The long-term health status of Q fever patients: the Dutch experience

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Chapter 1

General Introduction

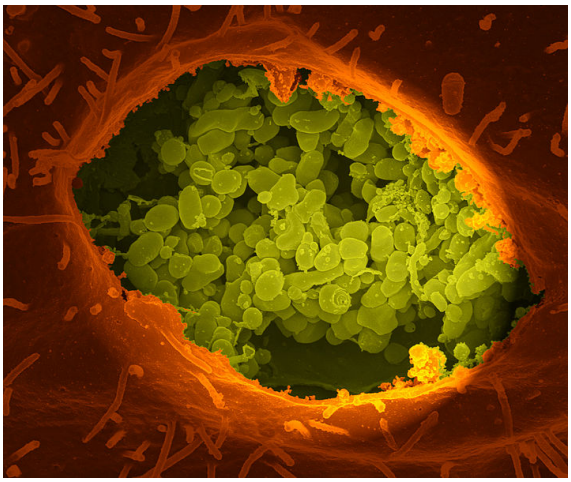
General Introduction

This thesis describes the long-term health status of Q fever patients, and the limitations patients are confronted with. These findings are relevant for clinicians who are involved in the care for Q fever patients, as it helps them to gain more insight in the expected disease progression. The introduction provides some background information on Q fever in general, its health impact and the large outbreak that affected the Netherlands between 2007 and 2011, and a detailed outline of the research objectives and outline of this thesis.

1. Q fever

Q fever is an infectious disease that was first discovered in 1937 in Australia[1]. Around 20 abattoir workers had fever symptoms that could not be diagnosed by blood cultures or agglutination tests. The disease was given the name Q fever, where the 'Q' stands for query, since a causative agent was not known at the time. Shortly thereafter, the bacterium causing the illness was discovered almost simultaneously by Frank Macfarlane Burnet in human patients in Australia[2] and by Herald Rea Cox in ticks in the United States[3], hence the name *Coxiella burnetii* (Figure 1).

Figure 1. A dry fracture of a Vero cell exposing the contents of a vacuole where Coxiella burnetii *are busy growing. Source: National Institute of Allergy and Infectious Diseases (NIAID), USA.*



Q fever is a zoonosis, and a wide variety of animal species can be infected with the bacterium, including domesticated animals such as goats, sheep and cows[4]. Humans can become infected with *Coxiella burnetii* after inhaling aerosol

particles from animal products of conception, such as amniotic fluid, or contaminated wool[5]. Another route of infection is the consumption of contaminated dairy products, such as milk[6]. Outbreaks of Q fever are usually associated with direct or indirect contact with animals or their products, although close contact with animals is not required for transmission[7]. Man-to-man transmission is rare, although cases of sexual transmission[8] and transmission via blood transfusion[9] have been described.

A number of factors make the *Coxiella burnetii* bacterium a highly pathogenic organism. It is judged to be one of the most infectious bacteria because a lone organism can cause disease[5]. In addition, it is very stable and may remain viable in the environment for years[10]. Since *Coxiella burnetii* fulfils these requirements for a biological weapon, it is considered a category B biological terrorist agent[11]. Q fever might in addition be very suitable for use as a biological weapon because of its widespread availability, natural potential for aerosolised use, environmental stability, and the possibility of producing large quantities of infectious material[5].

For a long time, Q fever was known as an occupational illness, mainly infecting farmers, veterinarians and laboratory workers. A large survey carried out by the World Health Organization (WHO) in the 1950s found the disease to be prevalent in 51 countries over five continents[12]. Nowadays it can be found in countries all over the world, with the notable exception of New Zealand[13]. Q fever is endemic in many countries within the European Union with a rate of 0.19 cases per 100,000 in 2011, ranging from 0.00 in nine EU countries to 0.60 per 100,000 in Cyprus[14]. However, the seroprevalence in humans (indicating whether they have been infected in the past) varies over time and between countries. The largest seroprevalence studies in Europe were carried out in pregnant women in Southern France in 1996 (seroprevalence of 0.2%, N = 12,716)[15], in unexposed patients in the UK between 1962-1966 (0.6%, N = 7,046)[16] and in the general population of the Netherlands in 2006-2007 (2.4%, N = 5,654)[17]. The variation in seroprevalence is partly attributable to testing methods, but also to potential sources of Q fever in a country.

Several outbreaks of Q fever have been documented, many of which occurred in Europe and other Western countries around the world[18-29]. The absence of documented outbreaks in non-Western countries is probably due to a bias in diagnostics and/or reporting. The largest outbreak to date took place in the

Netherlands between 2007-2011, with 4,107 registered cases[30]. Other notable outbreaks include one in Switzerland in 1983 with 415 laboratory confirmed cases[20], one in Bulgaria in 2004 with 220 cases[26], two in Germany in 2003 and 2005 with 167 and 160 cases respectively[23,25], and one in the UK in 1989 with 147 cases[21]. Most outbreaks are associated with livestock farming. For example, the outbreak in Switzerland occurred when flocks of sheep descended from the alpine pastures to the valley, and many people living in villages along the road contracted Q fever[20].

2. Clinical symptoms in the acute phase

Approximately 40% of all persons infected with Q fever develop symptoms, the remaining 60% of infections progress asymptomatically[20,31]. The clinical manifestation of an acute Q fever infection varies from a mild flu-like illness to a severe illness with hospitalisation (2% of all infections)[31]. Symptoms associated with a Q fever infection are a-specific, usually self-limiting and often include fever, pneumonia, hepatitis and neurological symptoms such as headache[31]. Pericarditis and myocarditis are each found in only 1% of cases[31]. An acute infection in pregnant women increases the risk of an abortion[32].

3. Long-term impact of Q fever

Long-term health impact of Q fever on patients

One long-term manifestation of Q fever is chronic Q fever, which often presents as endocarditis[31,33] or vascular infection[34]. Approximately 0-5% of Q fever patients are estimated to develop chronic Q fever[35]. It is most common in patients with a previous valvulopathy, and to a lesser extent in pregnant women and immunocompromised patients[36]. Patients with this diagnosis usually need antibiotic treatment for several years or even for life[31].

Another manifestation was first described in a study by Marmion et al. in 1996, as a variety of health problems that were reported by patients in Australia that contracted Q fever two or more years after recovery of the acute illness, including incapacitating fatigue, persistent headache and night sweats[37]. This was the first reference in the scientific literature to 'post Q fever fatigue syndrome' (QFS). Studies in the UK that were carried out after a large outbreak in 1989 confirmed these results and showed that 42.3% of patients fulfil the Centers for Disease Control and Prevention (CDC) criteria for chronic fatigue

syndrome at five years after infection, and 34.3% report idiopathic chronic fatigue at ten years after infection[38,39]. A study performed after an outbreak in Canada reported lower scores of Q fever patients compared to a control group in five out of eight health status subdomains of the Short Form 36 (SF-36), and fatigue in 51% of the patients at 27 months after the initial outbreak[40]. Not all patients with long-term fatigue are considered QFS patients, since this diagnosis consists of the following conditions: 1) fatigue for at least six months, 2) the patient underwent an acute Q fever infection but has no chronic Q fever, 3) fatigue cannot be explained by somatic or psychiatric co-morbidity, 4) fatigue causes significant limitations in the daily functioning of the patient, and 5) fatigue was not present before the Q fever infection or has increased significantly since then[41].

Most studies on the long-term health impact of Q fever were all performed in relatively small numbers of patients (approximately 100 cases or less). The outbreak in the Netherlands between 2007-2011 offered an opportunity to study the long-term health impact in a large group of patients. A cross-sectional study assessed health status of 54 patients with an onset of illness in 2007, and found that 52% suffered from severe fatigue after one year[42]. A retrospective study (N = 515) reported that 45% and 44% of patients were severely affected in their quality of life and fatigue respectively at 12-26 months after their onset of illness[43]. An important limitation of these studies was that health status of patients was measured at only one point in time and that the reference groups of healthy controls were small and not age-matched to the Q fever patients.

The mechanism that causes long-term fatigue after Q fever remains debatable. The first study that looked at this mechanism showed that cytokine dysregulation was observed in QFS patients[44]. The hypothesis was that this dysregulation results from chronic immune stimulation and modulation by persistence of *Coxiella burnetii* cells or their antigens. However, another study found no difference in cytokine production between patients with post-infectious fatigue syndrome, including patients who underwent a *Coxiella burnetii* infection, and controls, which contradicts this hypothesis[45]. Although studies have not detected viable *Coxiella burnetii* in QFS patients, it has been shown that immunomodulatory complexes containing *Coxiella burnetii* antigens are present in mice that have been inoculated with blood from QFS patients[46]. This leads to cytokine release in mice and provokes an immune

response in guinea pigs, which could be a possible pathogenetic link between initial infection and QFS[47]. A study by Helbig et al. showed a variation in immune response genes between groups with different long-term Q fever outcomes, which supports the concept of different immune states determined by genetic variation in host immune responses[48], and could be a reason why some persons are susceptible to QFS and others are not.

There is no standard treatment for Q fever patients with a long-term impaired health status in the Netherlands or elsewhere. Studies that evaluated the effectiveness of antibiotic therapy (minocycline or doxycycline) on patients with Q fever Fatigue Syndrome did not provide conclusive results[49,50]. A clinical trial is currently being carried out in the Netherlands that could provide more insight into effective therapies for these patients[51]. This randomized controlled trial compares the effectiveness of two potential treatments, namely Cognitive Behavioural Therapy and long-term doxycycline, on patients that underwent one of these treatments during six months, also in comparison to patients that received a placebo. The main outcome measure is severity of fatigue, which is assessed before and after treatment.

The long-term reduced health status of Q fever patients can also lead to limitations in daily life, such as absence from school and work. A Dutch retrospective study found that 40% of the working population reported sick leave for more than one month after their acute episode of Q fever[52], which is a serious burden on patients as well as society.

Long-term health impact of Q fever compared to other infections

Post-infectious chronic fatigue not only presents after Q fever, but has been reported after other infections as well. A study in the Netherlands after a large outbreak with Legionnaires' disease in 1999 showed that 75% of the patients suffered from fatigue at 1.5 years after onset of illness[53]. A study in the UK showed an increase in the number of patients suffering from fatigue after glandular fever, including patients with an Epstein-Barr virus infection, compared to patients with an ordinary upper respiratory tract infection at six months after onset of illness[54]. After an outbreak of dengue in Singapore, it was reported that patients were affected in their health after infection, specifically due to fatigue[55]. Large studies on Giardia infections in Norway showed that severe giardiasis seems to be a risk factor for post-infectious fatigue and that at

least 5% develops clinical characteristics and functional impairment comparable to post-infectious fatigue syndrome[56,57]. However, one study conducted in the UK failed to demonstrate the existence of a post-infectious fatigue syndrome. This prospective study compared fatigue levels of patients that visited their general practitioner with an infection (mostly flu-like episodes or infections of the upper respiratory tract, which are generally less severe than lower respiratory tract infections) and patients with complaints not related to a possible infection, but found no difference between the groups[58].

Only one study compared the long-term health impact of Q fever on patients to the health impact of other infectious illnesses on patients[59]. This was a prospective cohort study in Australia which measured self-reported health status, including fatigue, at six time points during the first year after onset of illness of patients with Q fever (n = 43), an Epstein-Barr virus infection (n = 68) and a Ross River virus infection (n = 60). This study found that a relatively uniform post-infectious fatigue syndrome persists in a minority of patients after six months or more, independent of the disease-causing agent. This type of study is important as it can provide useful information on whether long-term health effects are specific to a certain infection, or whether they are common after suffering from any severe infectious illness.

Q fever and Legionnaires' disease are both notifiable diseases. The clinical manifestation of the acute phase of these diseases is quite similar, since almost all patients with Legionnaires' disease and many Q fever patients suffer from pneumonia. Due to this similarity, it would be of interest to compare whether the long-term impact of Q fever and Legionnaires' disease on health is also similar.

Lower respiratory tract infections (LRTIs) can be caused by a variety of pathogens, including *Coxiella burnetii*. It was as of yet unclear if long-term health status of patients with an LRTI caused by *Coxiella burnetii* is more impaired than that of patients with an LRTI caused by another pathogen.

4. Q fever in the Netherlands

The first laboratory confirmed cases of *Coxiella burnetii* infection in humans in the Netherlands were discovered in 1956[60]. It concerned three patients in Rotterdam who suffered from atypical pneumonia. For one patient, the most

likely source of infection was through his work as a butcher, for the other two the mode of infection was not determined[60]. Up until that time, large serological studies in 1954 and 1955 on humans and domestic ruminants, and specifically on (healthy) workers in the meat processing and animal product industries, did not show any positive results[12,61]. In the years following these infections, only a handful of cases were described[62,63].

Q fever was added to the list of notifiable infectious diseases in the Netherlands in 1978[30]. The main reasons for notifying patients are source identification and possible implementation of control measures to protect public health. The Dutch case definition is based on the EU harmonised case definition for Q fever[64]. Table 1 shows how the Dutch case definition has changed over time. The current Dutch case definition includes an onset of illness within the previous 90 days and a clinical presentation with fever, pneumonia and/or hepatitis[29]. In addition, it includes one of the following laboratory confirmations:

- Identifying a seroconversion or a fourfold or higher increase in IgG antibody titre against *C. burnetti* in a paired serum sample (sera obtained in the acute phase and recovery phase with a time interval ≥ 2 weeks);
- Presence of IgM-antibodies against phase II of *C. burnetii*;
- Detection of *C. burnetii* DNA by PCR in blood or respiratory material.

Acute Q fever can be diagnosed using Polymerase Chain Reaction (PCR) or serology[36]. Serological assays that are used are indirect immunofluorescence assay (IFA), enzyme-linked immunosorbent assay (ELISA) and complement fixation assay, all of which are suitable methods[65]. The standard treatment used by general practitioners for patients with a Q fever 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)[30,66].

Table 1. The evolution of the Dutch case definition, in comparison to the EU case definition.

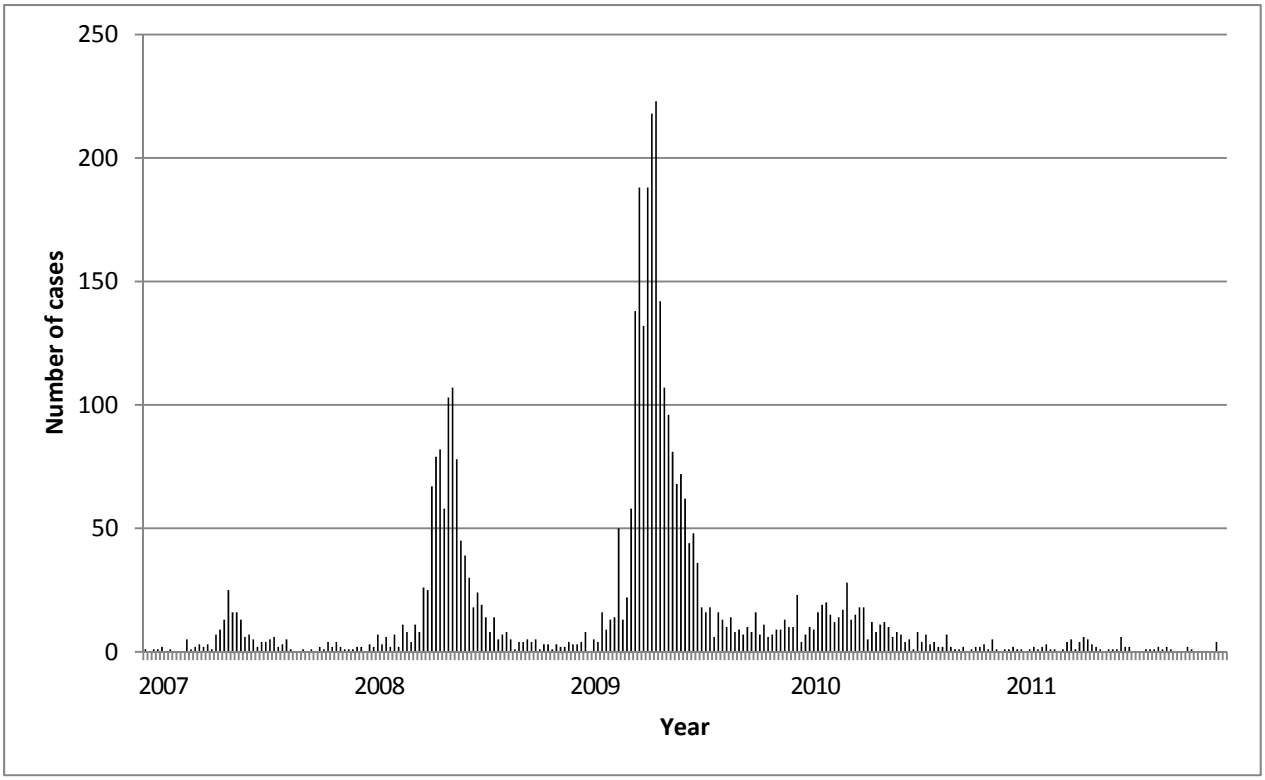
	Dutch Q fever case definition			**EU case definition**
	< 1978	1978-2008	> 2008	> 2008[1)]
Case definition	No	Yes	Yes	Yes
Laboratory confirmation	-	Yes	Yes	Yes
Clinical symptoms	-	Matching clinical symptoms	Fever, pneumonia and/or hepatitis	Fever, pneumonia and/or hepatitis
Onset of illness	-	-	Previous 90 days	-
Epidemiological criteria	-	-	-	Exposure to common source and/or animal to human transmission

[1)] The EU case definition was revised in 2012 (67), although the criteria did not change.

Up until 2007, the number of notified Q fever patients per annum in the Netherlands varied from 1 to 32, with a mean of 17[30]. In May 2007 however, a general practitioner in a small rural village was confronted with an unusually high number of pneumonia cases, for which a cause could initially not be discovered[68]. In the following weeks, almost 100 cases contracted similar symptoms, after which testing was intensified and the results showed that the majority of patients had a positive serology for Q fever. This was the beginning of the largest Q fever outbreak ever reported in the world, with a rate of 14.3 cases per 100,000 in 2009[14] and a cumulative total of 4,107 notified patients in the Netherlands between 2007 and 2011 (Figure 2)[30]. These high rates were not seen in other European countries over the same period, including neighbouring countries such as Belgium and Germany[14]. The main source of the infection was initially suspected to be dairy goats, since the area where most patients lived is known for intensive (goat) farming[69]. Therefore, veterinary measures were taken by the Dutch government in 2009 to prevent the further spread of the disease. These measures included the vaccination of dairy goats and sheep on farms with more than 50 animals, and the culling of pregnant goats and sheep at farms that were found to be infected[70]. This led to a massive reduction in the number of new patients from 2010 onwards (there were 74 cases in 2011), see Figure 2[30]. In 2010, a study showed that persons who lived in a 2 km radius from an affected dairy goat farm had indeed a much

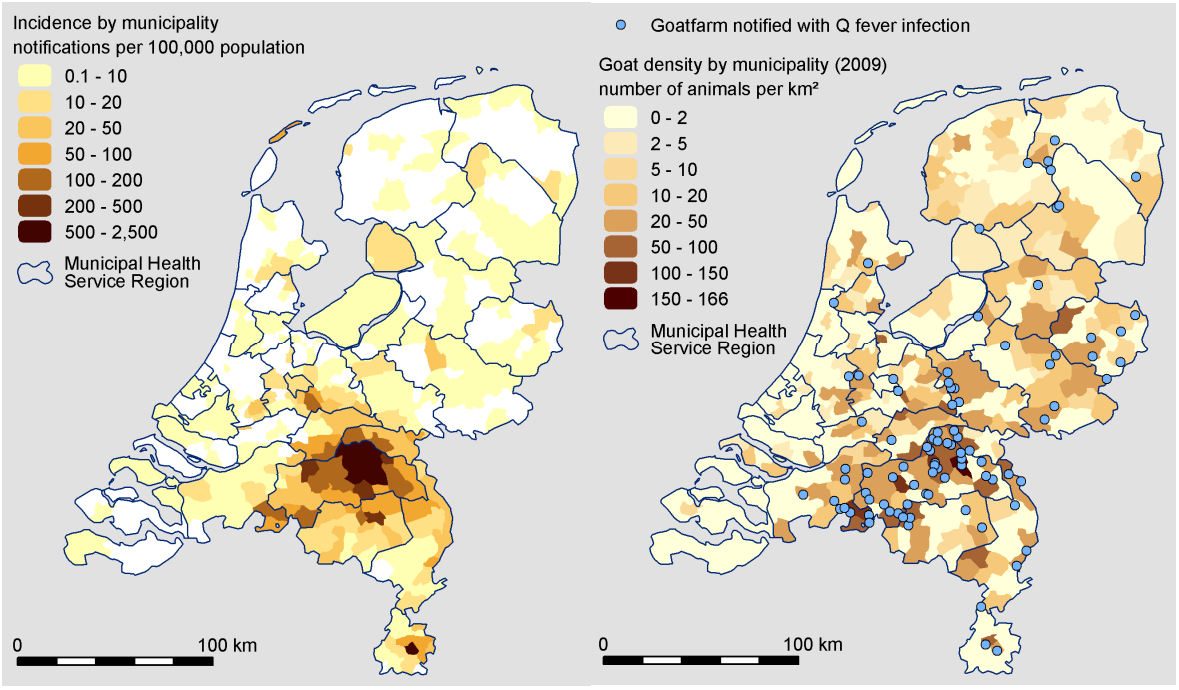
higher risk for Q fever than those living more than 5 km away[71] (Figure 3). In addition, a study that was performed after the outbreak showed that the incidence of Q fever was higher in areas where manure contaminated with *C. Burnetii* had been used[72].

Figure 2. The number of notified Q fever patients per week in the Netherlands during the epidemic between 2007-2011, based on onset of illness. Source: National Institute for Public Health and the Environment (RIVM).



Since most persons with a *Coxiella burnetii* infection do not develop any symptoms, and not all persons with symptoms visit their general practitioner, the reported number of 4,107 cases is a probable underestimation of the magnitude of the Q fever epidemic in the Netherlands. A study by van der Hoek et al. estimated the number of *Coxiella burnetii* infections over the period 2007-2009 to be 44,000, based on data by blood donors[73]. Preliminary results from a study that was carried out in the village of Herpen showed that one out of three persons underwent a Q fever infection at some point[74], although this village is located in the epicentre of the Dutch outbreak and is thus not representative for the whole country.

Figure 3. The cumulative incidence of notified Q fever patients per community between 2007 and 2010 (left) versus the goat density and the locations of infected goat farms in the Netherlands in 2009 (right). Maps compiled by Ben Bom, National Institute for Public Health and the Environment (RIVM).



Due to the large number of affected patients in the Netherlands and the severe impact of the illness on their lives, a Q fever patient organisation - called Q-uestion - was established in 2009[75]. The organisation sets up meetings with sufferers, looks after the interests of patients on a local, regional or national level, and provides information in the form of a website and newsletters. In 2013, a foundation named Q-Support was established, which advises and supports Q fever patients on an individual level, with the aim of improving their functioning in society[76]. In addition, this foundation financially supports studies on the impact of Q fever and its treatment.

5. Assessing health status

In 1946, the WHO defined health as 'a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity'[77]. Although this definition is still in use, it has been criticised for the word 'complete', since not many people are completely healthy. Huber et al. have proposed a formulation of health as the ability to adapt and to self manage, which they feel is more fitting in a time with a high prevalence of chronic

illnesses[78]. Human health can then be conceptualised with a set of dynamic features and dimensions that can be measured.

The field of health status assessment originated around 1970. Although different terms have been used to describe health status, e.g. functional status, quality of life, and health-related quality of life, all health status assessment tools aim to measure objective and subjective components of human functioning and well-being[79]. There are several ways to assess health status in patients for research purposes. The most extensive is by performing a physical examination. However, this is a costly and time-consuming process, especially when the number of patients is high. Since many aspects of health status, e.g. quality of life and complaints, are measured based on self-reported information by patients, a validated alternative is to use questionnaires, which are often used in clinical settings as well. This requires a relatively small investment per patient. By using questionnaires that have been validated, the results can be compared to other studies.

