous Q-fever studies in other countries.^{10, 11, 12 and 13} So far, only one study from Australia has compared long-term health status of Q-fever patients to health status of patients with other infections, in this case Epstein–Barr virus and Ross River virus.¹¹

The Netherlands was confronted with a large outbreak of Q-fever involving over 4000 patients between 2007 and 2011,¹⁴ and we assessed their health status, including fatigue and quality of life. In order to understand the role of different pathogens in the development of a long-term impaired health status, including post-infectious chronic fatigue, studies comparing the outcome of different infectious diseases are important. Q-fever and Legionnaires' disease are acute febrile diseases which may present with similar clinical manifestations.^{15 and 16} In addition, information on the long-term health status and quality of life of patients with Legionnaires' disease is limited, with only one study showing an impaired health status at 1.5 years after onset of illness.¹⁷ We performed a study to compare health status of Q-fever patients and patients with Legionnaires' disease at one year after onset of illness.

METHODS/DESIGN

The design used in this study is a cross-sectional survey of patients with Q-fever and patients with Legionnaires' disease one year after onset of illness. The study protocol was submitted to the Medical Ethical Review Board of the region Arnhem-Nijmegen, which indicated that ethical review was not required. The data on healthy controls were derived from a different study, for which approval was given by the Medical Ethical Review Board of the Radboud university medical center (reference number: 2006/243).

STUDY POPULATION

Patients with Q-fever

Patients diagnosed with Q-fever in 2010 and 2011 in the Netherlands ($n = 483$),¹⁴ who were at least 18 years of age and fulfilled the Dutch notification criteria of Q-fever, were eligible for this study (also described in the study protocol¹⁸). The Dutch notification criteria include a clinical presentation with fever, pneumonia or hepatitis and an onset of illness within the previous 90 days,¹⁹ combined with a positive serology by one of the following laboratory tests:

- Identifying a seroconversion or a quadrupled or higher increase in IgG antibody titre against *Coxiella burnetii* in a paired serum sample (sera

obtained in the acute phase and recovery phase with a time interval ≥ 2 weeks) by indirect immunofluorescence or complement fixation test;

- Presence of IgM-antibodies against phase II of *C. burnetii*;
- Identifying *C. burnetii* by PCR or culture in blood or respiratory material;
- Presence of antibodies against phase I of *C. burnetii* (chronic infection).

Eligible patients were informed about the study by the Municipal Health Services. 327 patients were invited to participate in this part of the study.

Patients with Legionnaires' disease

Patients diagnosed with Legionnaires' disease, an onset of illness in 2010 and fulfilling the Dutch notification criteria were eligible to participate in this study. The Dutch notification criteria include a case definition of matching clinical symptoms, usually pneumonia, confirmed by at least one but preferably two of the following laboratory diagnostic tests¹⁴:

- Isolation of *Legionella*-species from respiratory secretions or blood; Identification of the *Legionella pneumophila*-antigen in urine either by radio-immuno-assay or enzyme linked immunosorbent assay or immunochromatographic assay;

- Identification of the *Legionella*-species by PCR in clinical material; Identification of a significant titre of IgM-antibodies against *L. pneumophila* by ELISA;

Identification of a significant titre elevation of antibodies against *L. Pneumophila*.

In 2010, roughly 400 patients had an onset of illness and were notified to all 25 Municipal Health Services in the Netherlands. A subsection of patients was recruited through 14 Municipal Health Services with the highest numbers of patients with Legionnaires' disease, comprising 243 patients that could be contacted for this study.

Healthy controls

A control group consisting of healthy participants was formed by recruiting persons via advertisements in local newspapers in the city of Nijmegen area. The healthy controls were matched for age and gender to the group of Q-fever patients and were asked to visit Radboud university medical center, University Center for Chronic Diseases Dekkerswald, where they completed an electronic questionnaire, which included the Nijmegen Clinical Screening Instrument. The lung function of healthy controls was also tested, so that persons with an undiagnosed underlying respiratory illness that could affect their health status could be excluded.