Questionnaires that have been used to measure health status in Q fever patients are the Nijmegen Clinical Screening instrument (NCSI)[42,43] and the Short Form 36 (SF-36)[40]. The NCSI was originally developed at the University Lung Center Dekkerswald of the Radboud university medical center to provide a detailed assessment of health status of patients with Chronic Obstructive Pulmonary Disease (COPD), and has been available since 2009 in English, German and Dutch. It combines a number of existing health status questionnaires, including CIS (Checklist Individual Strength), SIP (Sickness Impact Profile) and PARS-D (Physical Activity Rating Scale – Dyspnoea)[80]. The SF-36 was developed in 1988, aims to assess the quality of life of patients and is available in over 170 languages[81]. Both instruments consist of 8 subdomains (Table 2).

6. Objectives

Due to the limited number of large Q fever outbreaks to date, data from studies on the long-term health impact are often based on small numbers of patients, which limits the accuracy and generalisability of the estimates. During the outbreak that confronted the Netherlands from 2007 onwards, patients and general practitioners repeatedly reported persisting symptoms to the public health authorities, in particular about fatigue[43]. These signals could not

be substantiated due to the lack of specific information on patients' health status. The outbreak therefore offered an opportunity to study the natural course and impact of Q fever infections. Cohort studies are considered the benchmark to measure disease progression. Indeed, in 2012 ECDC recommended the initiation of good prospective cohort studies to obtain more robust evidence on how to diagnose and treat acute Q fever[82].

Table 2. Domains and subdomains of the Nijmegen Clinical Screening Instrument (NCSI) and the Short Form 36 (SF-36).

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
		Satisfaction Relations	2
SF-36	Physical Health	Physical Functioning	10
		Role Physical	4
		Bodily Pain	2
		General Health	5
	Mental Health	Vitality	4
		Social Functioning	2
		Role Emotional	3
		Mental Health	5

The studies described in this thesis were preceded in 2009 by Morroy et al., who first described the long-term health impact and sick leave retrospectively in a large group of Q fever patients within the 2007-2008 Dutch outbreak[43,52]. Our studies built upon this expertise by setting up a prospective cohort of Q fever patients. The aim of this thesis was to gain insight into the long-term health status, including fatigue, of notified Q fever patients according to the Dutch case definition, using the NCSI and the SF-36. The following research questions were investigated:

- How does health status progress in Q fever patients until four years after onset of their illness, and which individual characteristics are associated with health status?
- How does long-term health status of Q fever patients compare to health status of patients that underwent another infectious disease, specifically a lower respiratory tract infection or Legionnaires' disease?
- How does work participation progress in Q fever patients until 24 months after onset of their illness, and which individual characteristics are associated with it?
- Is there a difference in health status between notified Q fever patients and non-notified Q fever patients, who do not fit the case definition based on the clinical criteria, at four years after onset of their illness?

7. Outline of this thesis

Chapter 2 describes the complete study protocol. Chapter 3 compares all subdomains of the NCSI and the SF-36 and aims to identify subdomains with conceptual similarity, since in subsequent publications we only wanted to focus on subdomains that measure unique concepts. In chapter 4, the health status of Q fever patients within the first 24 months after onset of illness is presented prospectively. In addition, individual characteristics associated with health status were identified. Two chapters describe health status of Q fever patients in relation to health status of patients that underwent another infection. Chapter 5 describes a comparison between two groups of patients that underwent a lower respiratory tract infection at approximately 15 months after onset of illness: one with a positive and one with a negative laboratory result for Q fever. Health status of Q fever patients and patients with Legionnaires' disease were compared at 12 months after onset of illness in chapter 6. The impact of Q fever in terms of work participation over the first 12 months after illness, also in comparison to patients with Legionnaires' disease, is described in chapter 7. In addition, characteristics associated with a reduced work participation were identified. The aim of chapter 8 was to compare health status at four years after onset of illness between notified Q fever patients, and patients who had a laboratory confirmation for Q fever but were not notified based on the clinical criteria (they did not have fever, pneumonia or hepatitis). This was important to help assess the true burden of disease due to a Q fever

outbreak and to evaluate the EU case definition for Q fever with respect to the long-term health status of patients. Finally, chapter 9 discusses the findings of this thesis and describes the implications of the results for research, policy and practice.

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Chapter 2

Assessing the long-term health impact of Q fever in the Netherlands: a prospective cohort study started in 2007 on the largest documented Q fever outbreak to date

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Abstract

Background: Between 2007 and 2011, the Netherlands experienced the largest documented Q fever outbreak to date with a total of 4,108 notified acute Q fever patients. Previous studies have indicated that Q fever patients may suffer from long-lasting health effects, such as fatigue and reduced quality of life. Our study aims to determine the long-term health impact of Q fever. It will also compare the health status of Q fever patients with three reference groups: 1) healthy controls, 2) patients with Legionnaires' disease and 3) persons with a Q fever infection but a-specific symptoms.

Methods/design: Two groups of Q fever patients were included in a prospective cohort study. In the first group the onset of illness was in 2007-2008 and participation was at 12 and 48 months. In the second group the onset of illness was in 2010-2011 and participation was at 6 time intervals, from 3 to 24 months. The reference groups were included at only one time interval. The subjective health status, fatigue status and quality of life of patients will be assessed using two validated quality of life questionnaires.

Discussion: This study is the largest prospective cohort study to date that focuses on the effects of acute Q fever. It will determine the long-term (up to 4 years) health impact of Q fever on patients and compare this to three different reference groups so that we can present a comprehensive assessment of disease progression over time.

Keywords

Q fever, *Coxiella burnetii*, Health status, Quality of life, Legionnaires' disease

Background

Q fever is a zoonosis that is caused by the intracellular bacterium *Coxiella burnetii*. A wide variety of animal species can be infected with the bacterium, including domesticated animals such as goats, sheep and cows[1]. Q fever was known as an occupational illness until 2007, mainly infecting farmers, veterinarians and laboratory workers. An obligatory notification for Q fever patients was introduced in the Netherlands in 1978 and the mean number of patients was around 17 cases per annum[2]. However, starting in 2007 the number of new patients increased annually, reaching a total of 4,108 notified acute Q fever patients over the period 2007-2011, of which at least 24 persons (0.6%) died[2].

Whilst the number of Q fever cases has gradually increased in Europe in recent years, no other country has experienced an epidemic of this scale and the Dutch outbreak has become the largest documented outbreak in the world[3-13]. In comparison, the highest number of patients reported in an outbreak before 2007 was 415 in Switzerland[5]. Several measures were taken by the Dutch government in late 2009 to prevent the further spread of the disease (including the vaccination of goats and sheep on farms with more than 50 animals, and the culling of pregnant goats and sheep at farms that were found to be infected[14]), which has led to a massive reduction in the number of new patients since 2010 (there were 74 cases in 2011)[2].

Approximately 40% of all persons infected with Q fever develop symptoms such as fever, pneumonia and hepatitis[5, 15]. Several studies have shown that a relatively large group of patients suffer from persistent fatigue after acute Q fever[16-18]. One study showed that the percentage of patients affected by persistent fatigue declines over time, ranging from 80% several weeks after infection, to less than 30% one year after onset of illness[17]. In another study, 42% of Q fever patients reported symptoms fulfilling the criteria of Chronic Fatigue Syndrome one year after onset of illness[16]. This illness is also known as Post Q fever Fatigue Syndrome, of which symptoms can last for as long as 10 years[18]. Among patients with an acute infection, an estimated 1.9% of patients develop chronic Q fever, a potentially life-threatening condition[19]. Due to the limited number of large outbreaks to date, data from these studies are often based on a small numbers of patients which limits the accuracy and generalisability of the estimates. The current Q fever outbreak in the

Netherlands offers a unique opportunity to study the natural history of Q fever infections, including the long term health impact, and ECDC has recommended the initiation of prospective cohort studies to better diagnose and treat acute Q fever[19].

A number of studies have been conducted in the Netherlands that focus on Q fever patients with an onset of illness in 2007/2008 and have monitored long-term symptoms (including fatigue), functional impairment and quality of life[20,21]. In a case-control study, Limonard et al. found severe fatigue levels in 52% of patients (N=54), one year after onset of illness. In a retrospective study (N=515), Morroy et al. found that 45% and 44% of patients were severely affected in their quality of life and fatigue respectively at least one year after they became ill. Both studies indicate that Q fever causes serious long-term health problems. Limitations of these studies were 1) the health status of patients was only measured at 12 months after onset of illness, 2) the healthy control groups were small and not age-matched to the Q fever patients, and 3) the health status of Q fever patients was not compared to that of patients with another infectious illness[20,21].

Both Limonard et al. and Morroy et al. used the Nijmegen Clinical Screening Instrument (NCSI) to assess the health impact of acute Q fever. This instrument was published in 2009 and combines a number of different health questionnaires. It was originally developed as a screening tool to assess the health status of patients with Chronic Obstructive Pulmonary Disease (COPD)[22], but has since been used in Q fever studies[20,21]. The NCSI measures eight aspects of health status, covering symptoms (including fatigue), functional impairment and quality of life. Another instrument for measuring quality of life is the widely used Short Form 36 (SF-36), which was developed in 1988 by Ware and Stewart for the Medical Outcomes Study, and aims to correctly assess the quality of life of patients with a limited number of questions[23]. To our knowledge, the NCSI and SF-36 have never before been used side by side.

Apart from an Australian study which compared the long-term health status of Q fever patients to the health status of patients infected with Epstein-Barr virus and Ross River virus[17], we have not found any other study that has compared the health status of Q fever patients to the health status of patients with another infectious disease. This type of study is important as it can provide useful information on whether long-term health effects are specific to

a certain infection, or whether they are common after suffering from any severe infectious illness. Patients suffering from Legionnaires' disease were included as a reference group, as 1) the clinical manifestation of the acute phase of Legionnaires' disease is similar to the acute phase of many of the Q fever patients (almost all patients with Legionnaires' disease and many Q fever patients suffer from pneumonia), 2) the pathogens causing Legionnaires' disease (*Legionella pneumophila*) and Q fever (*Coxiella burnetii*) belong to the same order of Proteobacteria known as Legionellales[24] and 3) there is limited information on the long-term health impact of Legionnaires' disease[25-27].
Not everyone who becomes infected with Q fever becomes a notifiable Q fever patient, as the majority of infected persons suffer from mild symptoms or no symptoms at all[5]. In this paper, we refer to this group as being *persons with a Q fever infection but a-specific symptoms* and it is currently unknown whether they are at risk of developing persistent fatigue or chronic Q fever. Our study has therefore included a group of persons with a-specific symptoms as an additional reference group.

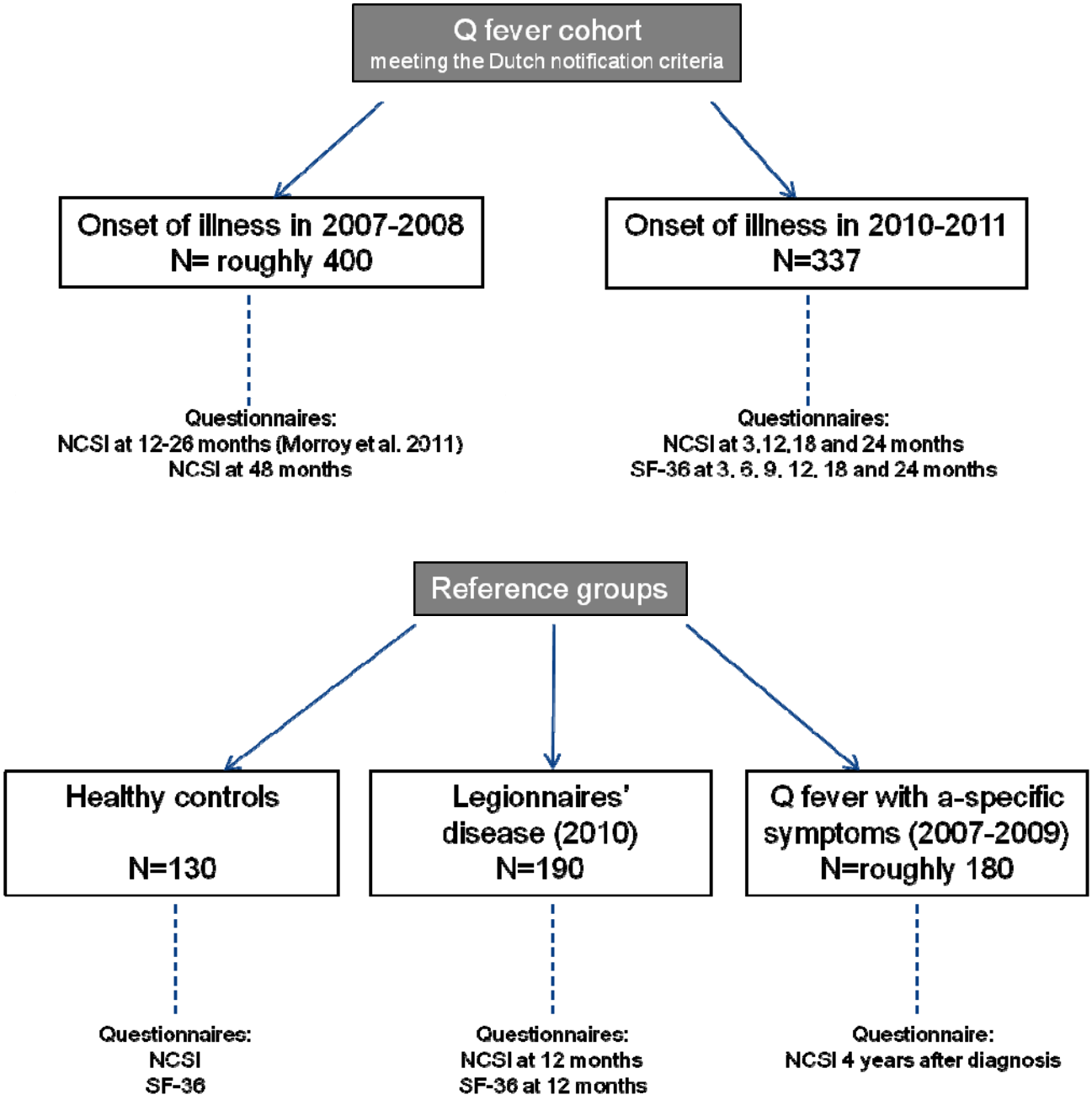
Methods/Design

The designs used in this study are:

- a prospective cohort study of Q fever patients: one group of patients over a period of 2 years and another group over a period of 4 years;
- three cross-sectional surveys of healthy controls, patients with Legionnaires' disease 12 months after infection and persons with a Q fever infection but a-specific symptoms roughly 4 years after infection.

All patients included in this study lived in the Netherlands, and were contacted between 2010 and 2013. The study protocol was submitted to the Medical Ethical Review Board of the Radboud University Nijmegen Medical Centre, which indicated that ethical review was not required as participation consists of filling out one or more anonymous questionnaires. The data on the healthy controls were derived from a different study, for which approval was given by the Medical Ethical Review Board of the Radboud University Nijmegen Medical Centre (reference number: 2006/243). Figure 1 shows which questionnaires were completed and at which time interval.

Figure 1. Explanation of the cohorts and reference groups and the timing of the questionnaires used.



Study population

Patients with Q fever

Our first cohort group consisted of patients with an onset of illness in 2007 and 2008 from two Municipal Health Service regions in the province of Noord-Brabant who participated in the study of Morroy et al.[21]. Patients from that study who also gave permission to be included in further research studies were

contacted by our researcher approximately 4 years after onset of illness. All patients fitted the Dutch notification criteria. This includes a positive serology by one of the following laboratory tests:

- Identifying a seroconversion or a quadrupled or higher increase in IgG antibody titre against C. burnetti 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).

Until July 2008 a further requirement was a clinical presentation matching acute Q fever. As of July 2008, this was refined and patients meeting the Dutch notification criteria had to have at least fever, pneumonia or hepatitis[28].

Patients diagnosed with Q fever in 2010 and 2011 in the Netherlands, who were at least 18 years of age and fulfilled the Dutch notification criteria of Q fever, were eligible for this prospective cohort. The notification criteria since 2010 include also an onset of illness within the previous 90 days. Eligible patients were informed about the study by the Municipal Health Service and after having received written consent, patients were included in the 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 age-matched to the group of Q fever patients and were asked to visit Radboud University Nijmegen Medical Centre, University Centre for Chronic Diseases Dekkerswald, where they completed electronic questionnaires (the NCSI and SF-36). The lung function of healthy controls was also tested, so that persons with an undiagnosed underlying illness that could affect their health status could be excluded.

Patients with Legionnaires' disease

Patients diagnosed with Legionnaires' disease according to the Dutch notification criteria and an onset of illness in 2010 were eligible to participate in this study. The Dutch notification criteria contain a case definition of an

infection confirmed by at least one but preferably two of the following laboratory diagnostic tests:

- Isolation of *Legionella*-species from respiratory secretions of blood;
- Identification of the *L. 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*.

Further requirements are matching clinical symptoms, usually pneumonia[2]. Patients were recruited through the Municipal Health Services. Of the roughly 400 patients with an onset of illness in 2010, a sub-sample of these patients were contacted for our study (N=243).

Persons with a Q fever infection but a-specific symptoms

The last reference group consists of persons with a Q fever infection but a-specific symptoms. Patients who tested positive for Q fever and were notified by the laboratory to the Municipal Health Service, but who did not have symptoms fulfilling the Dutch notification criteria (fever, pneumonia or hepatitis), were eligible for this study group. Consent was obtained through the patient's General Practitioner.

Data collection

All patients were contacted by postal mail at determined time intervals after the onsets of illness (Fig. 1). They received an information letter, a consent form and a questionnaire. Patients were asked to either 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 by telephone or postal mail. Patients who returned an incomplete questionnaire were contacted by telephone by a member of the research team.

Only those Q fever patients who reported severe fatigue and/or a severe impact on their quality of life at intervals 12 and 18 months after onset of illness were eligible to participate at intervals 18 and 24 respectively.
Since the onset of illness could not be determined for persons with a Q fever infection but a-specific symptoms, these persons will be contacted approximately 4 years after their positive serology was confirmed by the laboratory. Persons with an onset of infection in 2007 and 2008 will be contacted in 2012, persons with an onset of infection in 2009 will be contacted in 2013.

Questionnaire

Questionnaires were developed for the patients and reference groups in our study. The first questionnaire that patients receive collects information on risk factors for long-term impaired health status and symptoms due to Q fever. The risk factors collected include age, smoking behaviour, alcohol consumption, education, Body Mass Index, pre-existing health problems (e.g. immune deficiencies, cancer, diabetes) and hospitalisation. Symptoms include all health effects that could be caused by Q fever. Questions which may change over the course of the study are repeated in successive questionnaires (e.g. smoking behaviour, Body Mass Index, hospitalisation and symptoms). The NCSI and the SF-36 were used to measure aspects of health status, fatigue and quality of life. The NCSI[22] was included only every 6 months as it is longer and has not been tested at short time intervals (Fig. 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.

Data analysis

The main outcome measures are the health status, fatigue and quality of life of Q fever patients at different intervals. A secondary outcome is the health status of Q fever patients compared to the health status of healthy controls and patients with Legionnaires' disease. Data will be analysed using the software SPSS for windows (version 18).

Discussion

This study is the largest prospective cohort study that focuses on the long-term health effects of acute Q fever to date. It will provide more insight into the short- and long-term (up to 4 years) health status, fatigue and quality of life of acute Q fever patients. By comparing the long-term health effects to three reference groups (healthy persons, persons with a similar infectious disease (Legionnaires' disease) and persons with a Q fever infection but a-specific symptoms), a more comprehensive assessment of disease progression is better presented.

Even though there has been a major decline in the number of new acute Q fever patients during the last few years, the disease still requires attention. A recent study in the Netherlands suggests that only a fraction (7.9%) of all Q fever infections are notified to the public health authorities[29]. This is caused by a variety of factors, such as lack of clinical symptoms during the acute phase of the disease, not seeking medical attention, and not being tested for Q fever with a diagnostic laboratory test. Assuming this percentage, the total number of infections in the Netherlands between 2007 and 2011 would be about 52,000. Apart from the risks that are posed by chronic Q fever, roughly 50% of persons that were diagnosed one or more years ago still suffer from long-lasting health effects such as severe fatigue or Post Q fever Fatigue Syndrome, although the exact numbers are currently unknown[20,21]. Attention in the Netherlands is therefore now shifting from limiting the number of new infections to monitoring the long-term effects of acute Q fever and providing support to these patients[19,29,30].

The findings of our study will be used by general practitioners and medical specialists to plan and organise the care for new and existing Q fever patients, especially those with long-term symptoms. In addition, as a new Q fever outbreak could occur in the Netherlands, elsewhere in Europe or internationally, it is important to assess and present the long-term health impact of this zoonotic infection.

Our study started data collection in September 2010 and will continue until the beginning of 2013. Data analysis will start in 2013 and results are expected in 2013 and 2014.

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Chapter 3

Assessing health status and quality of life of Q fever patients: the Nijmegen Clinical Screening Instrument versus the Short Form 36

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Abstract

Background: The aim of the study was to assess the use of the Nijmegen Clinical Screening Instrument (NCSI) and Short Form 36 (SF-36) in providing a detailed assessment of health status of Q fever patients and to evaluate which subdomains within the NCSI and SF-36 measure unique aspects of health status.

Findings: Patients received a study questionnaire, which contained the NCSI and SF-36. Pearson correlation coefficients between subdomains of the instruments were calculated. The response rate was 94% (309 out of 330 eligible patients). Intercorrelations between subdomains of the NCSI were generally lower than of the SF-36. Four subdomains of the NCSI showed conceptual similarity (Pearson's $r \geq .70$) with one or more subdomains of the SF-36 and vice versa. Subdomains that showed no conceptual similarity were NCSI 'Subjective Pulmonary Symptoms', 'Subjective Impairment', 'Dyspnoea Emotions' and 'Satisfaction Relations', and SF-36 'Social functioning', 'Bodily Pain', 'Role Physical' and 'Role Emotional'.

Conclusions: Our results show that either the NCSI or SF-36 can be used to measure health status in Q fever patients. When the aim is to obtain a detailed overview of the patients' health, a combination of the two instruments, consisting of the complete NCSI and the four unique subdomains of the SF-36, is preferred.

Keywords

Q fever, *Coxiella Burnetii*, Health status, Quality of life

Findings

Introduction

Q fever is a zoonotic illness caused by the intracellular bacterium *Coxiella burnetii*. The disease was relatively uncommon in the Netherlands until 2007 and only known as an occupational illness, mainly affecting farmers, veterinarians and laboratory workers. Between 2007 and 2011, the Netherlands experienced the largest Q fever outbreak ever reported (a total of 4,108 acute notified Q fever patients)[1]. Approximately 40% of all persons infected with Q fever develop symptoms such as fever, pneumonia and hepatitis[2,3], but there remains a poor description of disease progression. We have established a detailed prospective cohort study to assesses the short- and long-term clinical progression of Q fever over time[4].

Several studies have shown that a relatively large group of patients suffer from persistent fatigue and long-lasting symptoms after acute Q fever[5-11]. Of seven published studies, two in the Netherlands used the Nijmegen Clinical Screening Instrument (NCSI)[10,11], one in Canada used the Short Form 36 (SF-36)[5] and the remaining studies used other instruments to measure health status of Q fever patients. In the Netherlands, studies that focused on the long-term effects on health status have shown that around 50% of patients suffered from severe fatigue at least one year after onset of illness[10,11].