DATA COLLECTION

The study collected patients' information at 12 months after onset of illness. Patients received an information letter, an informed consent form and a questionnaire. They were asked to either return the signed informed consent form and the questionnaire simultaneously, or only the informed consent form stating that they did not want to participate. Patients who did not respond received a reminder by telephone or postal mail. Patients who returned an incomplete questionnaire were contacted by telephone by a member of the research team in order to complete the questionnaire.

QUESTIONNAIRE

The study questionnaire contained two instruments to measure health status: the Nijmegen Clinical Screening Instrument (NCSI)²⁰ and the Short Form 36 (SF-36),²¹ see Table 1. The SF-36 used was the official Dutch translation obtained from Quality Metric, Lincoln RI, USA. The NCSI and SF-36 were used simultaneously since they gather information on different domains. The NCSI provides normative data indicating normal functioning, mild or severe problems for each subdomain. Only those subdomains of the SF-36 that were previously shown not to be conceptually similar to subdomains of the NCSI were used in the analyses ('Role Physical', 'Bodily Pain', 'Social Functioning' and 'Role Emotional').²² Information on confounders for long-term impaired health status due to Q-fever or Legionnaires' disease was also collected. The confounders were obtained at one year after onset of illness and consisted of socio-demographic aspects (gender, age, educational level), lifestyle aspects (Body Mass Index (BMI), smoking behaviour, alcohol consumption) and medical aspects (pre-existing health problems (e.g. immune deficiencies, cancer, diabetes), hospitalisation (during the first year after onset of illness)).

[TABLE 1]

DATA ANALYSIS

Demographic and health characteristics (gender, age, educational level, BMI, smoking behaviour, alcohol consumption, pre-existing health problems, hospitalisation) of the patient groups (Q-fever and Legionnaires' disease) were compared using Pearson Chi-square Tests and Independent Samples *t*-tests. For the NCSI, the proportion of patients that was severely affected was calculated for each subdomain for both Q-fever and Legionnaires' disease. Subdomains for which at least 40% of the patients for either illness were severely affected were considered relevant for comparison in our study and were therefore included in the subsequent analyses. For the SF-36, mean scores for the subdomains were calculated on a scale from 0 to 100% per patient group. These scores were compared to normative scores from the general adult population in a large U.S. study, also on a scale from 0 to 100% ($n = 2474$).²³ Subdomains for which the mean score for either illness was at least 20% lower than the normative score were considered relevant for comparison in our study and were therefore included in the subsequent analyses. Analyses in which health status of Q-fever patients was compared to health status of patients with Legionnaires' disease were performed for relevant subdomains only. The mean NCSI and SF-36 scores between the two groups were first compared by using Independent Samples *t*-tests. Second, multivariate regression analyses were performed in which the results were adjusted for confounders, because of large differences in confounders between the patient groups and because studies have shown that these confounders (e.g. gender and smoking behaviour) are associated with health status.^{24, 25 and 26} Therefore, all collected confounders were entered in the models. Finally, the fit of the multivariate regression models was compared to the fit of models expanded with interactions between the type of illness (Q-fever or Legionnaires' disease) and confounders using F-tests. The aim of these analyses was to discover whether including interactions leads to significant improvements in the fit

of the models, thus revealing subgroup differences in the relation between type of illness and health status.

Data were analysed using the software SPSS for Windows (version 20). A *p*-value of <.05 was considered to be statistically significant, based on two-sided tests.

RESULTS

PARTICIPATION AND CHARACTERISTICS OF THE STUDY POPULATION

We received 309 questionnaires from Q-fever patients (response of 94%) and 190 questionnaires from patients with Legionnaires' disease (response of 78%). There was a statistically significant difference in age between responders and non-responders among the Q-fever patients (49.9 vs. 43.1 respectively). There were no differences between responders and non-responders in gender among the Q-fever patients, and in age and gender among the patients with Legionnaires' disease (data not shown).