Patients with Q fever experience not only severe fatigue but also many other health problems, such as dyspnoea, anxiety and frustration with dyspnoea, functional impairments in daily life, and an impaired quality of life[10,11]. This means that in order to understand the apparent complexity of the health status problems of patients with Q fever, an instrument that provides a detailed picture of many different aspects of patient's health status is required.

There are eight subdomains in both the NCSI and SF-36 and these measure eight aspects of health status (Table 1)[12,13]. Until now it has never been investigated whether both instruments measure the same aspects of health status or whether they complement each other when assessing the health impact of Q fever on patients. The main aim of our study was to identify an instrument - or a combination of instruments - that would provide a detailed assessment of health status of Q fever patients. We assessed whether subdomains within each instrument measure unique aspects of health status, or whether there is conceptual similarity between subdomains of the NCSI and

SF-36. This was done by calculating intercorrelations (overlap within instruments) as well as correlations (overlap between instruments). The results will yield important information for future studies on how to measure health status of Q fever patients.

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

Instrument	Domain	Subdomain	Number of questions
NCSI	Symptoms	Subjective Pulmonary Symptoms	2
Health status		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
		Satisfaction Relations	2
SF-36	Physical Health	Physical Functioning	10
Quality of Life		Role Physical	4
		Bodily Pain	2
		General Health	5
	Mental Health	Vitality	4
		Social Functioning	2
		Role Emotional	3
		Mental Health	5

Methods

Patients diagnosed with Q fever in 2010 and 2011 who were at least 18 years of age and fulfilled the Dutch notification criteria for Q fever were eligible for this study[14]. Patients received a consent form and the study questionnaire by postal mail and those who did not respond received a reminder by telephone or postal mail. The study questionnaire consisted of the NCSI and SF-36, but it also collected socio-demographic and clinical information. The current study uses patients' information at 12 months after onset of illness[4].

The NCSI was originally developed to provide a detailed assessment of health status of COPD patients and has been available since 2009 in English, German and Dutch. It combines a number of existing health status questionnaires[12]. The

SF-36 was developed in 1988, aims to assess the quality of life of patients and is available in over 170 languages[13].

The relationships between the subdomains of the NCSI and SF-36 were calculated using Pearson correlation coefficients. A Pearson's r ≥ .70 was used as criterion for conceptual similarity[15]. A Pearson's r < .30 indicates no meaningful correlation.

Results

Questionnaires were returned by 309 out of 330 patients (response rate 94 %). The mean age of the study group was 49.9 (SD 13.8) and 53.7% was male. There was a statistically significant difference in age between responders and non-responders (49.9 vs. 43.1 respectively); other characteristics (gender, nationality, education level, BMI, smoking behavior, alcohol consumption) were not significantly different (data not shown).

Intercorrelations between the subdomains of the NCSI and SF-36 are presented in Table 2. In general, the NCSI shows lower intercorrelations between the subdomains than the SF-36. The proportion of intercorrelations ≤ .60 was 79% for the NCSI and 36% for the SF-36. Intercorrelations ≥ .70, indicating conceptual similarity, are found four times for the NCSI and three times for SF-36. In the NCSI, conceptual similarity is found between the subdomains 'Subjective Pulmonary Symptoms', 'Subjective Impairment' and 'Dyspnoea Emotions', and between 'Fatigue' and 'Health-Related Quality of Life'. In the SF-36, conceptual similarity is found between 'Vitality' on the one hand and 'General Health', 'Mental Health' and 'Social Functioning' on the other hand.

Correlations between the subdomains of the NCSI versus the SF-36 are presented in Table 3. All correlations were statistically significant (p < .01). NCSI 'Fatigue' reached the criterion for conceptual similarity with SF-36 'Vitality' and 'General Health'. NCSI 'Behavioural Impairment' is shown to be conceptually similar to SF-36 'Physical Functioning'. NCSI 'General Quality of Life' is conceptually similar to SF-36 'Mental Health', and NCSI 'Health-Related Quality of Life' is conceptually similar to SF-36 'General Health' and 'Vitality'.

Table 2. Intercorrelations between the subdomains of the NCSI and SF-36

NCSI	Subjective Pulmonary Symptoms	Dyspnoea Emotions	Fatigue	Behavioural Impairment	Subjective Impairment	General Quality of Life	Health-Related Quality of Life	Satisfaction Relations
Subjective Pulmonary Symptoms	1	.70	.53	.49	.81	.36	.47	.38
Dyspnoea Emotions		1	.50	.45	.70	.48	.50	.37
Fatigue			1	.53	.57	.50	.74	.42
Behavioural Impairment				1	.59	.37	.57	.40
Subjective Impairment					1	.45	.59	.42
General Quality of Life						1	.69	.61
Health-Related Quality of Life							1	.53
Satisfaction Relations								1

SF-36	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health
Physical Functioning	1	.65	.63	.64	.63	.63	.48	.47
Role Physical		1	.58	.62	.69	.66	.60	.50
Bodily Pain			1	.61	.61	.58	.39	.42
General Health				1	.76	.63	.46	.55
Vitality					1	.75	.54	.72
Social Functioning						1	.67	.69
Role Emotional							1	.66
Mental Health								1

Pearson's intercorrelations for the Nijmegen Clinical Screening Instrument (NCSI) and Short Form 36 (SF-36) for Q fever patients at 12 months after onset of illness. N = 309[1], $p < .01$ for all intercorrelations. Intercorrelations ≥ .70 are hatched.

1) N varies between 302 and 309 for individual intercorrelations, due to missing values within some of the questionnaires

Table 3. Correlations between the subdomains of the NCSI and SF-36

NCSI \ SF-36	Physical Functioning	Role Physical	Bodily Pain	General Health	Vitality	Social Functioning	Role Emotional	Mental Health
Subjective Pulmonary Symptoms	.53	.43	.46	.53	.50	.51	.46	.40
Dyspnoea Emotions	.50	.51	.46	.52	.50	.57	.53	.52
Fatigue	.59	.68	.61	.72	.85	.63	.47	.54
Behavioural Impairment	.71	.60	.51	.54	.58	.58	.44	.40
Subjective Impairment	.63	.54	.53	.59	.58	.59	.48	.45
General Quality of Life	.45	.49	.43	.53	.63	.59	.52	.76
Health-Related Quality of Life	.61	.64	.58	.71	.77	.66	.54	.66
Satisfaction Relations	.40	.43	.36	.46	.56	.58	.49	.60

Pearson's correlations between subdomains of the Nijmegen Clinical Screening Instrument (NCSI) and Short Form 36 (SF-36) for Q fever patients at 12 months after onset of illness. N = 309[1], $p < .01$ for all correlations. Intercorrelations ≥ .70 are hatched.

1) N varies between 302 and 309 for individual correlations, due to missing values within some of the questionnaires.

Discussion

The main aim of our study was to identify an instrument or a combination of instruments that would provide a detailed assessment of health status of patients with Q fever. We investigated whether there is conceptual similarity between the subdomains of the instruments NCSI and SF-36 or whether both instruments are complementary to each other.

The NCSI shows lower intercorrelations between the subdomains than the SF-36, indicating that the NCSI subdomains represent independent concepts to a higher degree. Some intercorrelations were very high where we did not expect this, such as between SF-36 'Vitality' (measuring fatigue, as indicated by the very high correlation with NCSI 'Fatigue') and SF-36 'General Health', 'Mental Health' and 'Social Functioning', which are clearly different concepts than fatigue. Similarly, NCSI 'Fatigue' showed conceptual similarity with NCSI 'Health-Related Quality of Life'. A possible explanation for these high intercorrelations is that fatigue is the most dominant symptom of Q fever patients and dominates the wellbeing of the patients as expressed by other subdomains. Previous studies have already shown that 'Fatigue' and 'General Quality of Life' are the NCSI subdomains most severely affected in Q fever patients at 12 months after onset of illness[10,11].

Several subdomains measure concepts of health status not measured by the other instrument. These are: NCSI 'Subjective Pulmonary Symptoms', 'Subjective Impairment', 'Dyspnoea Emotions' and 'Satisfaction Relations'; SF-36 'Social functioning', 'Bodily Pain', 'Role Physical' and 'Role Emotional'. This means that if one wants to assess these specific subdomains, one needs to use either the NCSI or SF-36.

Conceptual similarity was found between four subdomains of each instrument, which implies that these subdomains of both instruments measure the same aspects of health status. The highest correlations were found between SF-36 'Vitality' and NCSI 'Fatigue' and 'Health-Related Quality of Life' (Pearson's r of .84 and .77 respectively). There is conceptual similarity between NCSI 'Fatigue' and both SF-36 'General Health' and 'Vitality', and between NCSI 'General Quality of Life' and SF-36 'Mental Health'. This implies that both the NCSI and SF-36 can be used to evaluate the aspects of health status that are the most affected in Q fever patients[10,11]. Advantages of the SF-36 are its length (only 36 questions compared to 56 in the NCSI) and the fact that it is publically available

in more than 170 languages, due to which it is more often used in international studies, which makes it possible to compare the health impact of Q fever to other diseases. The results also show that the Dutch studies which used the NCSI can be compared to international studies that used SF-36 in Q fever patients[5]. Advantages of the NCSI are that the concepts of health status it measures are more unique and it allows a description of health status on the level of the individual (as a normal, mild or severe score is available for each subdomain).

Conclusions

When measuring the general health status of Q fever patients, our study shows that either the NCSI or the SF-36 can be used. Only if the aim is to obtain a detailed overview of patients' health status, we advise that both the NCSI and SF-36, or at minimum a combination of the two, should be used. When combining the instruments we recommend that the NCSI is used (since it measures more variation in aspects of health status and because of the normative data) and it is complemented with the SF-36 subdomains not covered by the NCSI (i.e. SF-36 'Role Physical', 'Bodily Pain', 'Social Functioning', 'Role Emotional'). When the aim is to formulate a patient-centered intervention, the NCSI is preferred as it covers the important health status subdomains and since it provides a description of clinically relevant scores (normal, mild, severe) on an individual level.

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Chapter 4

Q fever patients suffer from impaired health status long after the acute phase of the illness: results from a 24-month cohort study

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Summary

Objectives: During the largest Q fever outbreak ever reported, a cohort study was established to assess the health status of Q fever patients over a 24-month period and to identify factors associated with health status.

Methods: Laboratory-confirmed Q fever patients participated at six time points after onset of illness. Scores on twelve subdomains from two health status instruments were calculated for each time point to determine progression and compare to reference groups.

Results: The study included 336 Q fever patients. There is a significant linear improvement over time in nine of the twelve health status subdomains. For example, the proportion of patients with severe fatigue improved from 73.0% at three months to 60.0% at twelve months and 37.0% at twenty-four months, but this was still high compared to a healthy reference group (2.5%). For the three most severely affected subdomains -'Fatigue', 'General Quality of Life' and 'Role Physical'- the baseline characteristics significantly associated with a long-term reduced health status were being female, being a young adult and having pre-existing health problems.

Conclusions: Despite a significant linear improvement over time in nine of the twelve health status subdomains, more than one out of three patients still suffered from a reduced health status at 24 months.

Keywords

Q fever, *Coxiella burnetii*, health status, quality of life

Introduction

Q fever is a zoonosis caused by the intracellular bacterium *Coxiella burnetii*. Approximately 40% of all persons infected with Q fever develop symptoms such as fever, pneumonia and hepatitis[1,2]. Several studies have shown that many patients suffer from a severely impaired health status, including persistent fatigue, after Q fever[3-9]. These symptoms have been reported for as long as ten years after onset of illness[5], but there are no data on how symptoms evolve over time during the first two years after infection.

Q fever is known to occur in small local outbreaks in Western Europe (0.19 cases per 100,000 in 2011 in Europe, ranging from 0.00 in nine EU countries to 0.60 per 100,000 in Cyprus (10)), which are usually associated with livestock farming[1,11]. Between 2007-2009, the number of notified cases of Q fever increased annually in the Netherlands, a country of 17 million inhabitants, and reached a cumulative total of 4107 in 2011, making it the largest documented outbreak in the world[12]. Measures taken in late 2009 to prevent the further spread of the disease led to a massive reduction in notifications from 2010 onwards (there were 81 cases in 2011)[12].

A study carried out in the Netherlands in 2009 found that there were high levels of severe fatigue and low levels of general quality of life 12-26 months after infection[8]. In addition, the Dutch Q fever patient organisation reported many long-term impairments (e.g. severe symptoms of fatigue, depression and unemployment)[13]. In order to provide prospective data on Q fever patients, we established a cohort study to systematically asses health status progression over a 24-month period. We also identified individual characteristics associated with health status at 12 and 24 months.

Materials and Methods

The design used was a prospective cohort study of Q fever patients over a period of 24 months 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 study population was patients diagnosed with Q fever in 2010 and 2011 in the Netherlands, who were at least 18 years of age and fulfilled the Dutch notification criteria of Q fever[14]. The standard treatment for patients with a Q

fever infection used by general practitioners in the Netherlands is 2-3 weeks of antibiotics, preferably Doxycycline (200 mg per day)[12].

Data collection

All Municipal Health Services in the Netherlands were asked to invite Q fever patients who met the Dutch notification criteria to participate in the study. Patients who gave permission received an information letter and a consent form by postal mail. After receiving written consent, patients were contacted by postal mail at 3, 6, 9, 12, 18 and 24 months with a questionnaire, and patients who did not return the questionnaire received a reminder by telephone or postal mail. Patients were allowed to enter the study at 3, 6, 9 or 12 months after onset of illness

Questionnaire

The study questionnaires contained two instruments to measure health status and quality of life: the Nijmegen Clinical Screening Instrument (NCSI)[15] and the Short Form 36 (SF-36)[16]. The NCSI was originally developed to measure health status in COPD patients and provides normative data indicating normal functioning, mild or severe problems for each subdomain[15]. The NCSI and SF-36 were used simultaneously since they gather information on different domains. Only the four subdomains in the SF-36 that have been shown to be not conceptually similar to subdomains in the NCSI are presented in our study[17]. The NCSI was included at 3, 12, 18 and 24 months.

Information on the individual characteristics of Q fever patients that could affect health status was also collected at the time of inclusion and consisted of socio-demographic, lifestyle and medical aspects (self-reported). Characteristics which could change over time (e.g. smoking behaviour and BMI) were included in successive questionnaires.

Reference groups

To compare the NCSI scores of the Q fever patients, an existing reference group, consisting of healthy participants[15], was expanded to match our group of Q fever patients for age and gender. They were asked to visit Radboud university medical center, where they completed an electronic questionnaire, including the NCSI. The lung function of the healthy reference group was

tested, so that persons with an undiagnosed underlying respiratory illness that could affect their health status could be excluded. For the SF-36 scores, we compared our scores to a large general population study carried out in the US[18].

Data analysis

Study participation

Differences in gender and age of the Q fever patients were analysed between participants and non-participants. Since patients could drop out of the study at each time point, the health status scores of drop-outs and patients who continued to participate were assessed, using independent samples *t*-tests.

We assessed the health status scores of patients who participated in the cohort study from 3 months onwards and patients who entered the study at a later time point, and found there were no important differences (data not shown). We have therefore focused our analyses on the outcomes of all patients in the cohort study.

Health status

For the NCSI, the proportion of severely affected patients at three time points (3, 12 and 24 months) was calculated. In addition, mean scores for each subdomain were calculated for each follow-up time point and compared to scores from the healthy reference group. For the SF-36, mean scores for the subdomains were calculated on a scale from 0 to 100% per patient group for each time point. The scores were compared to normative scores from the general population in a large U.S. study, on a scale from 0 to 100%[18].

Only Q fever patients who reported severe fatigue and/or a severe impact on their quality of life at 12 and 18 months after onset of illness were eligible for follow-up at 18 and 24 months respectively, since we wanted to focus on the most severely affected patients and did not want to burden recovered patients with additional questionnaires. For the patients with no severe score on the subdomains 'Fatigue' and 'General Quality of Life', scores at 12 and 18 months were assumed to remain the same at 18 and 24 months respectively.

Individual characteristics associated with health status

These characteristics were assessed at 12 and 24 months, but only for the most relevant subdomains. NCSI subdomains were considered relevant if the proportion of severely affected patients on the 3-month time point was higher than 40%[19]. SF-36 subdomains were considered relevant if their score on the 3-month time point differed more than 20% with the normative score[19]. Only original health status scores were used for these analyses, not scores that were extrapolated to 24 months.

Statistical analysis

Score progression on each subdomain was analysed using a generalized estimating equation (GEE) model assuming an exchangeable correlation structure, both for the NCSI as well as for the SF-36. Individual characteristics associated with health status were first identified by univariate analyses, using linear regression. Characteristics that showed statistical significance in the univariate analyses were combined in a multivariate model for each subdomain. Additionally, characteristics that were not statistically significant in the multivariate model were removed via a backward analysis. To assess multicollinearity, correlation coefficients were calculated between all characteristics, and a Spearman's Rho ≥ .80 was considered to be too high. A *p*-value of < .05 was considered to be statistically significant, based on two-sided tests. Data were analysed using the software SPSS for Windows (version 20).

Results

Participation and individual characteristics of the study population

All but one of the 25 Municipal Health Services in the Netherlands participated in the study and a total of 376 Q fever patients were eligible. Of these, 336 agreed to participate, giving a response of 89%. Our analyses of participants and non-participants showed no differences in gender (p = .867) and age (p = .916) (data not shown).

During the course of the study, 58 patients dropped out between time points (17%). Our analyses of the drop-outs revealed that, even though the proportion of patients who were lost to follow up is small, the patients who dropped out early scored significantly worse more often than patients who continued to participate. This was the case for twelve subdomains on different time points,

compared to one subdomain for which drop-outs scored better (data not shown). A detailed outline of the number of participants at each time point and the number of drop-outs can be found in Supplementary Table 1.
The individual characteristics of all patients at baseline and of those eligible for follow-up after 12 months are listed in Table 1.

Table 1. Individual characteristics of Q fever patients at time of inclusion in the study and patients who were eligible for follow-up after 12 months after onset of illness, for which associations with health status were analysed.

Variable	Inclusion[1]	Out of[2] (N)	Eligible after 12 Months[3]	Out of[4] (N)
Male sex %	54.8	336	50.0	216
Age[5] (years) Mean (± SD)	48.5 (13.9)	336	48.0 (14.0)	216
Educational level %		335		216
Low	41.2		40.7	
Middle	30.4		32.4	
High	28.4		26.9	
Dutch Nationality[6] %	98.5	336	98.6	216
Pre-existing health problems[7,8] %	39.7	335	46.8	216
Diagnosis during Q fever episode[8,9] %		335		216
Pneumonia	48.4		52.8	
Meningitis	0.0		0.0	
Endocarditis	0.9		0.9	
Hepatitis	5.7		6.5	
Pregnancy complications (% of women)	0.7	152	0.9	108
Body Mass Index[10] %		334		215
Underweight	0.6		0.9	
Normal weight	40.7		39.5	
Moderately overweight	46.1		40.5	
Seriously overweight	12.6		19.1	
Smoking behaviour %		336		216
Current	30.4		30.1	
Former	37.5		38.4	
Never	32.1		31.5	
Alcohol consumption (beverages/week) %		336		216
0	34.8		36.1	
1-6	39.6		43.1	
≥ 7	25.6		20.8	
Use of medication[11] %	46.4	336	56.9	216
Hospitalisation[12] %	11.0	310	13.9	216
Additional treatment for Q fever[13,14] (N)		305		216
Cognitive Behavioural Therapy	14		4	

Table 1, continued

	Graded Exercise Therapy	19	11	
	Additional treatment with antibiotics	38	26	
	Participation in Qure study	14	0	
	Other	29	18	
Pregnancy[6,13] (N)		11	152	4	108
Working[15] %		74.0	335	76.3	215

1) Inclusion in the study was possible at time point 3, 6, 9 or 12;
2) The total number of participants included in the study was 336, the total number of women 152. Due to some missing data, this value is smaller for some characteristics. Hospitalisation and additional treatment were included from the 12-month time point onwards, with a maximum N of 310;
3) Patients were eligible for follow-up at 12 months after onset of illness if they had a severe score on the subdomains 'Fatigue' and/or 'General Quality of Life';
4) The total number of patients eligible for follow-up after 12 months was 216, the total number of women 108. The Body Mass Index of one patient was missing;
5) Age during onset of illness;
6) Associations between nationality and pregnancy on one side and health status on the other side were not analysed, due to the small numbers of observations;
7) Pre-existing health problems consists of a large number of conditions, including but not limited to cardiovascular, pulmonary, renal, neurological conditions, diabetes, depression;
8) Pre-existing health problems and Diagnosis during Q fever episode are self-reported;
9) In the analyses, a patient is considered as having a severe illness during the acute phase of Q fever if he/she suffered from pneumonia, meningitis, endocarditis, hepatitis or pregnancy complications;
10) Body Mass Index was analysed as a continuous variable;
11) Only patients with one or more prescribed medicines were categorised as using medication. Patients who only used self-prescribed medication and/or homeopathic remedies were not;
12) Hospitalisation was included from the 12-month time point onwards. This variable describes hospitalisation between 9 and 12 months after onset of illness;
13) The values given for Additional treatment for Q fever and Pregnancy are the number of patients during the course of the study for the inclusion column, and the number of patients at 12 months after onset of illness for the column presenting information of eligible patients;
14) Additional treatment for long-lasting health effects of Q fever (e.g. fatigue). Treatments for Q fever that are considered regular are Cognitive Behavioural Therapy, Graded Exercise Therapy, additional treatment with antibiotics or participation in the Qure study (31). Other treatments are considered non-regular;
15) Working is defined as patients who worked before their Q-fever infection.

Supplementary table 1. Participation of Q fever patients with an onset of illness in 2010/2011 in the Netherlands, at each time point. The total number of patients that participated in the study was 336.

Cohort	Number of patients per time point (months)								Drop-out[4] (between 3-24)
	3	6	9	12	Follow-up after 12 months[1]	18	Follow-up after 18 months[2]	24	
Inclusion at 3 months[3]	90	88	89	87	60	58	47	46	6
Inclusion at 6 months[3]		118	107	109	76	69	57	50	23
Inclusion at 9 months[3]			123	109	77	71	58	51	27
Inclusion at 12 months[3]				5	3	2	2	1	2
Total	90	206	319	310	216	200	164	148	

1) Only patients that had a severely affected score on the NCSI subdomains 'Fatigue' and/or 'General Quality of Life' at 12 months were eligible for participation at 18 months;

2) Only patients that had a severely affected score on the NCSI subdomains 'Fatigue' and/or 'General Quality of Life' at 18 months were eligible for participation at 24 months;

3) The number of patients that entered the study at each time point together form the total study population (n = 336);

4) Patients that stopped participating at a certain time point, although being eligible for further participation, are considered drop-outs. The total number of drop-outs was 58. The number of drop-outs per time point can be determined by calculating the difference between the number of patients at inclusion and at 12 months after onset of illness, and by adding the number of eligible patients that dropped out for 18 and 24 months. E.g. for the 3-month time point this results in: (90-87) + (60-58) + (47-46) = 6.

Health status

NCSI

At the 3-month time point, the highest proportion of patients who had a severely affected score were found in the subdomains 'Fatigue' (73.0%) and 'General Quality of Life' (42.2%) (data not shown). At the 12-month time point, these proportions were 60.0% and 50.2% and at 24 months 37.0% and 33.7% for 'Fatigue' and 'General Quality of Life' respectively, compared to 2.5% and 19.8% in the healthy reference group. There was a gradual improvement over time in the mean scores of Q fever patients on all NCSI subdomains, as visualised in Fig. 1A (a lower score indicates a better health). When the effect of time on mean subdomain scores is analysed via GEE models, there is a significant linear decline in the scores of five out of eight subdomains (Table 2). No significant linear decline was found for the subdomains 'Dyspnoea Emotions' (p = .061), 'General Quality of Life' (p = .084) and 'Satisfaction Relations' (p = .231).

Fig. 1A. Mean score of Q fever patients on each NCSI subdomain compared to a normative score of a healthy control group for each time point, from 3-24 months after onset of illness

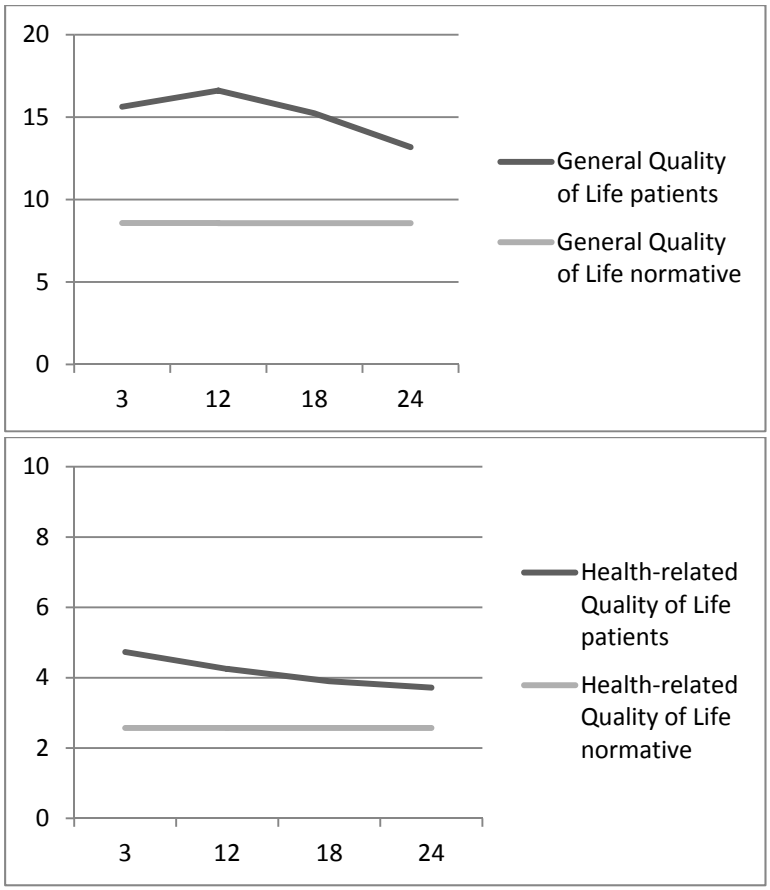
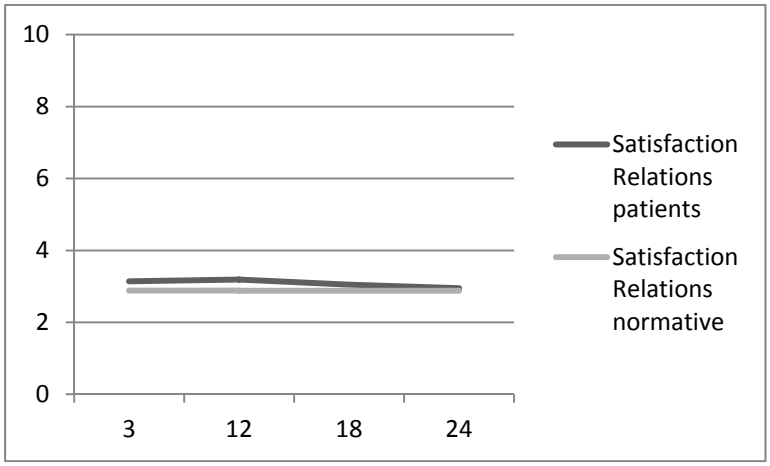
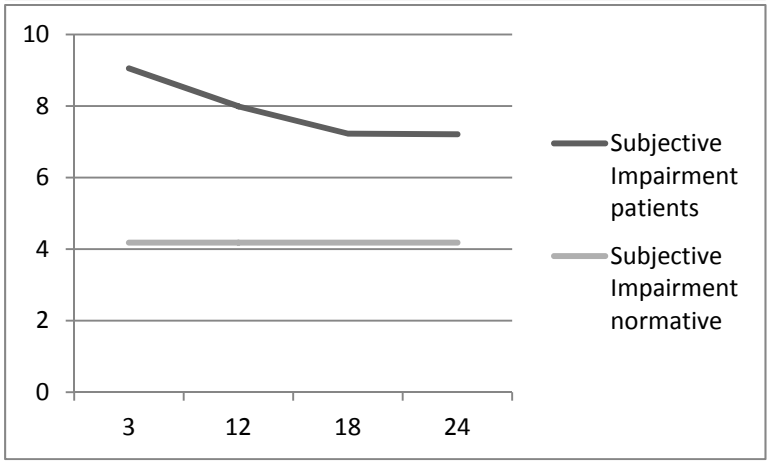
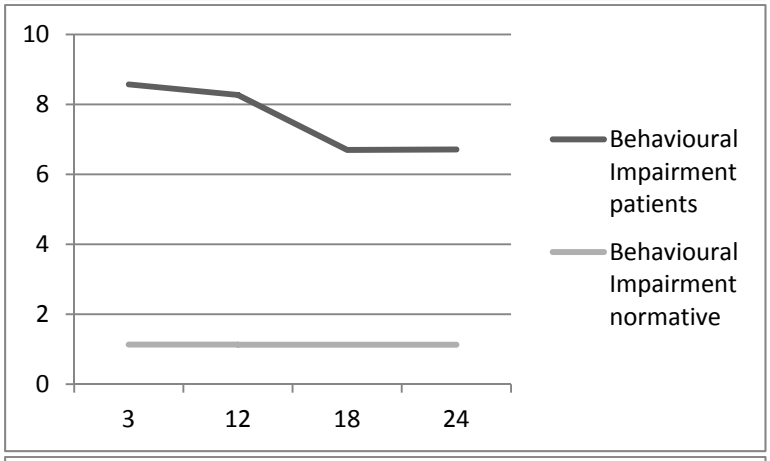


Figure 1A, continued







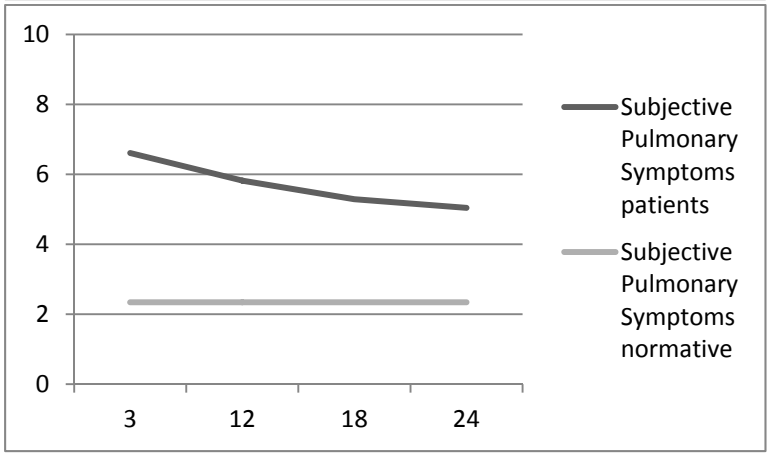
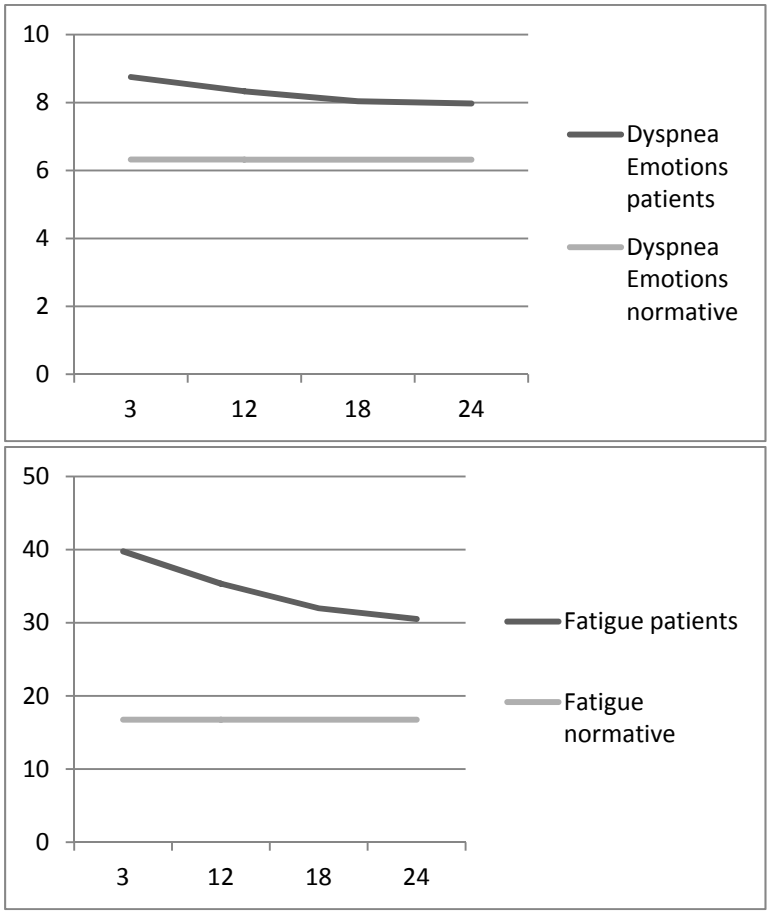


Figure 1A, continued

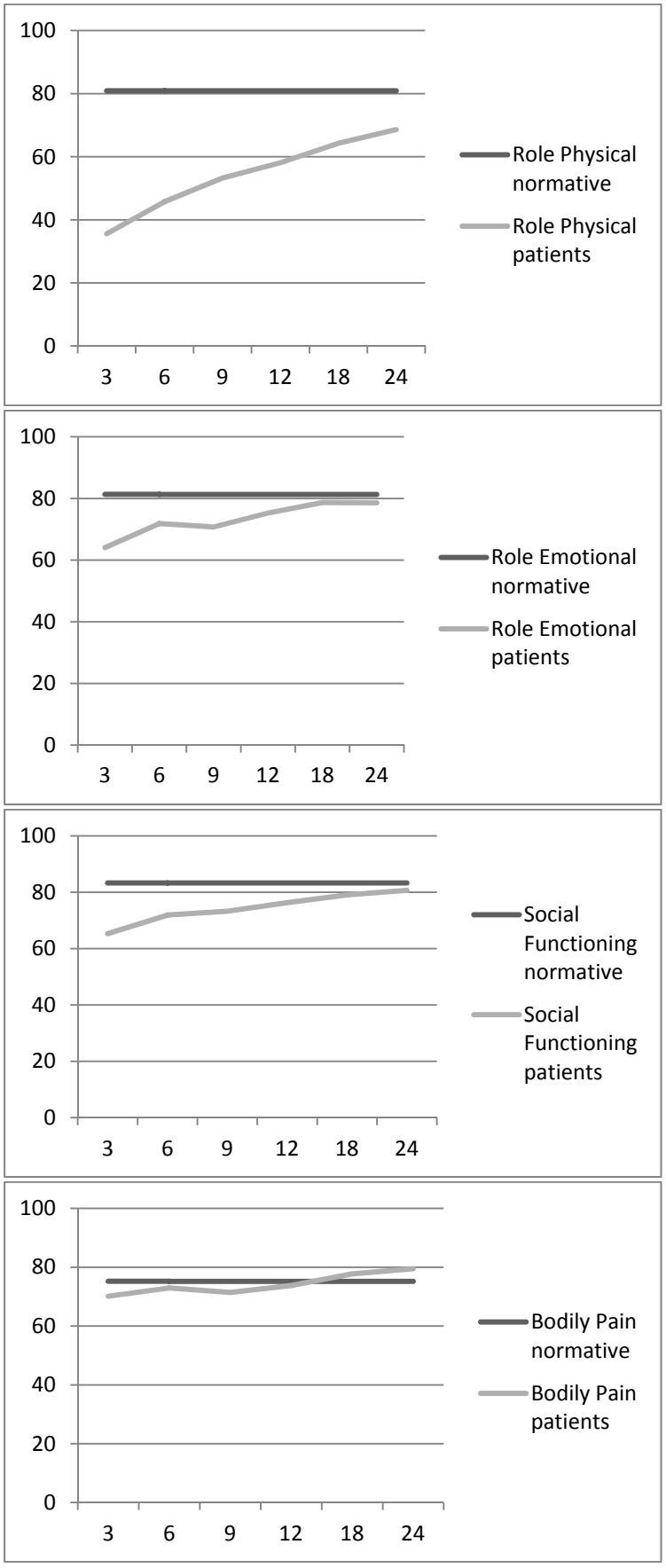


A lower score indicates better health

SF-36

For the SF-36 subdomain scores, there is an improvement in the mean scores of Q fever patients over time (Fig. 1B) (a higher score indicates better health). At 24 months after onset of illness, the mean score is close to the normative score for the general population for three out of four subdomains ('Role Emotional', 'Social Functioning' and 'Bodily Pain'). When this effect is analysed using GEE models, there is a statistically significant linear increase in the scores for all four subdomains (Table 2).

Fig. 1B. Mean score of patients on each SF-36 subdomain compared to a normative score of the general population for each time point, from 3-24 months after onset of illness



A higher score indicates better health

Table 2. B-values and significance levels for disease progression of Q fever patients over time (3-24 months) for each subdomain, using a GEE (n = 336 patients)

	Subdomain	b-value[1] (CI)	p-value	N[2]
NCSI[3]	Subjective Pulmonary Symptoms	-0.60 (-0.98 to -0.22)	.002	969
	Dyspnoea Emotions	-0.25 (-0.52 to 0.01)	.061	964
	Fatigue	-4.82 (-6.02 to -3.63)	< .001	957
	Behavioural Impairment	-1.02 (-1.88 to -0.16)	.020	970
	Subjective Impairment	-0.79 (-1.17 to -0.41)	< .001	966
	General Quality of Life	-0.98 (-2.09 to 0.13)	.084	968
	Health-Related Quality of Life	-0.44 (-0.58 to -0.30)	< .001	970
	Satisfaction Relations	-0.08 (-0.22 to 0.05)	.231	963
SF-36[3]	Role Physical	14.57 (11.58 to 17.57)	< .001	1492
	Bodily Pain	4.54 (3.02 to 6.06)	< .001	1495
	Social Functioning	5.71 (4.09 to 7.33)	< .001	1491
	Role Emotional	4.73 (1.73 to 7.73)	.002	1488

1) The unit of the listed b-values is the score difference per year, ranging from 3-24 months after onset of illness;

2) N is the total number of measurements on which the scores are based;

3) For the NCSI subdomains, a lower score indicates a better health. For the SF-36 subdomains, a higher score indicates a better health.

Individual characteristics associated with health status

Three subdomains were selected for the analysis at 12 and 24 months: NCSI 'Fatigue' and 'General Quality of Life', and SF-36 'Role Physical', as these were the most severely affected in patients (see above)[19]. In the multivariate analyses on the 12-month time point, using medication and following an additional treatment for long-lasting effects of Q fever are significantly associated with a lower health on all three subdomains. Being female, a young adult, having pre-existing health problems, consuming no alcohol and being hospitalised in the previous three months are associated with a lower health status on one or two subdomains (Table 3). For the severely affected patients at 24 months, having pre-existing health problems is associated with a lower health status on all three subdomains; consuming no alcohol, using medication and following an additional treatment for Q fever are associated with reduced scores on one or two subdomains (Table 4). The highest correlation between individual characteristics included in the multivariate analyses, using

Table 3. B-values and significance levels for the relation between individual characteristics and health status of Q fever patients for selected subdomains on the 12-month time point using multivariate analyses.

Independent Variable[1]	**Dependent Variables**[2]					
	Fatigue[3]		*General Quality of Life*[4]		*Role Physical*[5]	
	b-value (CI)	*p-value*	*b-value (CI)*	*p-value*	*b-value (CI)*	*p-value*
Intercept	41.57 (38.31 to 44.83)	< .001	29.85 (23.19 to 36.51)	< .001	45.64 (36.69 to 54.60)	< .001
Variables measured at baseline						
Gender						
Male	-4.21 (-7.58 to -0.85)	.014				
Female	Ref.					
Age			-0.17 (-0.28 to -0.06)	.003		
Pre-existing health problems						
Yes	4.45 (0.79 to 8.10)	.017	3.99 (0.70 to 7.27)	.018		
No	Ref.		Ref.			
Variables measured at 12 months						
Alcohol consumption (week)				.003		.013
≥ 7			-6.73 (-10.74 to -2.71)	.001	18.61 (6.14 to 31.07)	.004
1-6			-1.55 (-4.93 to 1.83)	.367	9.73 (-0.86 to 20.33)	.072
0			Ref.		Ref.	
Use of medication						
Yes	4.49 (0.96 to 8.03)	.013	3.40 (0.10 to 6.71)	.043	-19.30 (-28.62 to -9.99)	< .001
No	Ref.		Ref.			
Hospitalisation[6]						
Yes			5.23 (0.49 to 9.97)	.031	-15.26 (-30.04 to -0.49)	.043
No			Ref.		Ref.	

Table 3, continued

Additional treatment for Q fever[7]		.008		.018		< .001
Yes	7.38 (2.36 to 12.40)	.004	5.72 (1.17 to 10.27)	.014	-25.02 (-39.06 to -10.99)	.001
Non-regular treatment	6.15 (-2.07 to 14.36)	.142	5.71 (-1.51 to 12.93)	.121	-27.66 (-50.37 to -4.95)	.017
No	Ref.		Ref.		Ref.	

1) All variables were tested but only the significant variables were included in the final multivariate models. Additional characteristics that were tested but not significant in either of the models are Educational level, Diagnosis during the acute Q fever episode, BMI and Smoking behaviour, since they were not significantly associated with the selected subdomains in the multivariate analyses;

2) A lower score on the NCSI subdomains 'Fatigue' and 'General Quality of Life' indicates better health. A higher score on the SF-36 subdomain 'Role Physical' indicates better health;

3) For the subdomain 'Fatigue', also the characteristics Alcohol consumption and Hospitalisation were statistically significant in the univariate analysis. In the multivariate model, they were removed via a backward analysis;

4) For the subdomain 'General Quality of Life', also the characteristic Gender was statistically significant in the univariate analysis. In the multivariate model, it was removed via a backward analysis;

5) For the subdomain 'Role Physical', also the characteristics Gender, Pre-existing health problems and Diagnosis during the acute Q fever episode were statistically significant in the univariate analysis. In the multivariate model, they were removed via a backward analysis;

6) Hospitalisation comprises the period between 9 and 12 months after onset of illness;

7) Additional treatment for long-lasting health effects of Q fever (e.g. fatigue). Treatments for Q fever that are considered regular are Cognitive Behavioural Therapy, Graded Exercise Therapy, additional treatment with antibiotics or participation in the Qure study (31). Other treatments are considered non-regular.

Table 4. B-values and significance levels for the relation between individual characteristics and health status of Q fever patients with a severely affected health status for selected subdomains on the 24-month time point using multivariate analyses.

Independent Variable[1]	**Dependent Variables**[2]					
	Fatigue[3]		*General Quality of Life*[4]		*Role Physical*[5]	
	b-value (CI)	*p-value*	*b-value (CI)*	*p-value*	*b-value (CI)*	*p-value*
Intercept	42.18 (39.31 to 45.04)	< .001	25.55 (22.21 to 28.88)	< .001	30.76 (17.83 to 43.69)	< .001
Variables measured at baseline						
Pre-existing health problems						
Yes	7.41 (3.65 to 11.17)	< .001	5.47 (0.44 to 10.50)	.033	-18.45 (-31.53 to -5.37)	.006
No	Ref.		Ref.		Ref.	
Variables measured at 24 months						
Alcohol consumption (week)						.004
≥ 7					21.24 (4.14 to 38.33)	.015
1-6					24.27 (9.08 to 39.46)	.002
0					Ref.	
Use of medication						
Yes			6.48 (1.36 to 11.60)	.013		
No			Ref.			
Additional treatment for Q fever[6]		.018				.013
Yes	6.68 (1.78 to 11.57)	.008			-26.27 (-43.63 to -8.91)	.003
Non-regular treatment	5.63 (-3.26 to 14.53)	.213			-7.67 (-38.78 to 23.44)	.627
No	Ref.				Ref.	

Table 4, continued

1) All variables were tested but only the significant variables were included in the final multivariate models. Additional characteristics that were tested but not significant in either of the models are Gender, Age, Educational level, Diagnosis during the acute Q fever episode, BMI, Smoking behaviour and Hospitalisation, since they were not significantly associated with the selected subdomains in the multivariate analyses;
2) A lower score on the NCSI subdomains 'Fatigue' and 'General Quality of Life' indicates better health. A higher score on the SF-36 subdomain 'Role Physical' indicates better health;
3) For the subdomain 'Fatigue', also the characteristic Use of medication was statistically significant in the univariate analysis. In the multivariate model, it was removed via a backward analysis;
4) For the subdomain 'General Quality of Life', all characteristic that were statistically significant in the univariate analysis are included in the multivariate model;
5) For the subdomain 'Role Physical', also the characteristics Age and Use of medication were statistically significant in the univariate analysis. In the multivariate model, they were removed via a backward analysis;
6) Additional treatment for long-lasting health effects of Q fever (e.g. fatigue). Treatments for Q fever that are considered regular are Cognitive Behavioural Therapy, Graded Exercise Therapy, additional treatment with antibiotics or participation in the Qure study (31). Other treatments are considered non-regular.

Spearman's Rho, was found between use of medication and pre-existing health problems (r = .40), indicating no problem with multicollinearity.

Discussion

We present the long-term health status of Q fever patients in the Netherlands. It is the first time that such a large prospective cohort study is performed. Our study shows that many Q fever patients suffer from a reduced health status long after the acute phase of their illness. Despite a significant and linear improvement in nine out of twelve health status subdomains of patients between 3 and 24 months after onset of illness, patients generally had low health status scores after 24 months compared to a healthy reference group. For example, the proportion of severely affected patients for the subdomain 'Fatigue' ranges from 73.0% at 3 months to 37.0% at 24 months. We feel that it is not likely that patients exaggerate their fatigue status to participate within a disability policy, as this leads to a reduced income and is thus not beneficial for them.

Wildman et al. hypothesised that the excess fatigue that was observed in Q fever patients in their study might be (partly) explained by psychological distress (e.g. anxiety and depression), caused by uncertainty about their illness and repeated medical contacts reinforcing perceptions of ill health[5]. The NCSI subdomain 'General Quality of Life' consists of the instrument 'Beck Depression Inventory' (BDI), which provides a measure of psychological distress[15]. A study by van Loenhout et al. in a group of Q fever patients showed that Pearson's correlation between the subdomains 'General Quality of Life' and 'Fatigue' was .50, leading to an r^2 of .25[17]. These results suggest that psychological distress is not an important factor in explaining the high levels of excess fatigue found in our study.

For several subdomains, there is no significant linear improvement in health status over time (Table 2). We cannot explain why 'General Quality of Life' scores at 12 months are more impaired than at 3 months, although general quality of life of people is influenced by many factors besides their illness. For the subdomains 'Satisfaction Relations' and 'Dyspnoea Emotions', we assume there is no improvement since scores on these subdomains are relatively close to scores of the healthy controls from the 3 month follow-up period onwards.

We were only able to identify a handful of studies with a prospective study design which have been used to assess the long-term health status of patients affected by an infectious disease. A study carried out in Australia looked at patients with post-infective fatigue syndrome (among whom were 42 patients infected with *Coxiella burnetii*) in the first year after illness[4] and two other studies in the U.S. and the Netherlands reviewed health status of patients with Community-Acquired Pneumonia until 90 and 540 days after onset of illness respectively[20,21]. All three studies support our finding that Q fever patients, as well as those with Epstein-Barr Virus, Ross River virus and Community-Acquired Pneumonia, show post-infective fatigue and recover gradually from their infection.