The characteristics of both patient groups are presented in Table 2. The patient groups differed significantly for gender, age, educational level, smoking behaviour, alcohol consumption, pre-existing health problems and hospitalisation. There was no significant difference in BMI between the two groups. The mean age of the healthy controls was 51.4 and 55.% was male.

[TABLE 2]

HEALTH STATUS

NCSI

Health status of a large proportion of the patients (both Q-fever and Legionnaires' disease) was severely affected at one year after onset of illness as measured by the NCSI, ranging from 17.5% for the subdomain 'Behavioural Impairment' to 60.2% for the subdomain 'Fatigue' (Table 3). In both patient groups, the subdomains 'Fatigue' and 'General Quality of Life' are the most severely affected. Severe 'Fatigue' is reported more often by Q-fever patients (60.2%) compared to patients with Legionnaires' disease (50.0%), as is a severely affected 'General Quality of Life' (50.0% vs. 42.6% respectively). On all subdomains, the proportion of severely affected patients was higher compared to the healthy control group.

[TABLE 3]

SF-36

For the SF-36, higher scores indicate a better health status. The largest differences between the patient groups and the normative data were found for the subdomain 'Role Physical' (Table 4). For 'Bodily Pain' the patients with Legionnaires' disease

actually scored 4.6% higher compared to the normative data of the general population.

[TABLE 4]

DIFFERENCE IN HEALTH STATUS

To compare health status at one year after onset of illness between Q-fever patients and patients with Legionnaires' disease, we selected the subdomains which scores were most relevant in both patient groups. For the NCSI, the proportions of patients severely affected are clearly highest for 'Fatigue' and 'General Quality of Life' compared to the other subdomains. For the SF-36, only scores for the subdomain 'Role Physical' differ with more than 20% compared to the normative group. Although Q-fever patients scored worse on all tested subdomains compared to patients with Legionnaires' disease (higher scores for 'Fatigue' and 'General Quality of Life', lower score for 'Role Physical'), Independent Samples *t*-tests showed that these results were not statistically significant (Table 5).

[TABLE 5]

Corrected models

When health status of the two patients groups was compared via multivariate regression analyses that adjusted for all collected confounders, Q-fever patients still scored worse for all three subdomains (Table 5). However, these results were statistically significant for the subdomain 'Role Physical' only ($p = .037$). Furthermore, adding interactions to the models did not result in a significant improvement in the fit for each of the subdomains 'Fatigue' ($p = .312$), 'General Quality of Life' ($p = .182$) and 'Role Physical' ($p = .555$).

DISCUSSION

To our knowledge, this is the first study to assess health status of Q-fever patients and patients with Legionnaires' disease at one year after onset of illness using validated questionnaires. The sample sizes were large, which makes this an important study with generalisable results. Our study demonstrates that many Q-fever patients and patients with Legionnaires' disease at one year after onset of illness are affected on one or more aspects of health status, especially 'Fatigue', 'General Quality of Life' and 'Role Physical' (Tables 3 and 4). Although both patient groups are affected, in general the impact of Q-fever seems to be somewhat higher.

The observed impaired health status scores at 12 months after onset of illness in patients from both patient groups compared to a normative group are in line with other prospective studies on health status in Q-fever patients and patients with