Individual characteristics associated with health status at 12 months

We found that women score worse on the subdomain 'Fatigue' than men, which is supported by general studies on gender and health where women are more prone to report health problems[22,23]. The relationship between age and 'General Quality of Life' suggests that older people can accept their health problems more easily. Having pre-existing health problems was associated with a lower health status on all three subdomains, which is supported by other studies (e.g. on cardiovascular illnesses, rheumatoid arthritis, diabetes)[24-26]. Although the proportion of patients with pre-existing health problems is high (39.7%), this figure is in line with persons with underlying conditions in the general Dutch population (46.8%)[27], and low compared to patients with Legionnaires' disease (59.5%), even though there is no difference in long-term health status of Q fever patients and patients with Legionnaires' disease[19].

For all individual characteristics measured at 12 months, we cannot infer a causal relationship with health status, as these characteristics can change over time. Characteristics which were, as expected, associated with concurrent reduced health status, are using medication and being hospitalised. More surprising is the finding that a lower alcohol consumption is associated with a reduced health status on two subdomains. Another unexpected result is the reduced score of patients who follow an additional treatment for long-lasting effects of Q fever. A possible explanation is that patients only seek additional treatment for Q fever when their health status is seriously impaired.

Individual characteristics associated with health status of severely affected patients at 24 months

Since only patients with a severely affected score at 12 and 18 months on the subdomains 'Fatigue' and 'General Quality of Life' were eligible for subsequent follow-up, the group of patients at 24 months is different to the 12-month group (e.g. the higher proportion of women and persons with pre-existing health problems, see Table 1). Having pre-existing health problems at baseline is the only characteristic which is associated with a reduced score on all three health status subdomains and seems to be the most influential in affecting health status in the group of patients with a severely affected long-term health status[24-26]. Individual characteristics measured at 24 months associated with a reduced health status on at least one subdomain are, consistent with 12 months, not consuming alcohol, using medication and following an additional treatment for Q fever. Having pre-existing health problems and these three characteristics are all negatively associated with health status of the most severe patients.

Limitations

One limitation of our study is the reference groups that we used to interpret our findings. For the SF-36 subdomains, we compared the mean scores of Q fever patients to the mean scores of the general population in a large U.S. study. For the NCSI, only normative data from a healthy reference group were available. In addition, both groups were not serologically tested for Q fever, so it is possible that persons are included who previously underwent a Q fever infection (more likely for the Dutch than for the U.S. reference group). Since the reference group for the NCSI consists of healthy controls, they are by definition more healthy than the general population, which leads to an overestimation of health status. Studies on fatigue in the general population imply that baseline fatigue levels are already quite high[28,29], and this means the high proportion of patients who are severely affected on the subdomain 'Fatigue' might also include fatigue due to other reasons than the infectious illness under study.

Due to the fact that all patients were included through Municipal Health Services, our study included only patients who fitted the Dutch case definition for acute Q fever. A population-based surveillance study would provide more

insight into the long-term health problems of all persons with a Q fever infection and such a study (n = 2,163) is currently ongoing[30].

The results of our study might be an underrepresentation of the actual patient scores, for two reasons. First, the small number of patients who dropped out of the study early generally had a lower health status compared to patients who continued to participate. Second, patients who were not severely affected on the subdomains 'Fatigue' and 'General Quality of Life' at the 12- or 18-month time points were not eligible for further participation. Their scores were extrapolated to subsequent time points, although in reality health status of some patients could have decreased again. Finally, our results do not provide insight into the reasons why some patients have a severely affected long-term health status while others have not, as this is a population-based analysis.

Conclusion

This large prospective study showed that there is a significant linear improvement over time in nine of the twelve health status subdomains from 3 to 24 months after onset of illness. However, more than one out of three patients still had reduced health status scores at 24 months (37% suffered from severe fatigue). This information can be used to present the expected disease progression to newly infected Q fever patients. Our analyses also helped identify baseline characteristics associated with a reduced long-term health status, namely being female, being a young adult, and suffering from pre-existing health problems, which can be used by health care workers (e.g. General Practitioners) to identify patients with a higher risk for a reduced health status. These findings show there is a substantial long-term impact of Q fever, and they are important for healthcare workers around the world who are confronted with a Q fever outbreak in the community. Although there is no standard treatment for Q fever patients with a long-term impaired health status, a clinical trial is currently being carried out in the Netherlands that could provide more insight into effective therapies for these patients[31].

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Chapter 5

A cross-sectional study to assess the long-term health status of patients with lower respiratory tract infections, including Q fever

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Summary

Patients with a lower respiratory tract infection (LRTI) might be at risk for long-term impaired health status. We assessed whether LRTI patients without Q fever are equally at risk for developing long-term symptoms compared to LRTI patients with Q fever. The study was a cross-sectional cohort design. Long-term health status information of 50 Q fever-positive and 32 Q fever-negative LRTI patients was obtained. Health status was measured by the Nijmegen Clinical Screening Instrument. The most severely affected subdomains of the Q fever-positive group were 'General Quality of Life' (40%) and 'Fatigue' (40%). The most severely affected subdomains of the Q fever-negative group were 'Fatigue' (64%) and 'Subjective Pulmonary Symptoms' (35%). Health status did not differ significantly between Q fever-positive LRTI patients and Q fever-negative LRTI patients for all subdomains, except for 'Subjective Pulmonary Symptoms' (p = .048).

Keywords

Health status, LRTI Quality of life, Q fever

Introduction

Each year, around 25% of the Dutch population visit their General Practitioner (GP) with respiratory symptoms[1]. Part of this group presents with a lower respiratory tract infection (LRTI), which is generally more serious than an upper respiratory infection. A Dutch study showed that patients with community-acquired pneumonia still have an impaired health status 18 months after onset of illness compared to a control population, although these results were attributed more to the effects of age and/or co-morbidity than the pneumonia[2]. Furthermore, several studies have shown that Q fever, an infectious illness which presents with high rates of pneumonia in patients in some countries[3] (61.5% in the Netherlands[4]), may have a long-term impact on patients' health[5-10]. We found limited information on long-term health status of LRTI patients in general[2]. We assessed the health status of patients who experienced an LRTI the previous year by using a standard questionnaire. Special attention was paid to Q fever in this study, because of the large outbreak that affected the Netherlands during that period[11]. Since patients with Q fever as well as patients with other causes of LRTI appear to be at risk for long-term impaired health status, including fatigue, we investigated whether an LRTI caused by Q fever is a more severe infection in terms of health status at roughly 15 months after onset of illness than other LRTIs.

Methods

Design

In a cross-sectional cohort study, patients presenting with an LRTI to their GP in 2009 were included, and subsequently their health status was assessed at roughly 15 months after onset of illness.

Study site

GP practices (n=14) in the provinces of Northern Brabant and Gelderland, located in or around the epicentre of the Q fever outbreak in the Netherlands, registered patients with an LRTI.

Study population

Patients with an LRTI, as diagnosed by their GP, were included in the study. Diagnosis was based on clinical symptoms. Patients were categorised in one of

the following International Classification of Primary Care (ICPC) groups: R78 acute bronchitis, R80 influenza, R81 pneumonia and R83 other lower respiratory tract infections. Patients aged < 18 and > 75 years were excluded since the proportion of Q fever infections compared to other infections is limited for these age groups. The inclusion period was from 1 May until 30 September 2009, to exclude a high proportion of pathogens specific for the winter period. All included patients were serologically tested for Q fever in one out of two hospital laboratories as part of regular care. Diagnostic tests were polymerase chain reaction (PCR), immunofluorescence assay (IFA) and complement fixation assay (CFA). Patients were diagnosed as either Q fever positive or Q fever negative. Regular care for Q fever-positive patients also included serological follow-up to diagnose potential cases of chronic Q fever, but these results were not included in our study. Of the 194 registered LRTI patients who were tested for Q fever in 2009, 19 patients could not be contacted, two patients died and six patients moved to a GP practice not included in the study area. This left a total of 167 patients that were invited to participate.

Data collection

Information on hospitalisation of patients during the acute phase of the disease was obtained through their GPs. Between July and September 2010, patients received a health status questionnaire with a consent form from their GP. If the patient did not return the questionnaire within 4 weeks, a reminder was sent by the GP.

Health status questionnaire

Health status was assessed using the Nijmegen Clinical Screening Instrument (NCSI). The NCSI is a validated instrument and measures health status on eight subdomains of three domains: 'Symptoms', 'Functional Impairment' and 'Quality of Life'. The NCSI consists of a battery of instruments (Table 1) and provides a valid and detailed picture of a patients' health status[12]. It allows a description of health status at the individual level (as a normal, mild or severe score is available for each subdomain). In addition, the questionnaire contained questions on personal characteristics (gender, age, smoking behaviour) and co-morbidity.

Table 1. Nijmegen Clinical Screening Instrument subdomains.

Subdomain	**Definition**	**Instruments**
Symptoms		
Subjective Pulmonary Symptoms	The patient's overall burden of pulmonary symptoms	PARS-D Global Dyspnoea Activity PARS-D Global Dyspnoea Burden
Dyspnoea Emotions	The level of frustration, and anxiety a person experiences when dyspnoeic	DEQ Frustration DEQ Anxiety
Fatigue	The level of fatigue experienced	CIS Subjective Fatigue
Functional Impairment		
Behavioural Impairment	The extent to which a person cannot perform specific and concrete activities as a result of having the disease	SIP Home Management SIP Ambulation
Subjective Impairment	The experienced degree of impairment in general, and in social functioning	QoLRiQ General Activities
Quality of Life		
General Quality of Life	Mood and the satisfaction of a person with his/her life as a whole	BDI Primary Care Satisfaction With Life Scale
Health-related Quality of Life	Satisfaction related to physiological functioning and the future	Satisfaction Physiological Functioning Satisfaction Future
Satisfaction Relations	Satisfaction with the (absent) relationships with spouse and others	Satisfaction Spouse Satisfaction Social

PARS-D, Physical Activity Rating Scale – Dyspnoea; DEQ, Dyspnoea Emotions Questionnaire; CIS, Checklist Individual Strength; SIP, Sickness Impact Profile; QoLRiQ, Quality of Life for Respiratory Illness Questionnaire; BDI, Beck Depression Inventory.

Statistical analysis

SPSS for Windows v. 20 (IBM SPSS Statistics, USA) was used for data entry and analyses of the data. A value of $p < .05$ was considered as statistically significant. All identifiers were removed and data were analysed anonymously. The baseline data of 2009 (from the GP registration of LRTI patients) enabled us to compare responders and non-responders with regard to gender, age, ICPC, hospitalisation and Q fever status. χ^2 tests and an unpaired *t*-test were used for comparison of characteristics between patients who tested positive for Q fever *vs.* patients who tested negative for Q fever.

Scores of all eight subdomains of the NCSI were calculated and the proportion of patients with normal, mild and severe scores on the different subdomains were determined, as described in a study by Peters *et al*.[12].

Differences in NCSI subdomain scores between the group of Q fever-positive and Q fever-negative LRTI patients were analysed using a multivariate model for each subdomain, with correction for relevant confounding characteristics, i.e. gender, age, smoking behaviour, ICPC and co-morbidity. ICPC was dichotomised into two items; pneumonia (R81) and other LRTI (an aggregation of R78, R80 and R83). Co-morbidity was also dichotomised into two items due to small numbers: no co-morbidity *vs*. one or more underlying diseases (e.g. heart or vascular disease, chronic disease, cancer, immune disorder, diabetes, lung disease, depression).

Results

Eighty-two patients returned the questionnaire, resulting in a response rate of 49%. Patients completed the questionnaire 10-19 months after initial infection in 2009, with a mean response time of 15 months. There was no significant difference in gender, age and hospitalisation between responders and non-responders (data not shown). Responders more often had pneumonia as an ICPC classification (65% *vs*. 42%, $p = .004$) and more often tested positive for Q fever in 2009 (61% *vs*. 45%, $p = .035$) compared to non-responders.

Characteristics of the study population

Of the responders, 50 (61%) patients tested positive for a Q fever infection (Table 2). Significantly more Q fever-positive patients were diagnosed with pneumonia compared to Q fever-negative patients (76% *vs*. 47%, $p = .004$). Q

fever-positive patients were younger (mean age 48.1 years) than Q fever-negative patients (mean age 57.2 years), although the difference was not significant. There were no significant differences between the two groups for hospitalisation at baseline, gender, smoking behaviour and co-morbidity.

Table 2. Comparison of the characteristics of the study groups, consisting of Q fever-positive and Q fever-negative LRTI patients.

Variable	Q fever positive (N=50)	Q fever negative (N=32)	Difference (*p* value)
Male sex %	60	50	.373
Age (years) Mean (± SD)	48.1 (14.3)	57.2 (14.4)	.189
Smoking Behaviour[1]			.238
Current	40	30	
Former	28	47	
Never	32	23	
ICPC %			.004
Acute bronchitis (R78)	6	38	
Influenza (R80)	6	6	
Pneumonia (R81)	76	47	
Other LRTI (R83)	12	9	
Hospitalisation[2] %	10	7	.591
Co-morbidity[3] %	42	56	.208

LRTI, Lower Respiratory Tract Infection; ICPC, International Classification of Primary Care.

1) There were two missing values for smoking behaviour;
2) Hospitalisation was measured at baseline and there were three missing values;
3) Co-morbidities consist of (among others) heart or vascular disease, chronic disease, cancer, immune disorder, diabetes, lung disease, depression.

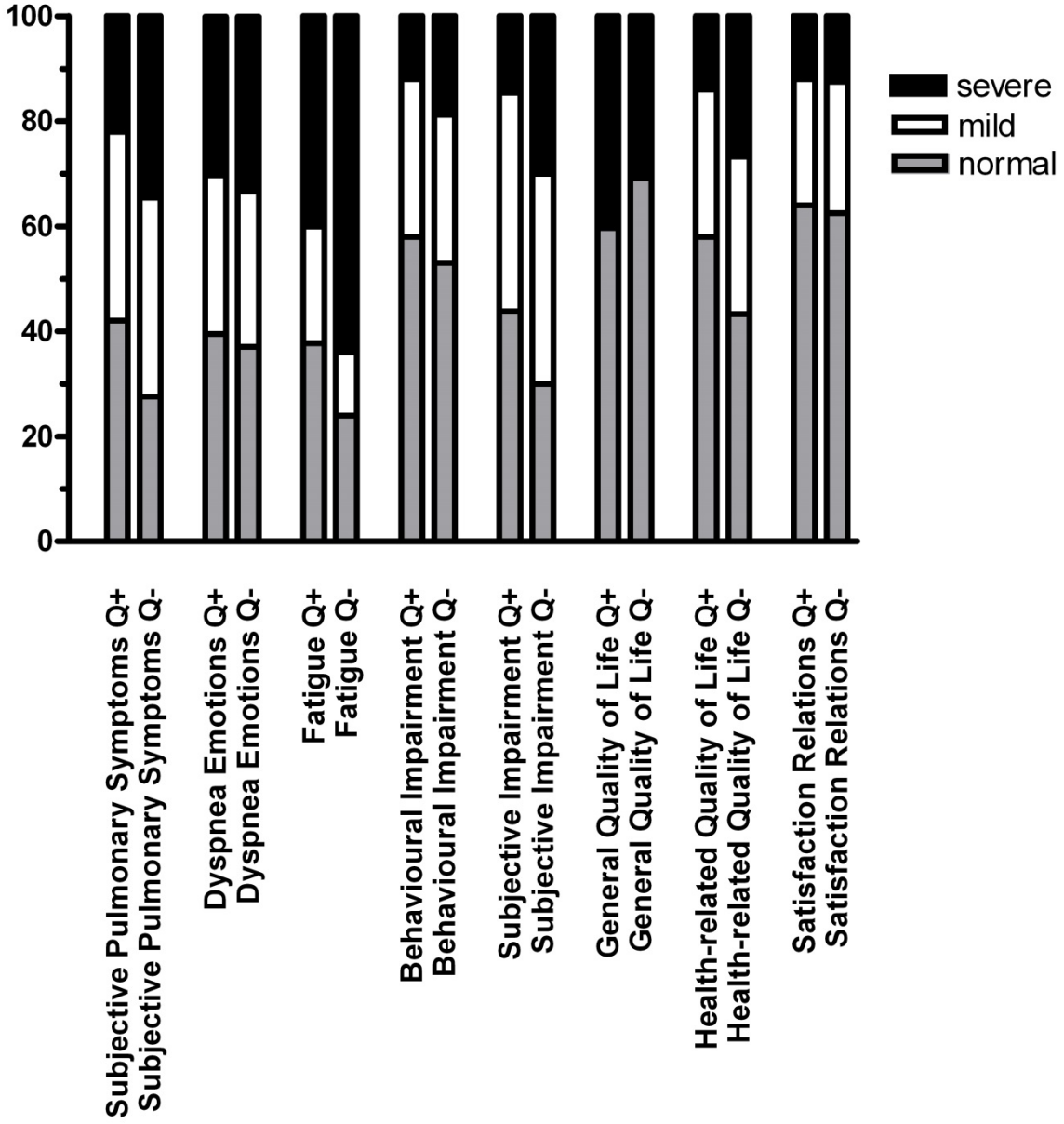
Health status

Health status of a large proportion of the patients within each group was severely affected at roughly 15 months after onset of illness as measured by the NCSI, ranging from 12% on the subdomains 'Satisfaction Relations' and 'Behavioural Impairment' to 64% on the subdomain 'Fatigue' (Fig. 1). Within the Q fever-positive LRTI group, 'General Quality of Life' (40%) and 'Fatigue' (40%) were the most severely affected subdomains, while most severely affected subdomains of the Q fever-negative LRTI group were 'Fatigue' (64%) and 'Subjective Pulmonary Symptoms' (35%). The proportions of patients who were severely affected on more than one subdomain at roughly 15 months

after onset of illness were 40% and 56% for the Q fever-positive and Q fever-negative LRTI patients, respectively.

Health status scores between Q fever-positive and Q fever-negative LRTI patients were compared at roughly 15 months after initial illness. Q fever-negative patients scored significantly worse for the subdomain 'Subjective Pulmonary Symptoms' after correcting for the confounders gender, age, smoking behaviour, pneumonia and co-morbidity (2.62, p= .048) (Table 3).

Figure 1. Proportion of patients with normal/mild/severe scores on the different subdomains of the Nijmegen Clinical Screening Instrument at roughly 15 months after lower respiratory tract infection, presented for Q fever-positive (Q+) and Q fever-negative (Q-) patients.



QoL, Quality of Life; HrQoL, Health-related Quality of Life

Table 3. Linear regression models presenting the NCSI scores for each subdomain at roughly 15 months after LRTI for Q fever-positive and Q fever-negative LRTI patients, corrected for gender, age, smoking behaviour, ICPC (pneumonia or other) and co-morbidity (yes or no). Q fever-positive patients are the reference group.

Subdomain	**Min-Max NCSI score**	**Q fever positive patients Mean (SD)**	**n**	**Q fever negative patients Mean (SD)**	**n**	**Difference between groups corrected for confounders (CI 95%)**	**P-value**
Subjective pulmonary symptoms	2-20	5.64 (4.54)	50	7.90 (5.53)	29	2.62 (0.03 to 5.22)	.048
Dyspnea emotions	6-22	9.14 (4.18)	43	9.15 (3.54)	27	0.73 (-1.41 to 2.87)	.498
Fatigue	8-56	31.24 (14.59)	45	35.84 (13.46)	25	3.49 (-4.69 to 11.67)	.397
Behavioral impairment	0-61.42	6.09 (10.25)	50	9.16 (16.62)	32	0.32 (-5.82 to 6.45)	.919
Subjective impairment	4-28	7.71 (5.32)	48	10.13 (7.27)	30	2.34 (-0.88 to 5.56)	.151
General QoL	1-66	11.85 (11.83)	47	11.61 (14.35)	26	-0.19 (-7.30 to 6.93)	.958
HRQoL	2-10	3.60 (1.71)	50	4.53 (2.53)	30	0.84 (-0.20 to 1.88)	.110
Satisfaction relations	2-9	2.86 (1.51)	50	2.84 (1.61)	32	-0.09 (-0.91 to 0.73)	.829

NCSI, Nijmegen Clinical Screening Instrument; LRTI, Lower respiratory tract infection; ICPC, International Classification of Primary Care; CI, confidence interval.

Discussion

This study demonstrates that a large group of GP-registered LRTI patients was affected on one or more aspects of health status at roughly 15 months after LRTI, especially on 'Fatigue', 'General Quality of Life' and 'Subjective Pulmonary Symptoms'. These long-term symptoms have also been described in a study by Moussaoui *et al*. in community-acquired pneumonia patients with an impaired health status 18 months after their initial illness, especially in patients with a co-morbidity[2]. Long-term symptoms and an impaired health status were also seen in patients with Legionnaires' disease, for which most patients experience pneumonia during the acute phase of the disease[13].

There was no significant difference in health status scores at roughly 15 months between LRTI patients who were diagnosed with Q fever compared to patients who did not have Q fever, except for the subdomain 'Subjective Pulmonary Symptoms'. The Q fever-negative group experienced significantly more subjective symptoms (overall burden of pulmonary symptoms) than the Q fever-positive group, although we cannot explain why this group had more symptoms. A previous study in the Netherlands identified having Q fever as well as pneumonia as risk factors for a long-term impaired health status[5], which is why one would expect a larger impact on health in the Q fever-positive group of LRTI patients. The main outcome of our study is, however, that long-term health status of Q fever-positive and Q fever-negative LRTI patients was very similar.

Results concerning Q fever patients within this study are comparable to previous Dutch Q fever studies, even though this study only considers Q fever patients with an LRTI (in contrast to other studies, where all Q fever patients are considered). 'Fatigue' and 'General Quality of Life' were the subdomains with the highest proportions of severe scores; these results were also found in the other Dutch studies[5,6]. Forty per cent of the Q fever patients showed severe fatigue at roughly 15 months after their initial illness, which is similar to the 44% and 52% from the other studies as well. Studies outside the Netherlands also showed fatigue as one of the main long-term health problems for Q fever patients[7-9]. However, it has been shown that over 30% of the general population suffer from chronic fatigue[14,15], which raises uncertainty about the proportion of fatigue in patients that can be attributed to Q fever.

Strengths and limitations of the study

Despite the fact that reminders were sent and that patients received the questionnaire from their own GP, the response rate was relatively low (49%). The fact that responders were more often Q fever positive may have been due to the fact that Q fever and its burden of disease received a great deal of media attention during the outbreak. Q fever patients may therefore have deemed it more important to complete a questionnaire on their health status, despite the fact that the letter and questionnaire that were sent to patients did not contain the word 'Q fever'. The low response rate may have resulted in a relatively high proportion of study participants with an impaired health status, especially in the Q fever-negative group (patients with symptoms are considered more eager to participate in studies), indicating that our results might show an overrepresentation of their health impact.

Patients were tested for Q fever by two different laboratories, using different diagnostic methods. The most frequently used laboratory tests in Q fever-positive patients were the IFA (50%) and PCR (43%). However, all tests used are considered suitable serodiagnostic assays to diagnose acute Q fever[16,17].

A potential limitation of our study was that we did not further diagnose the microbiological cause of illness of the Q fever-negative LRTI patients. A study conducted in the Netherlands showed that a wide variety of pathogens is present in patients with acute respiratory tract infections[18], which indicates that it is often difficult to establish the source of an infection in this population. Moreover, Marrie *et al*. were unable to find any difference in disease recovery at 30 days after onset of illness in patients with atypical pneumonia with unknown microbiological cause and patients with atypical pneumonia due to a pathogen from a series of underlying agents[19]. We do not therefore feel this disproves the overall findings and conclusions.

More generally, studies on the health impact of infectious diseases have demonstrated that long-term recovery in patients with varying microbiological diseases, such as Epstein-Barr virus, enteroviruses and *Coxiella burnetii*, all experience long-term fatigue[10,20], and that post-infective fatigue syndrome is largely predicted by severity of the acute illness rather than by microbiological factors[10]. The observation in our study that Q fever-positive as well as Q fever-negative LRTI patients showed a long-term impaired health status is in line with these studies.

Conclusions

This study showed that a large group of LRTI patients was affected on more than one aspect of health status at roughly 15 months after LRTI. We demonstrated that there is little difference in long-term health status between Q fever-positive and Q fever-negative LRTI patients. GPs should be aware of long-term health problems in LRTI patients, not only those that are Q fever positive but also those that are Q fever negative.

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Chapter 6

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

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Abstract

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.

Keywords

Q fever, Legionnaires' disease, Health status, Fatigue, Quality of life

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[2-5], although other studies have failed to demonstrate its existence[6,7]. The persistence of an impaired health status, including fatigue, of patients after acute Q fever was recently shown in studies in the Netherlands[8,9]. These results are in line with previous Q fever studies in other countries[10-13]. 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 4,000 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[15,16]. 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 protocol[18]). 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 burnetti* 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 tests[14]:

- 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. 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
		Satisfaction Relations	2
SF-36	Physical Health	Role Physical	4
		Bodily Pain	2
	Mental Health	Social Functioning	2
		Role Emotional	3

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 = 2,474)[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[24-26]. 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 55.4% was male.

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

Variable	**Q fever patients**	**Patients with Legionnaires' disease**	**Difference**
	N=309	**N=190**	***p*-Value**
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

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. 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**
	%	**%**	**%**
	n = 121	n = 309	n = 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

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. 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[1] (%) n = 2,474	Mean[1] (%) n = 309	Difference[2] (%)	Mean[1] (%) n = 190	Difference[2] (%)
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

1) Scores were calculated on a scale from 0 to 100%;

2) Score differences were obtained by subtracting the patient score from the normative score.

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.

Uncorrected models

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).

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).

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**[2]	
		Q fever	*Legionella*	*Q fever*	*Legionella*
Fatigue[1]	*b-Value (CI)*	2.51 (-0.24 to 5.27)	Ref	2.52 (-0.56 to 5.59)	Ref
	p-Value	.074		.108	
General Quality of Life[1]	*b-Value (CI)*	1.87 (-0.61 to 4.35)	Ref	1.27 (-1.49 to 4.03)	Ref
	p-Value	.139		.366	
Role Physical[1]	*b-Value (CI)*	-1.80 (-9.62 to 6.01)	Ref	-9.16 (-17.75 to -0.58)	Ref
	p-Value	.651		.037	

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

2) 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.

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[13,17]. 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[8,9]. 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[2-5].

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 study[18]). 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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Chapter 7

Work participation in Q fever patients and patients with Legionnaires' disease: a 12 month cohort study

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Abstract

Aims The aim of the study was to assess long-term work participation of Q fever patients and patients with Legionnaires' disease, and to identify which factors are associated with a reduced work participation in Q fever patients.

Methods Q fever patients participated at four time points until 12 months after onset of illness, patients with Legionnaires' disease only at 12 months. Data was self-reported, using questionnaires on the amount of hours that patients worked, and on socio-demographic, medical, psychosocial and lifestyle aspects.

Results Our study included 336 Q fever patients and 190 patients with Legionnaires' disease. There was a decrease in the proportion of Q fever patients with a reduced work participation over time, from 45% at 3 months to 19% at 12 months (versus 15% of patients with Legionnaires' disease at 12 months). Factors associated with a reduced work participation of Q fever patients in a multivariate model were having symptoms, a higher level of sorrow, being a former smoker (compared to never smoking), not consuming any alcohol and following an additional treatment for the long-term health effects of Q fever.

Conclusions Despite an increase in work participation of Q fever patients over time, almost one in five Q fever patients and one in six patients with Legionnaires' disease still suffer from reduced work participation at 12 months. Occupational and insurance physicians need to be aware of the long-term impact of these diseases on work participation.

Keywords

Q fever, Legionnaires' disease, *Coxiella burnetii*, *Legionella pneumophila*, work participation, symptoms, psychosocial factors

Introduction

Q fever is a zoonosis caused by the intracellular bacterium *Coxiella burnetii*. Apart from symptoms and conditions that are commonly reported during the acute phase of the disease, which include fever, pneumonia, hepatitis and neurological symptoms such as headache[1], many patients also report long-term health problems. Several studies have shown that a large proportion of Q fever patients suffer from long-term fatigue[2-9], even up to ten years after onset of illness[4]. Although this has never been assessed in Q fever patients, it is also possible that Q fever has a psychosocial impact, due to patients being confronted with many experiences of loss (e.g. health, work, independence, social activities)[10].

Following the large outbreak of Q fever in the Netherlands, with a total of 4,107 notified patients over the period 2007-2011[11], there were a number of reports regarding the long-term impact of Q fever on work participation of patients[12,13]. In the latter study, work participation was reported retrospectively by patients, and this limited the accuracy of the results.

It is unclear whether the reduction in work participation is higher in patients that underwent a Q fever infection compared to patients that underwent other major health events, e.g. another infectious disease. Q fever and Legionnaires' disease are both acute febrile diseases which may present with similar clinical manifestations[1,14], and there are currently no data on work participation of patients with Legionnaires' disease. The aim of our study was to compare work participation in these two groups. Another aim was to quantify the progress of work participation of Q fever patients prospectively over the period 3-12 months after onset of illness, and to identify which individual, lifestyle, medical and psychological factors are associated with work participation.

Methods

The design used was a prospective cohort study of Q fever patients, and a cross-sectional survey of patients with Legionnaires' disease. The study protocol was submitted to the Medical Ethical Review Board of the region Arnhem-Nijmegen, which indicated that ethical review was not required.

Study population

Patients with Q fever

Patients diagnosed with Q fever in 2010 and 2011 in the Netherlands, who were at least 18 years of age and fulfilled the Dutch notification criteria for Q fever[11], were eligible for this study (as described in the study protocol[15]). 376 patients were invited to participate.

Patients with Legionnaires' disease

Patients fulfilling the Dutch notification criteria for Legionnaires' disease[11], with an onset of illness in 2010, were eligible for this study (as described in the study protocol[15]). 243 patients were invited to participate.

Data collection

Municipal Health Services in the Netherlands were asked to invite Q fever patients and patients with Legionnaires' disease to participate in our study. Patients who gave permission received an information letter and a consent form by postal mail. After receiving written consent, Q fever patients were contacted by postal mail at 3, 6, 9 and 12 months after onset of illness with a questionnaire[15]. Patients with Legionnaires' disease were contacted only at 12 months after onset of illness. Patients who did not return the questionnaire received a reminder by telephone or postal mail.

Questionnaire

The first study questionnaire that patients received collected information on the number of hours per week they worked before their infection (Q fever or Legionnaires' disease) and currently, for paid work as well as voluntary work. If they worked currently less than before their illness (defined in this manuscript as a 'reduced work participation'), patients indicated whether this was due to Q fever or Legionnaires' disease, according to their opinion. Further, patients reported from which symptoms they had suffered during the previous two weeks, and for each symptom whether they suspected this was due to their previous infection. We included an instrument to assess the different stages of the grieving process due to the infection that patients underwent: the Acceptance of Disease and Impairments Questionnaire (ADIQ), which has so far been used in patients with Chronic Obstructive Pulmonary Disease (COPD)[16].

Patients who answered 'not applicable' on one of the questions of this instrument were given the lowest possible score for denial, resistance and sorrow, and the highest possible score for acceptance for the respective question. Information on the individual characteristics of Q fever patients that could affect work participation was also collected and consisted of socio-demographic, lifestyle and medical aspects (self-reported).
For the Q fever patients, the number of hours worked per week and symptoms were included in all successive questionnaires, and the ADIQ only on time points 3 and 12 months. A question on additional treatment due to the long-lasting health effects of Q fever was included on the 12 month time point.

Data analysis

Differences in gender and age of the patients were analysed between participants and non-participants using independent samples *t*-tests and Chi square tests. Baseline characteristics were determined for the complete groups of Q fever patients and patients with Legionnaires' disease, and separately for the patients that performed paid work before their illness (defined in the manuscript as 'working patients'). For the working patients, we determined work participation (separately also for patients that performed voluntary work), the number of symptoms, and a score for each stage of the grieving process. Grief scores were compared between the patient groups using independent samples *t*-tests.
Factors associated with work participation of working Q fever patients were identified using univariate logistic regression models. These analyses were only performed for Q fever patients due to the relatively small number of working patients with Legionnaires' disease. All factors that showed statistical significance in the univariate analyses were combined in a multivariate model. In addition, factors that were not statistically significant in the multivariate model were removed through backward analysis. To assess multicollinearity, correlation coefficients were calculated between all significant factors, and a Spearman's Rho ≥ .80 was considered to be too high. A *p*-value of <.05 was considered to be statistically significant, based on two-sided tests. Data were analysed using the software SPSS for Windows (version 20).

Results

Participation and characteristics of the study population

The number of participants was 336 Q fever patients (response of 89%) and 190 patients with Legionnaires' disease (response of 78%). There were no differences between participants and non-participants for gender and age (data not shown). The number of Q fever patients that entered and dropped out of the study at each time point is presented in Table 1. The composition of the groups of Q fever patients differed only slightly between the different time points, in terms of gender and age (data not shown).

Table 1. Participation of Q fever patients with an onset of illness in 2010/2011 in the Netherlands, at each time point. The total number of patients that participated in the study was 336.

Cohort	Number of patients per time point[a] (months)				Drop-out[b] (between 3-12)
	3	6	9	12	
Inclusion at 3 months	90	88	89	87	3
Inclusion at 6 months		118	107	109	9
Inclusion at 9 months			123	109	4
Inclusion at 12 months				5	n/a
Total	90	206	319	310	

a) The number of patients that entered the study at each time point together form the total study population (n = 336);

b) Patients that stopped participating at a certain time point are considered drop-outs. The total number of drop-outs was 16.

The characteristics of both patient groups are presented in Table 2, for the whole study populations as well as separately for the working patients (74% of the Q fever patients and 54% of the patients with Legionnaires' disease). For both patient groups, the working population consists of a higher proportion of males, is younger, had a higher education and a lower proportion of pre-existing health problems compared to the total population. The group of patients with Legionnaires' disease was older, and had a higher proportion of males, (former) smokers and patients with pre-existing health problems than the group of Q fever patients. The descriptive information on the patient groups that performed voluntary work is not presented in Table 2, as this group was too small for further analyses. They consist of 54.8% and 61.0% males, and

a mean age of 54.3 and 62.2 years for 84 Q fever patients and 41 patients with Legionnaires' disease, respectively.

Table 2. Individual characteristics of Q fever patients and patients with Legionnaires' disease at time of inclusion in the study, both for the complete study populations as well as for the working populations separately.

	Q fever		Legionella	
Variable	**All (n=336)**	**Working[a] (n=248)**	**All (n=190)**	**Working[a] (n=102)**
Age[b] (years) Mean (± SD)	48.5 (13.9)	44.7 (12.1)	60.1 (11.5)	54.1 (10.7)
Male sex %	54.8	60.1	68.9	77.5
Educational level %				
Low	41.2	31.6	54.0	48.0
Middle	30.4	35.6	21.2	19.6
High	28.4	32.8	24.9	32.4
Pre-existing health problems[c] %	39.7	34.3	59.5	51.0
Severe Q fever episode[d] %	51.0	47.2	n/a	n/a
Body Mass Index %				
Underweight	0.6	0.8	0.0	0.0
Normal weight	40.7	38.9	36.0	33.7
Moderately overweight	46.1	47.4	41.3	41.6
Seriously overweight	12.6	13.0	22.8	24.8
Smoking behaviour %				
Current	30.4	31.9	37.4	37.3
Former	37.5	35.1	47.4	46.1
Never	32.1	33.1	15.3	16.7
Alcohol consumption (beverages/week) %				
0	34.8	31.9	24.2	21.6
1-6	39.6	41.1	33.7	36.3
≥ 7	25.6	27.1	42.1	42.2
Additional treatment for Q fever[e] %				
Regular treatment	12.5	11.5	n/a	n/a
Non-regular treatment	4.3	5.3	n/a	n/a
No additional treatment	83.3	83.2	n/a	n/a
Working Full-time[f] %	n/a	66.1	n/a	75.5
Reduction in work participation %				
Due to Q fever / Legionnella[g]	n/a	26.2	n/a	14.7
Due to other circumstances[h]	n/a	8.1	n/a	19.6
No reduction in work participation	n/a	65.7	n/a	65.7

Table 2, continued

a) The working populations consist of patients that were performing paid labour before they became infected by Q fever or Legionnaires' disease;

b) Age during onset of illness;

c) Pre-existing health problems consists of a large number of conditions, including but not limited to cardiovascular, pulmonary, renal, neurological conditions, diabetes, depression;

d) A patient is considered as having a severe Q fever episode if he/she suffered from pneumonia, meningitis, endocarditis, hepatitis or pregnancy complications;

e) Additional treatment for long-lasting health effects of Q fever (e.g. fatigue). Treatments for Q fever that are considered regular are Cognitive Behavioural Therapy, Graded Exercise Therapy, additional treatment with antibiotics or participation in the Qure study (23). Other treatments are considered non-regular. The values are the proportion of patients at 12 months after onset of illness (N = 305 for all Q fever patients and N = 226 for the working Q fever patients);

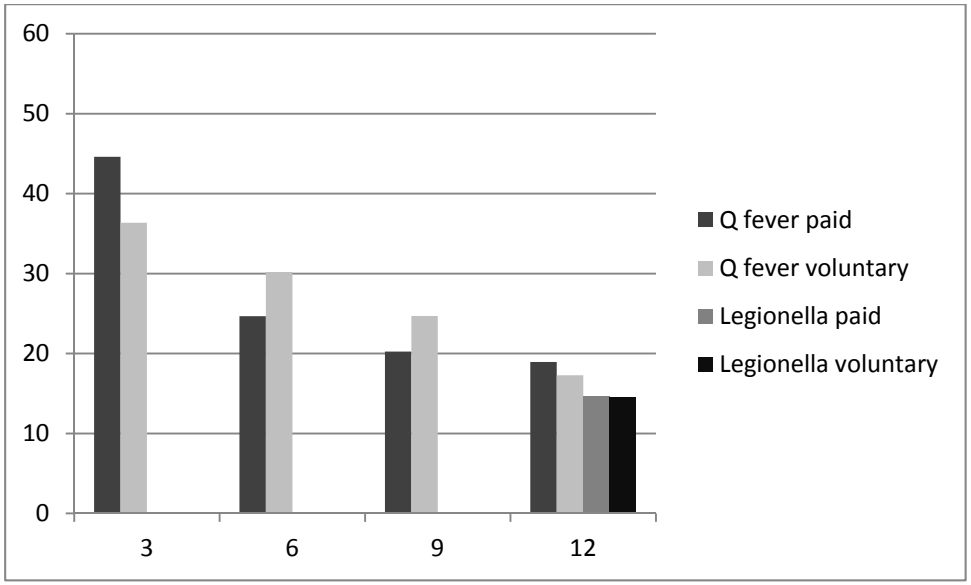
f) Patients who worked at least 32 hours per week are considered full-time workers;

g) The proportion of patients that worked less due to Q fever or Legionnaires' disease, compared to before they became ill (according to their opinion) at inclusion in the study;

h) The proportion of patients that worked less compared to before they became ill, but due to another reason than their infection (according to their opinion) at inclusion in the study. These reasons were not further specified.

Figure 1. The proportion of all patients from the working population that had a reduced work participation due to Q fever from 3 to 12 months after onset of illness (n = 248 for paid work and 84 for voluntary work over all time points) or Legionnaires' disease at 12 months after onset of illness (n = 102 for paid work and 41 for voluntary work).

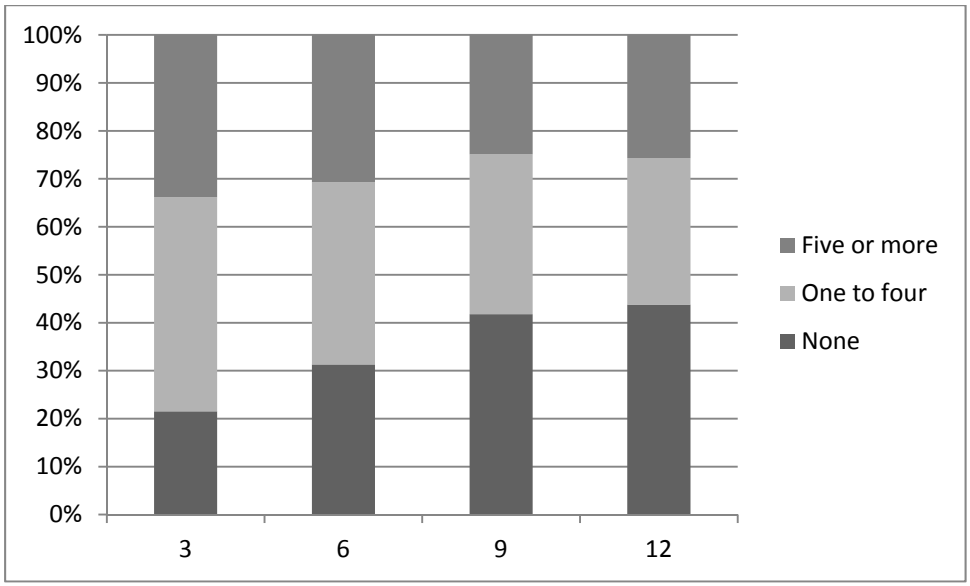
i)



Work participation

Figure 1 shows the proportion of working patients with a reduced work participation, both for paid and voluntary work, due to Q fever (at each time point) or Legionnaires' disease (at 12 months). There is a general decrease in the proportion of Q fever patients with a reduced work participation over time, for both paid and voluntary work, up until 12 months. At 12 months, a slightly higher proportion of working Q fever patients had a reduced work participation compared to patients with Legionnaires' disease (19% vs. 15% respectively). The median proportion of hours that patients worked less remained fairly stable over time, varying from 60% at 3 months to 50% at 12 months for paid work and around 80% overall for voluntary work for Q fever patients, compared to approximately 40% and 90% respectively for patients with Legionnaires' disease at 12 months after onset of illness (data not shown).

Figure 2. Distribution of the number of symptoms experienced by working Q fever patients up until 12 months after onset of illness (n = 248 over all time points).



Symptoms

The progress in the number of symptoms in working Q fever patients is presented in Figure 2. This shows an increase in the proportion of patients that do not report symptoms up until 12 months. Of the working patients with Legionnaires' disease, the proportion that reported no symptoms at 12 months

was 57%, which is higher than the respective group of Q fever patients at 12 months (44%, Figure 2). The most frequently reported symptoms in working Q fever patients at 12 months were concentration and memory problems, severe fatigue, headache (all 24%) and muscular pain (23%); the most frequently reported symptoms in working patients with Legionnaires' disease were concentration and memory problems (21%), severe fatigue, respiratory problems and pain in the joints (all 13%).

Grief

For each stage of the grieving process, we calculated the levels for working Q fever patients (at 3 and 12 months) and working patients with Legionnaires' disease (at 12 months). The mean score of Q fever patients is significantly higher at 12 months for denial and resistance, and significantly lower for acceptance compared to patients with Legionnaires' disease (Table 3). Each of the four stages of the grieving process remains fairly constant between 3 and 12 months for the group of Q fever patients (data not shown).

Table 3. Mean scores and standard deviations of the four stages of the grieving process (denial, resistance, sorrow, acceptance) for working Q fever patients (n = 248) and working patients with Legionnaires' disease (n = 102), at 12 months after onset of illness. Each score has a range of 1-4.

	Q fever[a] (n = 228)		Legionnaires' disease (n = 102)		Difference[c]
	Mean	SD[b]	Mean	SD[b]	*p*-value
Denial	2.6	1.1	2.1	1.1	< .001
Resistance	1.9	1.0	1.6	0.9	.017
Sorrow	1.7	0.9	1.6	0.9	.128
Acceptance	2.8	1.0	3.1	0.9	.034

a) n for the Q fever patients was 224 for Denial and Sorrow and 223 for Acceptance due to some missing values;

b) SD = Standard Deviation;

c) Whether the difference between the patient groups was statistically significant was tested using an independent samples t-test.

Factors associated with a reduced work participation (paid work)

The highest correlation between individual characteristics that were significant in the univariate analyses, using Spearman's Rho, was found between resistance and sorrow (r = .70). Since this was below .80, there was no multicollinearity in the model. Factors that were significantly associated with a

reduced work participation in the multivariate analysis were having symptoms, having a higher level of sorrow, being a former smoker (compared to never smoking), not consuming any alcohol and following an additional treatment for the long-term health effects of Q fever (Table 4).

Table 4. Factors associated with a reduced work participation in working Q fever patients at 12 months using logistic regression (n = 168).

Independent Variable[a,b]	**Affected in work**		
	OR[c]	95% CI[d]	p-value
Symptoms			.005
5 or more	11.71	1.99 to 68.78	.006
1 to 4	17.21	3.04 to 97.41	.001
None			
Sorrow	2.19	1.29 to 3.74	.004
Smoking behaviour			.031
Current	2.11	0.60 to 7.40	.242
Former	6.05	1.57 to 23.28	.009
Never	Ref.		
Current alcohol consumption (week)			.070
0	3.73	0.86 to 16.17	.079
1-6	5.05	1.26 to 20.16	.022
≥ 7	Ref.		
Additional treatment for Q fever			.001
Regular treatment	12.09	2.90 to 50.42	.001
Non-regular treatment	8.88	1.11 to 70.98	.040
No additional treatment	Ref.		

a) Factors that were tested but which did not have a significant association with work participation due to Q fever in the univariate analyses were gender, age, educational level, pre-existing health problems, BMI (tested as a continuous variable) and denial;

b) Factors associated with a reduced work participation that were statistically significant in the univariate analysis but not in the multivariate analysis were having a higher level of resistance, a lower level of acceptance, and a severe Q fever episode. They were removed via a backward analysis.

c) OR = Odds Ratio. The dependent variable was binary, with 0 = patients with an equal or higher number of working hours compared to their hours before Q fever and 1 = patients with less working hours due to Q fever. Patients who were working less hours due to another reason than Q fever were excluded on those respective time points. This led to an inclusion of 168 patients (out of a working population of 248);

d) CI = Confidence Interval.

Discussion

Our study shows that the outcomes for Q fever patients and patients with Legionnaires' disease, in terms of symptoms, work participation and grief, are similar at 12 months after onset of illness, although the impact of Q fever seems to be somewhat higher. A higher proportion Q fever patients report symptoms (56% vs. 43% with one or more symptoms), they have a higher reduction in work participation (19% vs. 15%) and have significantly higher scores for denial and resistance and lower scores for acceptance of their illness, although all these findings lie in the same order of magnitude. This is striking since patients with Legionnaires' disease are older and have more pre-existing health problems, which are generally associated with more limitations[17-19]. A previous study that compared Q fever patients and patients with Legionnaires' disease found that the self-reported health impact of Q fever is slightly higher[9], which supports our findings. The response rate and number of participants for both patient groups were high (especially for the Q fever patients), suggesting that the results from this study are representative for the two patient groups, although there might be a small response bias.