Legionnaires' disease.^{13 and 17} Consistent with our findings (Table 4), 'Role Physical' was the most affected subdomain in those studies, as compared to a control population. Furthermore, we demonstrated that severely affected scores are found within our patient groups for the subdomains 'Fatigue' (60.2% and 50.0% of Q-fever patients and patients with Legionnaires' disease respectively) and 'General Quality of Life' (50.0% and 42.6% respectively) (Table 3). These results are consistent with previous Q-fever studies, where around 50% of patients were found to be severely affected on subdomains 'Fatigue' and 'General Quality of Life' at one year after onset of illness.^{8 and 9} In addition, this supports the hypothesis on observed long-term fatigue after various infectious diseases, such as demonstrated in studies on infectious mononucleosis, dengue and infections with *Giardia*.^{2, 3, 4 and 5} When comparing health status scores between Q-fever patients and patients with Legionnaires' disease, Q-fever patients score worse on each of the tested subdomains ('Fatigue', 'General Quality of Life' and 'Role Physical'), although this difference is only statistically significant for the subdomain 'Role Physical' in a multivariate regression model adjusting for confounders (Table 5). This subdomain describes problems with work or other daily activities as a result of physical health. It includes questions such as whether someone cut down the amount of time they spent on work or other activities, and whether someone accomplished less than they would like as a result of their physical health. The difference between the patient groups for 'Role Physical' is only significant when an adjustment for confounders is made in the analysis, which can be explained by the fact that some characteristics that are more prevalent in patients with Legionnaires' disease (e.g. pre-existing health problems) have a negative influence on 'Role Physical'. Although Q-fever patients are more affected on this subdomain than patients with Legionnaires' disease, the scores of both patient groups are much lower than those of a normative group (Table 4). Since the fit of the model which included interactions was not significantly better than the fit of the multivariate regression model, there are no grounds to expect any differences between subgroups of Q-fever patients and patients with Legionnaires' disease (e.g. patients with different educational levels), which strengthens the above results.

Both patient groups demonstrated demographic characteristics were in line with previous studies. It is known that risk factors for obtaining Legionnaires' disease are being >50 years of age, being male, smoking and having an underlying illness.²⁷ Q-fever is more common in males and smokers as well, while age is not a risk factor (except for the fact that children are rarely affected).¹⁹ This is consistent with the findings in our study. The response rate and number of participants for both patient groups were high (especially for the Q-fever patients, since they are part of a larger prospective cohort study¹⁸). These points indicate that the results from this study are representative for Q-fever patients and patients with Legionnaires' disease in general. A minor limitation is that our study lacks information on the proportion of persons with a severely affected 'Fatigue' or 'General Quality of Life' in the general population. In the group of healthy controls, the proportion of persons 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 in a random sample of the population in the city of Nijmegen (NL) found that over 30% suffered from chronic fatigue (fatigue present for longer than 6 months).²⁸ In a German study, approximately 30% of persons from the general population reported moderate fatigue during the last six months, while almost 10% of subjects reported substantial fatigue lasting six months or longer.²⁹ These studies imply that baseline fatigue levels are already quite high in the general population and that the high proportion of patients that is severely affected on the subdomain 'Fatigue' in our study might also include fatigue due to other reasons than the infectious illness under study.

CONCLUSIONS

Within this study, health status of Q-fever patients and patients with Legionnaires' disease were compared for the first time, providing unique data. The results support the hypothesis that certain infectious illnesses are often followed by a long-term impaired health status, including post-infectious chronic fatigue. While evidence for Q-fever was already more apparent, it appears that many patients with Legionnaires' disease also suffer from an impaired long-term health, although in general the impact of Q-fever seems to be somewhat higher. We recommend that medical staff be made aware that both patients with Q-fever as well as patients with Legionnaires' disease may suffer from a long-term health impact and may thus need adequate care.

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TABLES

Table 1 Domains, subdomains and number of questions for both NCSI and SF-36 in our study.

Instrument	Domain	Subdomain	Number of questions
NCSI	Symptoms	Subjective Pulmonary Symptoms	2
		Dyspnoea Emotions	6
		Fatigue	8
	Functional Impairment	Behavioural Impairment	22
		Subjective Impairment	4
	Quality of Life	General Quality of Life	12
		Health-Related Quality of Life	2
SF-36	Physical Health	Satisfaction Relations	2
		Role Physical	4
		Bodily Pain	2
	Mental Health	Social Functioning	2
		Role Emotional	3

Table 2 Comparison of the characteristics of the patient groups at 12 months after onset of illness.