This first prospective study on work participation of Q fever patients showed that there is an increase in work participation over time, both for paid and voluntary work. Compared to the proportion of sick leave in the general Dutch population (4.0% in 2012)[20], the proportion of patients who have a reduced work participation due to Q fever at 12 months after onset of illness is high (19%, Figure 1). The reduction in work participation is also high compared to a study on return to work of patients after infectious mononucleosis, since this study found that only 2-3% of those patients was still absent from work at 12 months after infection, although the mean age of this group was lower than of patients in our study (31 vs. 49 years) and the results from this study are based on data from a national sickness registration database[21]. Finally, we compared our results to a Swedish study that reported the median duration of return to work for a large number of diagnoses, based on data from the national sickness insurance scheme in 617,611 cases[22]. The diseases with the longest median duration until return to work were malign neoplasms, severe mental disorders and severe cardiovascular diseases, with a return to work varying between two months and twelve months, while infectious diseases usually had a short return to work of one month or less[22]. Based on Figure 1, we estimate the median full

return to work of our Q fever population as a little under three months (since 55% of the patients does not have a reduced work participation at three months), which is long compared to other infections in Sweden but short compared to the more severe diagnoses mentioned above. Our results show that despite a general improvement in work participation of Q fever patients over time, almost one in five patients has a reduced work participation due to their illness at 12 months after onset of illness.

Our study found that Q fever patients generally have higher levels of denial and resistance and a lower level of acceptance compared to patients with Legionnaires' disease (Table 3), possibly due to the lower mean age of Q fever patients. Compared to a group of COPD patients in a Dutch study, Q fever patients show similar levels of grief[16]. This suggests that undergoing Q fever actually leads to a process of grief similar to undergoing a progressive disease that leads to persistent airway limitations such as COPD, which underlines the severity.

We identified several factors that are associated with a reduced work participation in a multivariate model (Table 4). For all associations, we cannot infer a causal relationship with work participation, as the characteristics we used in the analysis were measured after onset of illness. Since we were interested in work participation, we chose this as the outcome variable. Some associations were to be expected, such as having more symptoms and a higher level of sorrow. We are not sure why former smokers have a more reduced work participation than non-smokers, while this is not seen for current smokers, and why patients who consume no alcohol have the highest reduction of work participation. One explanation may be that the patients who are the most severely affected by their illness change their lifestyle due to their health problems. Patients who follow an additional treatment for long-lasting effects of Q fever are more reduced in their work participation, which may be explained by the fact that patients only seek additional treatment for Q fever when their health is seriously impaired.

Limitations

All data were self-reported by the patients. Information on reasons for a reduced work participation are registered in employer databases, but it was not possible to obtain these data within the context of our study, which is a

minor limitation in the reliability of our data. All the data were collected prospectively, except for the amount of hours that patients worked before their illness. We assume that patients gave a fairly good estimate of this amount, even after 12 months, since for most patients this was based on a work contract. 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

Despite an increase in work participation of Q fever patients over time, 19% of the patients is still affected at 12 months. The proportions of working Q fever patients and patients with Legionnaires' disease with a reduced work participation and symptoms are comparable at 12 months after onset of illness, although the impact of Q fever is slightly higher. This study has important implications for occupational and insurance physicians, who should be aware of the long-term impact of these diseases on work participation. It would be of interest to assess whether similar results are found after other infectious diseases, e.g. Lyme disease. The Dutch foundation Q-Support is currently providing individual guidance and information to Q fever patients with long-term health problems[12], and this might lead to higher levels of disease acceptance and work participation in this group of patients. We recommend a study to assess the effectiveness of this intervention.

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Chapter 8

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

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Abstract

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 four 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 EU case definition are considered.

Keywords

Q fever, *Coxiella burnetii*, health status, quality of life, fatigue

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 ten years after onset of illness[3], but follow-up of health status for more than two years has so far only occurred in a relatively small number of patients (around 100 cases or less)[1,3]. The current study is part of a cohort study on the long-term health status of Q fever patients[10].

Q fever is a notifiable infectious disease within the European Union. 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 harmonised 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]. So, 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 3,522 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 carried out 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 is a cross-sectional study of Q fever patients four 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 below.

	EU case definition since 2008 (revised in 2012)
Laboratory criteria	- Isolation of *Coxiella burnetii* from a clinical specimen
	- Detection of *Coxiella burnetii* nucleic acid in a clinical specimen
	- *Coxiella burnetii* specific antibody response (IgG or IgM phase II)
Clinical criteria	- Fever
	- Pneumonia
	- Hepatitis
Epidemiological criteria	- Exposure to a common source
	- Animal to human transmission

We refer to patients who fulfil the EU case definition as 'notified Q fever patients', versus '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 four million cows, one million sheep, 400,000 goats in 2013[14]). Figure 1 shows the classification of the two study groups.

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. In addition, general practitioners or consulting physicians who requested the laboratory test were informed on the laboratory results and provided patients with adequate treatment. The standard treatment used by general practitioners 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 the Q fever patients)[12,15]. Following a standard protocol, all reported patients were contacted by an expert (a physician or nurse) from the local Municipal Health Service 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 Municipal Health Service, were checked to classify all patients in the correct study groups according to the EU definition, since the case definition used by the Municipal Health Service 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 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 more than 90 days before diagnosis.

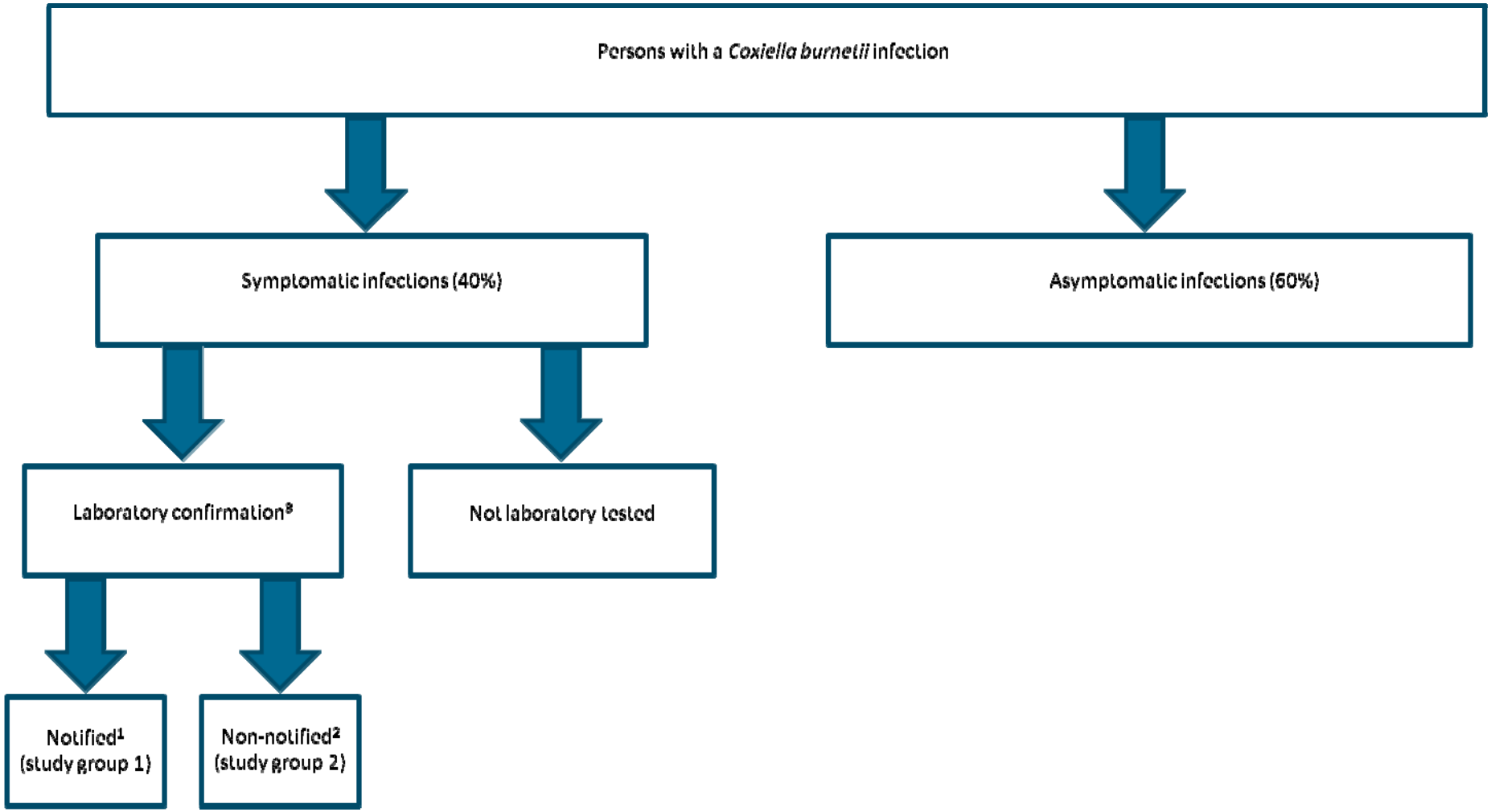
Notified Q fever patients (study group 1, Fig. 1)

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 Municipal Health Service. Since they did not fulfil the clinical criteria of the case definition, they were considered non-notified.

Fig. 1. Classification of the study groups in relation to all persons with a Coxiella burnetii *infection.*



1) Notified patients fulfil the EU case definition for Q fever (fever, pneumonia and/or hepatitis);

2) Non-notified patients do not fulfil the clinical case definition because they had no fever, pneumonia and/or hepatitis;

3) All patients were tested for Q fever in the laboratory after a request by their general practitioner or consultant physician.

Data collection

Notified Q fever patients from 2007 and 2008 were contacted in 2011 and 2012, respectively (approximately four years after their onset of illness). Non-notified Q fever patients were contacted approximately four 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 postal mail. 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 four weeks later by postal mail. Patients who returned an incomplete questionnaire were contacted by telephone, postal mail 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 the Radboud university medical center. It provides normative data 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 COPD patients respectively[17]. To compare the health status scores of the patients, the aforementioned 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 persons with an undiagnosed underlying respiratory illness could be excluded. The healthy references were not serologically tested for Q fever, so it is possible that persons 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 (co-morbidity, any additional treatment for long-lasting effects of Q fever).

Data analysis

Differences in baseline characteristics between the patient groups were tested with Pearson Chi-square Tests and Independent Samples *t*-tests. The proportion of patients that was severely affected 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 the software SPSS for Windows (version 20). A *p*-value less than .05 was considered to be statistically significant, based on two-sided tests.

Results

We received 448 questionnaires from notified Q fever patients (response of 80%) and 193 questionnaires from non-notified Q fever patients (response of 69%). 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 1. Notified patients were significantly older and more often male than non-notified patients. There were no significant differences in educational level and co-morbidity 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 four 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 2). 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 four years were compared. There were no significant differences in subdomain scores between the groups after correcting for differences in gender and age (Table 3).

Table 1. 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[1] *p*-value
Male sex %	57.6	45.1	.004
Age (years) Mean (± SD)	54.4 (12.4)	50.2 (15.3)	< .001
Educational level[2] %			.883
Low	47.8	49.1	
Middle	28.9	29.6	
High	23.2	21.3	
Co-morbidity[3] %	51.1	52.6	.731
Additional treatment for Q fever[4] %			
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	

1) For age, the difference between the groups was tested using an independent samples t-test. For the other characteristics, Pearson Chi-square tests were used; We did not test the difference for the characteristic 'Additional treatment for Q fever'

2) 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);

3) Co-morbidity can be either a serious medical event or medical intervention in the past five 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;

4) 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 2. Proportion of severely impaired patients within each NCSI subdomain in the groups of notified and non-notified Q fever patients at four years after onset of illness / diagnosis, and persons 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

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 four years after the acute episode, and the first study in which health status of notified and non-notified Q fever patients was compared. A large proportion of notified and non-notified patients still suffer from a severely affected health status at approximately four 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 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 one and four years after onset of illness. These results are especially striking 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 five and ten 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 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 changing 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 3,522 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 general practitioner 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 persons 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 = 2,163) might provide more insight into the long-term health impact of persons infected with *C. burnetii* without being previously diagnosed as such.

Table 3. Linear regression models presenting the NCSI scores for each subdomain at approximately four 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		**Notified Q fever patients**		**Non-notified Q fever patients**		**Difference between groups corrected for confounders (95% CI[1])**	***P*-value**
	Min-Max (Δ)	*Mean (SD)*	*n*	*Mean (SD)*	*n*		
Subjective Pulmonary Symptoms	2-20 (18)	6.1 (4.9)	447	6.1 (4.9)	192	0.0 (-0.8 to 0.9)	.964
Dyspnoea Emotions	6-22 (16)	8.6 (3.4)	445	8.6 (3.4)	191	0.1 (-0.5 to 0.7)	.759
Fatigue	8-56 (48)	33.5 (14.9)	440	33.4 (13.8)	185	1.2 (-1.3 to 3.7)	.362
Behavioural Impairment	0-78 (78)	7.8 (11.3)	447	7.9 (11.9)	191	-0.6 (-2.6 to 1.3)	.523
Subjective Impairment	4-28 (24)	7.7 (4.9)	446	7.3 (4.7)	192	0.2 (-0.6 to 1.1)	.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)	.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)	.323
Satisfaction Relations	2-10 (8)	3.1 (1.5)	443	3.2 (1.7)	192	0.0 (-0.3 to 0.2)	.739

1) 95% CI = 95% Confidence Interval

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 Municipal Health Service 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 persons with severe 'Fatigue' or a severely affected 'General Quality of Life' in the general population. In the healthy reference group, 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) (21). 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 (22). 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 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 this study). This can partly be explained by the fact that these groups only received one reminder by postal mail, 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 four 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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Chapter 9

General Discussion

General Discussion

The main aim of the studies described in this thesis is to provide better insight into the long-term health status of Q fever patients after the largest documented outbreak in the world. We achieved this by prospectively assessing health status over different time points until four years after onset of illness, and by comparing long-term health status of Q fever patients to that of patients with Legionnaires' disease or another lower respiratory tract infection, using two validated questionnaires: the Nijmegen Clinical Screening Instrument (NCSI) and the Short Form 36 (SF-36). Health status was measured subjectively, since we felt that this was the only feasible way to obtain data from a large number of patients and on different points in time. Since we used validated questionnaires, our results can be compared to results from other studies. This section discusses the main outcomes and overall results from our studies, and outlines the implications and recommendations of our studies.

1. Long-term impact of Q fever on patients

Impact of Q fever on health status

The results from our 2010-2011 prospective cohort study (**Chapter 4**) showed that within two years after onset of illness, the most severely affected subdomains in Q fever patients overall were 'Fatigue', 'General Quality of Life' (as measured by the NCSI) and 'Role Physical' (as measured by the SF-36), although other subdomains were affected as well (e.g. 'Dyspnoea Emotions', 'Health-related Quality of Life' and 'Subjective Impairment'). Patients have the most severely affected health status 3 months after their Q fever infection (73% of patients suffered from severe fatigue and 42% from a severely affected general quality of life). Over six time points from 3 to 24 months, there is a significant improvement in 9 out of the 12 health status subdomains that we assessed. However, despite this improvement, more than one in three patients still had low health status scores at 24 months: 37% of patients suffered from severe fatigue and 34% from a severely affected general quality of life (compared to 2.5% and 19.8% in a healthy control group, respectively). These results are in line with a study by Hickie et al., which presented a gradual decrease over time in the proportion of Q fever patients that seemed to have post-infective fatigue syndrome[1]. Risk factors for a long-term impaired health

status that we identified are being female, having pre-existing health problems and being a young adult. This last factor was associated with 'General Quality of Life', which suggests that older people can accept their health problems more easily.

When health status was measured in the 2007-2008 cohort at four years after onset of illness, the most severely affected NCSI subdomains were 'Fatigue' (51% of the patients) and 'General Quality of Life' (42% of the patients) (**Chapter 8**). These are the same subdomains as in the study over the 3-24 month time points.

Comparison of cohorts of Q fever patients

We found that the health status of the 2007-2008 cohort after four years is more impaired than the health status of the 2010-2011 cohort at 24 months, suggesting a decrease in health status between 24 months and four years (37% vs. 51% of the patients have severe fatigue and 34% vs. 42% suffer from a severely affected general quality of life, respectively). Although we cannot fully explain these findings, we hypothesise that this outcome is more attributable to differences between the two cohorts than to a relapse of long-term symptoms due to Q fever. Some possible explanations are: *first*, the results of the 2010-2011 cohort at 24 months might be an underrepresentation of the actual patient scores. Patients from this cohort who were not severely affected on the subdomains 'Fatigue' and 'General Quality of Life' at the 12- or 18-month time points were not eligible for further participation. Their scores were extrapolated to subsequent time points, although in reality health status of some patients could have decreased again. *Second*, the number of hospital admissions due to Q fever in 2007 was much higher than in subsequent years (46% in 2007 vs. approximately 20% in 2008 and 2009)[2]. It was hypothesised that there was a delay in the correct diagnosis, and accordingly in adequate treatment, of patients in 2007 compared to patients with a later onset of illness, since awareness in general practitioners, specialists and medical microbiologists increased from 2008 onwards[3]. *Third*, the response rate of the 2007-2008 cohort is lower than the 2010-2011 cohort (80% versus 89%) and this may have resulted in a higher proportion of study participants with an impaired health status (as patients with symptoms are usually considered more eager to participate in studies) in the 2007-2008 cohort.

Impact of Q fever on work participation

In addition to health status, we also measured indicators for daily functioning of patients within the 2010-2011 cohort prospectively, in particular work participation and associated factors (e.g. symptoms and grief) (**Chapter 7**). Around 45% of the Q fever patients had a reduced work participation at three months after onset of illness, which decreased to 19% at twelve months. Despite this improvement over time, almost one in five patients were still affected in their work at twelve months, which is much higher than the amount of sick leave in the general Dutch population (4% in 2012)[4]. Between three and twelve months, the proportion of working patients with one or more symptoms due to Q fever decreased from 78% to 56%, implying that almost half of the patients within this group did not experience any symptoms related to Q fever at twelve months anymore.

We assessed the stages of grief - denial, resistance, sorrow and acceptance - which remained fairly stable over time in working Q fever patients and were similar to levels of patients with Chronic Obstructive Pulmonary Disease (COPD)[5]. This suggests that undergoing Q fever actually leads to levels of grief similar to undergoing a chronic disease that leads to persistent airway limitations such as COPD, which underlines the impact of Q fever. Factors associated with a reduced work participation in Q fever patients are having symptoms, a high level of sorrow, being a former smoker, consuming no alcohol and following an additional treatment for the long-term effects of Q fever.

Health status of notified vs. non-notified patients

The official number of acute Q fever patients in the Netherlands over the entire 2007-2011 period was 4,107[6]. This figure only includes patients that fitted the Dutch case definition for notification of Q fever. The Dutch case definition is based on the EU harmonised case definition[7] and comprises patients with a laboratory confirmed Q fever infection and at least one of the following clinical criteria: fever, pneumonia or hepatitis (see General Introduction). We compared health status of 448 notified and 193 non-notified (who met the laboratory criteria but not the clinical criteria) Q fever patients at four years after onset of illness, and found no differences between these two groups (**Chapter 8**). These results imply that the magnitude of the Q fever epidemic

over the period 2007-2011 was underestimated in terms of long-term health impact. Based on the outcomes of our studies, we were able to roughly estimate a lower and an upper limit for the number of patients with long-term fatigue due to the Dutch Q fever outbreak. For this estimation, we assume that at least one in three patients suffered from long-term severe fatigue (**Chapter 4**), although there might be a slight overrepresentation of patients with a long-term reduced health status in our study, due to a response bias in patients without long-term symptoms.

The estimation of the lower limit is based solely on the 4,107 notified Q fever patients between 2007 and 2011. If one in three patients suffered from long-term severe fatigue, this leads to roughly 1,400 patients. This is a conservative estimate, as we know this figure is an underestimation since non-notified patients (who met the laboratory criteria but not the clinical criteria) were equally impaired in their long-term health status compared to notified patients (**Chapter 8**).

The estimation of the upper limit is based on the total number of Q fever infections over the period 2007-2011. This was estimated at 52,000 (**Chapter 2**), which was extrapolated from a study by van der Hoek et al. on the seroprevalence in blood donors[8]. Since 40% of the patients undergo the infection symptomatically[9,10], an estimated 20,800 infected patients may have developed symptoms during the acute phase. Assuming this whole group is susceptible for long-term health problems, it leads to an estimated 7,000 (one in three)patients (identified and non-identified) suffered from long-term severe fatigue.

We estimate that an excess of 1,400-7,000 patients in the Netherlands, compared to a non-outbreak situation, suffered from long-term severe fatigue until at least two years after onset of illness. There are also patients with normal fatigue levels but severe scores on other aspects of health status, e.g. a severely affected general quality of life. Since these patients are not included in the above estimations, the number of patients with a severely affected long-term health status is even higher.

2. Long-term impact of Q fever compared to other infections on patients

Besides the (healthy) reference groups, we also wanted to compare our results to other groups, which is why we assessed whether the persistence of an impaired health status is specific after acute Q fever or whether it is also found after suffering from another severe infectious disease.

Q fever vs. lower respiratory tract infections

We found a similar result when we compared the health status of two groups of patients at approximately 15 months after suffering from a lower respiratory tract infection: one group with and one group without Q fever (**Chapter 5**). The only difference was found for the subdomain 'Subjective Pulmonary Symptoms', where the Q fever negative group scored worse after correcting for relevant confounders. For both groups, roughly half of the patients were severely impaired on two or more aspects of health status.

Q fever vs. Legionnaires' disease

When we compared Q fever and Legionnaires' disease, we found that roughly half of both patient groups suffered from severe fatigue or a severely affected general quality of life at 12 months after onset of illness (**Chapter 6**). Only for the subdomain 'Role Physical' did Q fever patients score significantly worse than patients with Legionnaires' disease after correcting for relevant confounders (e.g. patients with Legionnaires' disease are generally older, more often male, more often smoker). The fact that Legionnaires' disease has a long-term health impact is consistent with another study, which showed that patients with Legionnaires' disease scored worse on seven out of eight SF-36 subdomains compared to a Dutch age- and sex-matched reference population at 17 months after onset of illness[11]. We also used other indicators to compare the long-term impact of Q fever and Legionnaires' disease, namely work participation, symptoms and levels of grief (**Chapter 7**). We found that the impact is comparable, although Q fever patients seemed to have somewhat lower work participation (19% vs. 15%), more symptoms (57% vs. 47%) and significantly higher levels of grief and a lower level of acceptance than patients with Legionnaires' disease.

Apart from the impact on an individual patient level, it is also possible to compare the impact of Q fever and Legionnaires' disease on a public health

level. In 2011 (currently the most recent year for which data are available), the case rate for Q fever within the EU was 0.19 per 100.000 (759 cases), compared to a case rate of 0.97 per 100.000 for Legionnaires' disease (4881 cases)[12], which is over five times higher. In addition, the case fatality rate for Legionnaires' disease is much higher (5-10% vs. less than 1%)[6,13]. Even though the long-term impact on an individual level might be comparable, these figures imply that the public health impact of Legionnaires' disease is much higher, based on the number of notified cases within the EU and the severity of the acute infection. However, due to the size of the epidemic between 2007 and 2011 (N = 4,107), the impact of Q fever on the Netherlands has been higher than the impact of Legionnaires' disease over this period (N = 1,690)[12].

3. Implications for patients

Q fever

Because the Dutch Q fever outbreak started in 2007, some of the patients with a long-term impaired health status have been affected for at least seven years. Although a Q fever Fatigue Syndrome guideline was developed in 2012 to reach uniformity in the diagnosis and treatment of this disease[14], there is no standard treatment for the long-term health status impairment of Q fever patients. A study is currently being carried out to assess the effectiveness of cognitive behavioural therapy and long-term antibiotics[15]. Apart from long-term medical care, we also recommend psychological care and support with issues related to everyday life (e.g. work, education, social life) for the group of severely affected patients.

Lower respiratory tract infections

The long-term health impact after an infection is not only seen in Q fever patients, but also in patients who suffered from a lower respiratory tract infection due to another infectious agent, including patients with Legionnaires' disease. Medical professionals should be aware that these patients may also need adequate care. In addition, it may be useful, after interventions for fatigue in Q fever patients have proven to be effective, to study the effectiveness in patients who have suffered from another infection as well.