Variable	Q-fever	Patients with Legionnaires' disease	Difference <i>p</i> -Value
	<i>N</i> = 309	<i>N</i> = 190	
Male sex %	53.7	68.9	.001 ^a
Age (years) Mean (±SD)	49.9 (13.8)	61.1 (11.5)	<.001 ^b
Educational level %			.011 ^a
Low	40.5	53.7	
Middle	30.4	21.1	
High	28.8	24.7	
Unknown	0.3	0.5	
Body Mass Index %			.171 ^a
Underweight	1.0	0.0	
Normal weight	39.6	36.0	
Moderately overweight	43.2	41.3	
Seriously overweight	16.2	22.7	
Smoking behaviour %			<.001 ^a
Current	28.8	37.4	
Former	37.9	47.4	
Never	33.3	15.2	
Alcohol consumption (beverages/week) %			<.001 ^a
0	34.3	24.2	
1–6	43.4	33.7	
7–14	17.5	32.1	
≥15	4.8	10.0	
Pre-existing health problems %	40.6	59.5	<.001 ^a
Hospitalisation %	36.6	61.1	<.001 ^a

^a *p*-Values were calculated using a Pearson Chi-Square test.

^b *p*-Values were calculated using an Independent Samples *t*-test.

Table 3 Severely impaired persons within each NCSI subdomain: patients with Q-fever or Legionnaires' disease at 12 months after onset of illness and persons in a healthy control group.

NCSI subdomain	Healthy controls	Q-fever patients	Patients with Legionnaires' disease
	%	%	%
	<i>n</i> = 121	<i>n</i> = 309	<i>n</i> = 190
Subjective Pulmonary Symptoms	0.8	23.0	22.9
Dyspnoea Emotions	1.7	28.2	23.9
Fatigue	2.5	60.2	50.0
Behavioural Impairment	0.8	17.5	23.7
Subjective Impairment	0.0	23.3	18.5
General Quality of Life	19.8	50.0	42.6
Health-Related Quality of Life	2.5	26.5	23.2
Satisfaction Relations	10.7	19.0	18.9

Table 4 SF-36 subdomain scores for a normative group, compared to mean scores of Q-fever patients and patients with Legionnaires' disease (both at 12 months after onset of illness).

SF-36 subdomain	Normative group	Q-fever patients		Patients with Legionnaires' disease	
	Mean ^a (%)	Mean ^a (%)	Difference ^b (%)	Mean ^a (%)	Difference ^b (%)
	<i>n</i> = 2474	<i>n</i> = 309		<i>n</i> = 190	
Role Physical	80.9	58.2	22.7	60.0	20.9
Bodily Pain	75.2	73.7	1.5	79.8	-4.6
Social Functioning	83.3	76.2	7.1	79.9	3.4
Role Emotional	81.3	75.2	6.1	74.6	6.7

^a Scores were calculated on a scale from 0 to 100%.

^b Score differences were obtained by subtracting the patient score from the normative score.

Table 5 Models (uncorrected and corrected for confounders) describing the difference in health status between Q-fever patients and patients with Legionnaires' disease for selected subdomains at 12 months after onset of illness.

Subdomain		Uncorrected models		Corrected models ^b	
		Q-fever	Legionella	Q-fever	Legionella
Fatigue ^a	<i>b</i> -Value (CI)	2.51 (−0.24 to 5.27)	Ref	2.52 (−0.56 to 5.59)	Ref
	<i>p</i> -Value	.074		.108	
General Quality of Life ^a	<i>b</i> -Value (CI)	1.87 (−0.61 to 4.35)	Ref	1.27 (−1.49 to 4.03)	Ref
	<i>p</i> -Value	.139		.366	
Role Physical ^a	<i>b</i> -Value (CI)	−1.80 (−9.62 to 6.01)	Ref	−9.16 (−17.75 to −0.58)	Ref
	<i>p</i> -Value	.651		.037	

^a For 'Fatigue' and 'General Quality of Life', a lower score indicates a better health. For 'Role Physical', a higher score indicates a better health.

^b Confounders that were included in the corrected models are gender, age, educational level, BMI, smoking behaviour, alcohol consumption, pre-existing health problems and hospitalisation. BMI is divided in three groups instead of four (underweight and normal weight are combined) since the proportion of patients with underweight was very small.