4. Limitations of this thesis

All the data collected for the studies within this thesis were self-reported, using questionnaires. For aspects of health status, e.g. fatigue and general quality of life, this is the only feasible way in which they can be measured, but for data on work participation this may lead to a limitation in the reliability compared to data obtained from medical records of occupational physicians. We feel that it is not likely that patients exaggerated their health status to participate within a disability programme, as this leads to a reduced income and is thus not beneficial for them. Apart from serological confirmation and medical conditions during the initial diagnosis, our follow-up studies lack serological (e.g. inflammatory markers, such as C-reactive protein) and medical data of patients. We aimed to obtain information on chronic Q fever status of our study participants using our questionnaire, but the responses were not valid. However, since the proportion of patients suffering from chronic Q fever is estimated to be only 0-5% of patients with an acute infection[16], we feel this does not lead to a large bias.

The response rates varied between our studies from 89% in the 2010-2011 Q fever cohort, to 80% in the 2007-2008 Q fever cohort, 78% in the Legionella cohort and 69% in the non-notified cohort. This can partly be explained by the fact that some groups only received one reminder by postal mail (2007-2008 and non-notified cohorts), while other patients received several reminders by telephone (2010-2011 and Legionella cohorts). Only in the 2007-2008 and non-notified cohorts did participants differ from non-participants in terms of age and gender (respondents were older and more often female) and this might have led to an overestimation of the impact on health of patients, since women generally report more symptoms than men[17,18].

Another limitation is the reference groups that we used in our studies to interpret our findings with respect to health status. For the NCSI, only normative data from a healthy reference group were available. For the SF-36 subdomains, we compared the mean scores of Q fever patients to the mean scores of the general population in a large U.S. study. Both reference groups were not serologically tested for Q fever, so it is possible that persons were included who previously underwent a Q fever infection (more likely for the Dutch than for the U.S. reference group). In addition, since the reference group for the NCSI consists of healthy controls, they are by definition more healthy

than the general population. Studies on fatigue in the general population imply that baseline fatigue levels are already quite high[19, 20], and this means the high proportion of patients who are severely affected on the subdomain 'Fatigue' might also include fatigue due to other reasons than Q fever.

5. Recommendations for future research

Prospective cohort studies on infectious diseases are rare, since they are usually more costly and time-consuming than retrospective or cross-sectional studies. However, they offer important advantages as well, such as offering insight in progression of the disease over time and identifying risk factors. The large Q fever outbreak in the Netherlands between 2007 and 2011 offered a unique opportunity to study this infectious disease in a relatively large number of patients, which was an important factor in our decision to undertake a prospective cohort study on long-term health status. Our study was carried out in collaboration with a number of other studies on Q fever, to obtain insight in many aspects of the disease. These studies looked at e.g. diagnosis, treatment, serological follow-up and screening, and epidemiology. In addition to the studies that were already carried out, we identified several topics for future research, based on the outcomes of our own studies.

Follow-up after 8-10 years

So far, only one study focussed on patients' health ten years after infection, and found more fatigue in patients than in controls[21]. However, this study group was relatively small (N = 108), which is why we advise a follow-up of health status after eight or ten years of the 2007-2008 cohort. This would provide detailed insight in very long-term health status in a large number of notified patients (N = 448 patients that could be contacted). Recently, a population-based surveillance study in the Netherlands (n = 2,163) looked at serological status and health status of inhabitants in a village with a high seroprevalence against *Coxiella burnetii*, which might provide the first Dutch data on health status approximately seven years after onset of illness[22].

Clinical information

In addition to the self-reported information that we collected in our studies, information about patients' health can be obtained through medical records of

their general practitioners. When this information is linked to data on self-reported health status, it would provide more detail on the progress of health of Q fever patients over time.

Health impact

Other indicators that can be used to measure the impact of Q fever on patients are their level of physical activity and their concentration level. Activity levels can be measured using a motion sensor device. A study showed that patients with chronic fatigue syndrome are generally less active compared to healthy controls, although some patients had activity patterns similar to those of controls[23]. Another study showed a high correlation between activity levels and self-reported fatigue in patients with chronic fatigue syndrome, but not in healthy controls and patients with multiple sclerosis[24]. A study on the activity level of Q fever patients could help to gain more insight in the relationship between activity and fatigue in this patient group. Since one in four working Q fever patients reported problems with memory and concentration (**Chapter 7**), a study which assesses concentration levels of patients would provide more insight in the exact impact of these problems on patients.

Reference group

The questionnaires that we used in assessing patients' health status, both the NCSI and the SF-36, are valid instruments for this purpose. One advantage of the NCSI is that it provides normative data indicating normal functioning, mild or severe problems for each subdomain[25]. One problem that we faced within our study was that we lacked good reference data. When using these questionnaires in future studies on Q fever, we recommend setting up a control group consisting of persons from the general population, age- and gender-matched to the population of Q fever patients under study, who were tested negative for Q fever.

Societal impact

One of our studies showed a reduction in work participation of Q fever patients. However, this study was solely based on self-reported data. To gain more detailed insight into the societal and economic impact of Q fever, we advise that a study be carried out based on information from sickness

registration systems, which also looks at the impact on different types of professions (e.g. agriculture, manual labour, office work). In addition, the effect of intervention programmes aimed at increasing work participation, e.g. in collaboration with occupational physicians, should be studied. Similar studies could also be relevant in relation to schooling of students, e.g. in universities.

6. Recommendations for policy and practice

Our findings suggest that the magnitude of the Q fever epidemic over the period 2007-2011 was underestimated in the Netherlands when only notified patients according to the EU case definition are taken into account. Only 4,107 were notified, although a higher number was at risk for an important long-term health status impairment. We suggest a more sensitive EU case definition is considered, which includes a wider range of clinical symptoms.

The results from our studies can be used to update guidelines on Q fever that are used by public health officers and health care workers in the Netherlands and abroad, e.g. the Q fever and the Q fever Fatigue Syndrome guidelines at the National Institute for Public Health and the Environment (RIVM)[6]. Our results on the progression of Q fever over time can be used by health care workers to present the expected disease progression to newly infected patients. In addition, the knowledge that certain characteristics are associated with a reduced long-term health status (being female, being a young adult, suffering from pre-existing health problems) is important for health care workers to identify patients with a higher risk for a reduced health status. It is important for occupational physicians to be aware of the long-term impact of these diseases on work participation. Finally, medical staff should be aware that not only Q fever patients, but also patients with other lower respiratory tract infections, including Legionnaires' disease, may suffer from a long-term health impact and may thus need adequate care.

7. Conclusion

We have found that a large outbreak of Q fever, such as the one that took place in the Netherlands between 2007 and 2011, has a major impact on public health with respect to the long-term health status - in particular fatigue, general quality of life and role physical - of patients. Other affected aspects of health status include dyspnoea emotions, health-related quality of life and

subjective impairment, and the most impaired scores were found shortly after onset of illness. For example, at three months after onset of illness, almost three out of four patients suffer from severe fatigue. This proportion declines over time, although severe fatigue persists until 24 months for more than one in three patients. Even more than half of the patients suffered from severe fatigue after four years, although this is possibly partly attributable to other factors specific for this group of patients. Women, young adults and persons with pre-existing health problems have a higher risk to develop a long-term reduced health status after undergoing a Q fever infection.

There is little difference in long-term health status of Q fever positive and Q fever negative patients that suffered from a lower respiratory tract infection. Compared to patients with Legionnaires' disease, the effects at twelve months after onset of illness are also quite similar, although Q fever patients seem to be somewhat more affected. Our results indicate that the long-term effects on health status are not specific for Q fever but can also be seen in patients with other lower respiratory tract infections.

There is no difference in long-term health status between notified Q fever patients and non-notified patients, who matched the laboratory but not the clinical criteria for Q fever. This leads to an underestimation in the magnitude of the impact of Q fever in the Netherlands. We estimated that 1,400-7,000 patients suffered from long-term severe fatigue.

Almost half of the Q fever patients suffer from a reduced work participation at three months after onset of illness, although this decreases over time to one in five at twelve months. The impact of Q fever on work participation is relatively similar to the impact of Legionnaires' disease, although Q fever patients seem to be a bit more affected.

Although most Q fever patients recover, at least one in three patients suffer from a long-term health status impairment. This has a major impact on public health in the Netherlands due to the magnitude of the 2007-2011 Q fever outbreak. Health care workers and the health care sector should be aware of this impact and provide adequate care for these patients.

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Summary

Q fever is a zoonosis that is caused by the intracellular bacterium *Coxiella burnetii*. Around 40% of the infections progress symptomatically, in which case it usually presents as a flu-like illness with a-specific symptoms, often including fever, pneumonia, hepatitis and neurological symptoms such as headache. It has been shown that Q fever can also have a long-term term impact on health, with one manifestation that can persist for many years being Post Q fever Fatigue Syndrome. Although several studies have described an impaired health status, including fatigue, after Q fever, these studies were based on small numbers of cases, and only a few studies have looked at the progress of health over time.

Between 2007 and 2011, the Netherlands was confronted with an unprecedented outbreak of Q fever. The total number of notified cases over this period was 4,107. This outbreak offered an opportunity to study the long-term health status, defined as human functioning and well-being, in a large number of laboratory confirmed Q fever patients, and it was the motivation for the studies described in this thesis. The following research questions were investigated:

- How does health status progress in Q fever patients four years after onset of illness, and which individual characteristics are associated with health status?
- How does long-term health status of Q fever patients compare to health status of patients that underwent another infectious disease, specifically a lower respiratory tract infection or Legionnaires' disease?
- Is there a difference in health status between notified Q fever patients and non-notified Q fever patients, who do not fit the case definition based on the clinical criteria, at four years after onset of their illness?
- How does work participation progress in Q fever patients until twelve months after onset of their illness, and which individual characteristics are associated with it?

The complete study protocol is described in **Chapter 2**.

We used two validated instruments to measure health status in this thesis: the Nijmegen Clinical Screening Instrument (NCSI) and the Short Form 36 (SF-36). Both instruments consist of eight subdomains and measure eight aspects of health status. To make sure that only subdomains measuring unique aspects of health status would be described in subsequent publications, we assessed conceptual similarity by calculating correlations between the subdomains of these instruments in **Chapter 3**. We used data from 309 Q fever patients who completed our study questionnaire, which included both health status instruments, at twelve months after onset of illness. Intercorrelations between subdomains of the NCSI were generally lower than of the SF-36. Four subdomains of the NCSI showed conceptual similarity (defined as a Pearson's r ≥ .70) with four subdomains of the SF-36. We concluded that both instruments can be used to measure health status in Q fever patients. When the aim of a study is to obtain a detailed overview of patients' health, a combination of the instruments, consisting of the complete NCSI and the four unique subdomains of the SF-36, is preferred.

The progress in health status in a group of 336 Q fever patients over the first 24 months after onset of illness is described in **Chapter 4**. There is a significant linear improvement over time in nine out of the twelve NCSI and SF-36 subdomains that were assessed. For example, the proportion of patients with severe fatigue improved from 73.0% at three months to 60.0% at twelve months and 37.0% at twenty-four months. However, despite a significant improvement over time, more than one in three patients still suffered from a reduced health status at 24 months. The most severely affected subdomains in patients overall were 'Fatigue', 'General Quality of Life' and 'Role Physical'. We identified several baseline characteristics that were associated with a reduced long-term health status on these subdomains, namely being female, being a young adult and suffering from pre-existing health problems.

Patients with a lower respiratory tract infection (LRTI) not caused by Q fever might also be at risk for a long-term impaired health status. In **Chapter 5** we assessed whether 32 LRTI patients without Q fever were equally affected in their long-term health status as 50 LRTI patients with Q fever. At approximately 15 months after onset of illness, 40% of the Q fever positive group was severely

affected on two or more NCSI subdomains, and 56% of the Q fever negative group. The most severely affected subdomains of the Q fever positive LRTI group were 'Fatigue' and 'General Quality of Life' (both 40% of the patients), versus 'Fatigue' (64%) and 'Subjective Pulmonary Symptoms' (35%) in the Q fever negative LRTI group. The only significant difference in subdomain scores between the groups was found for 'Subjective Pulmonary Symptoms', for which the group of Q fever negative LRTI patients had a more reduced score.

We compared health status of 309 Q fever patients to health status of 190 patients with Legionnaires' disease at twelve months after onset of illness in **Chapter 6**. Both groups of patients were most impaired on the NCSI and SF-36 subdomains 'Fatigue', 'General Quality of Life' and 'Role Physical': roughly half of the patients suffered from severe fatigue, and a group similar in size suffered from a severely affected general quality of life, both of which are much higher than these proportions in a healthy reference group. After correcting for relevant confounders (e.g. gender, age, smoking behaviour), we found no significant differences in scores on the subdomains 'Fatigue' and 'General Quality of Life' between Q fever patients and patients with Legionnaires' disease. Only for the subdomain 'Role Physical', Q fever patients scored significantly worse.

In addition to health status, we also measured work participation of 336 Q fever patients prospectively between three and twelve months after onset of illness, and we compared work participation at twelve months to work participation of a group of 190 patients with Legionnaires' disease in **Chapter 7**. There was a decrease in the proportion of working Q fever patients with a reduced work participation due to Q fever over time: from 45% at three months to 19% at twelve months (versus 15% of working patients with Legionnaires' disease). Factors associated with a reduced work participation of Q fever patients in a multivariate model were having symptoms, a higher level of sorrow, being a former smoker (compared to never smoking), not consuming any alcohol and following an additional treatment for the long-term health effects of Q fever.

During the 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). We assessed and compared the health status of 448 notified and 193 non-notified patients at four years after onset of illness in **Chapter 8**. The most severely affected NCSI subdomain in both groups was 'Fatigue': 50.5% of the notified and 54.6% of the non-notified patients suffered from severe fatigue. Long-term health status did not differ significantly between notified and non-notified patients. These findings suggest that the magnitude of the 2007-2009 Q fever outbreak in the Netherlands was underestimated as only notified patients according to the EU case definition were taken into account.

Finally, **Chapter 9** presents a general discussion of the results, as well as recommendations and implications that derive from this thesis. In conclusion, we found that most patients who underwent a Q fever infection recover. However, at least one in three patients still suffered from an impaired health status at 24 months after onset of illness, including severe fatigue. This has a major impact on public health in the Netherlands due to the magnitude of the 2007-2011 Q fever outbreak. Since a large proportion of patients with Legionnaires' disease and other LRTI patients also suffer from a severely affected health status at twelve months, we recommend additional support for these patients as well. Health care workers (e.g. general practitioners, occupational physicians) and the health care sector should be aware of the impact and provide adequate care for these patient groups. Apart from long-term medical care, we also recommend psychological care and support with issues related to everyday life (e.g. work, education, social life) for the groups of severely affected patients.

Samenvatting

Q-koorts is een zoönose die wordt veroorzaakt door de intracellulaire bacterie *Coxiella burnetii*. Ongeveer 40% van de geïnfecteerden ontwikkelt symptomen. In die gevallen gaat het meestal om een griepachtig ziektebeeld met aspecifieke klachten, voornamelijk koorts, pneumonie, hepatitis en neurologische symptomen zoals hoofdpijn. Het is aangetoond dat Q-koorts de gezondheid ook langdurig kan beïnvloeden, waarbij het Q-koortsvermoeidheidssyndroom één van de manifestaties is. Hoewel verscheidene studies een verminderde gezondheidsstatus, waaronder vermoeidheid, na Q-koorts hebben beschreven, zijn deze uitkomsten gebaseerd op kleine aantallen patiënten, en slechts enkele studies hebben het ziekteverloop over de tijd onderzocht.

Tussen 2007 en 2011 werd Nederland geconfronteerd met een ongeëvenaarde uitbraak van Q-koorts. Het totale aantal gemelde patiënten binnen deze periode was 4.107. Deze uitbraak bood de mogelijkheid om de gezondheidsstatus, gedefinieerd als het functioneren en welzijn van mensen, op de lange termijn in een groot aantal labbevestigde Q-koortspatiënten te onderzoeken, en was de aanleiding voor de in dit proefschrift beschreven studies. De volgende vragen zijn onderzocht:

- Hoe is het verloop in gezondheidsstatus van Q-koortspatiënten tot vier jaar na aanvang van de ziekte, en welke persoonlijke karakteristieken zijn geassocieerd met gezondheidsstatus?
- Hoe verhoudt de gezondheidsstatus van Q-koortspatiënten op de lange termijn zich tot die van patiënten die een andere infectieziekte hebben ondergaan, te weten een lage luchtweginfectie of de veteranenziekte?
- Is er een verschil in gezondheidsstatus tussen gemelde en niet-gemelde Q-koortspatiënten, patiënten die niet aan de klinische criteria van de meldingscriteria voldoen, op vier jaar na aanvang van de ziekte?
- Hoe verloopt de arbeidsparticipatie van Q-koortspatiënten tot twaalf maanden na aanvang van de ziekte, en welke persoonlijke karakteristieken zijn hiermee geassocieerd?

Het volledige studieprotocol staat beschreven in **Hoofdstuk 2**.

In dit proefschrift hebben we twee gevalideerde instrumenten gebruikt om gezondheidsstatus te meten: de Nijmegen Clinical Screening Instrument (NCSI) en de Short Form 36 (SF-36). Beide instrumenten bestaan uit acht subdomeinen en meten acht aspecten van gezondheidsstatus. Om ervoor te zorgen dat in navolgende publicaties alleen subdomeinen zouden worden beschreven die unieke aspecten van gezondheidsstatus meten, hebben we onderzocht welke subdomeinen vergelijkbare concepten meten door correlaties te berekenen tussen de subdomeinen van deze instrumenten in **Hoofdstuk 3**. We hebben data gebruikt van 309 patiënten die onze onderzoeksvragenlijst (met daarin beide instrumenten) op twaalf maanden na aanvang van de ziekte hebben ingevuld. Intercorrelaties tussen subdomeinen van de NCSI waren over het algemeen lager dan van de SF-36. Vier subdomeinen van de NCSI vertoonden een conceptuele overeenkomst (gedefinieerd als een Pearson's $r \geq .70$) met vier subdomeinen van de SF-36. De conclusie was dat beide instrumenten gebruikt kunnen worden om de gezondheidsstatus in Q-koortspatiënten te meten. Wanneer het doel van het onderzoek is om een gedetailleerd inzicht te krijgen in de gezondheidsstatus van patiënten is een combinatie van beide instrumenten, bestaande uit de volledige NCSI en de vier unieke subdomeinen van de SF-36, aan te bevelen.

Het verloop in gezondheidsstatus in een groep van 336 Q-koortspatiënten gedurende 24 maanden na aanvang van de ziekte staat beschreven in **Hoofdstuk 4**. Er bleek een significante lineaire verbetering over de tijd te zijn in 9 van de 12 NCSI en SF-36 subdomeinen die we onderzocht hebben. Het percentage patiënten met ernstige vermoeidheid nam bijvoorbeeld af van 73.0% op drie maanden tot 60.0% op twaalf maanden en 37.0% op vierentwintig maanden. Ondanks deze significante verbetering over de tijd, leed nog steeds meer dan één op de drie patiënten aan een verminderde gezondheidsstatus op 24 maanden. De subdomeinen 'Vermoeidheid', 'Algemene Kwaliteit van Leven' en 'Rolvervulling-Fysiek' waren het ernstigst aangedaan. We hebben verscheidene risicofactoren geïdentificeerd die geassocieerd waren met een verminderde gezondheidsstatus op deze subdomeinen, namelijk vrouw zijn, een jongvolwassene zijn en lijden aan onderliggende gezondheidsproblematiek.

Patiënten met een lage luchtweginfectie, welke niet veroorzaakt wordt door Q-koorts, kunnen ook een verhoogd risico hebben op een verminderde gezondheidsstatus op de lange termijn. In **Hoofdstuk 5** hebben we onderzocht of 32 patiënten met een lage luchtweginfectie zonder Q-koorts evenzeer aangedaan waren in hun gezondheidsstatus op de lange termijn als 50 patiënten met een lage luchtweginfectie met Q-koorts. Op ongeveer 15 maanden na aanvang van de ziekte was 40% van de Q-koorts-positieve groep ernstig aangedaan op twee of meer NCSI subdomeinen, versus 56% van de Q-koorts-negatieve groep. De meest ernstig aangedane subdomeinen in de Q-koorts-positieve groep patiënten met een lage luchtweginfectie waren 'Vermoeidheid' en 'Algemene Kwaliteit van Leven' (beide 40% van de patiënten), versus 'Vermoeidheid' (64%) en 'Subjectieve Ademhalingsklachten' (35%) in de Q-koorts-negatieve groep. Het enige significante verschil in subdomeinscores tussen de groepen is vastgesteld voor 'Subjectieve Ademhalingsklachten', waarvoor de groep Q-koorts-negatieve patiënten slechter scoorde.

In **Hoofdstuk 6** hebben we de gezondheidsstatus van 309 Q-koortspatiënten vergeleken met die van 190 patiënten met veteranenziekte op twaalf maanden na aanvang van hun ziekte. Beide groepen patiënten scoorden het slechts voor de NCSI en SF-36 subdomeinen 'Vermoeidheid', 'Algemene Kwaliteit van Leven' en 'Rolvervulling-Fysiek': ongeveer de helft van de patiënten leed aan ernstige vermoeidheid, en een even grote groep aan een ernstig aangedane algemene kwaliteit van leven, wat beide veel hoger is dan de percentages in een gezonde referentiegroep. We vonden geen significant verschil in scores voor de subdomeinen 'Vermoeidheid' en 'Algemene Kwaliteit van Leven' tussen Q-koortspatiënten en patiënten met veteranenziekte na correctie voor relevante confounders (o.a. geslacht, leeftijd, rookgedrag). Alleen voor het subdomein 'Rolvervulling-Fysiek' scoorden Q-koortspatiënten significant slechter.

Naast gezondheidsstatus hebben we in **Hoofdstuk 7** ook arbeidsparticipatie prospectief in kaart gebracht bij 336 Q-koortspatiënten tussen drie en twaalf maanden na aanvang van de ziekte, en hebben we hun arbeidsparticipatie op twaalf maanden vergeleken met arbeidsparticipatie in een groep van 190 patiënten met veteranenziekte. Het percentage werkende Q-koortspatiënten

met een verminderde arbeidsparticipatie door Q-koorts over de tijd bleek af te nemen: van 45% op drie maanden tot 19% op twaalf maanden (versus 15% van de werkende patiënten met veteranenziekte). Factoren die geassocieerd zijn met een verminderde arbeidsparticipatie in Q-koortspatiënten in een multivariaat model waren het hebben van symptomen, een hogere score voor verdriet, een voormalig roker zijn (in vergelijking tot nooit gerookt hebben), geen alcohol gebruiken en het volgen van een aanvullende behandeling voor de effecten van Q-koorts op de lange termijn.

Tijdens de Q-koortsepidemie in Nederland zijn veel patiënten met een laboratoriumbevestigde *Coxiella burnetii* infectie niet gemeld als acute Q-koorts, omdat zijn niet voldeden aan de klinische criteria van de casusdefinitie van acute Q-koorts (koorts, pneumonie en/of hepatitis). Wij onderzochten en vergeleken de gezondheidsstatus van 448 gemelde en 193 niet-gemelde patiënten op vier jaar na aanvang van de ziekte in **Hoofdstuk 8**. Het meest aangedane NCSI subdomein in beide groepen was 'Vermoeidheid': 50.5% van de gemelde en 54.6% van de niet-gemelde patiënten leed aan ernstige vermoeidheid. De gezondheidsstatus op de lange termijn verschilde niet significant tussen gemelde en niet-gemelde patiënten. Deze resultaten suggereren dat de omvang van de Q-koortsuitbraak in Nederland tussen 2007 en 2009 onderschat werd wanneer alleen gemelde patiënten volgens de EU casusdefinitie werden meegenomen.

Hoofdstuk 9 beschrijft ten slotte een algemene discussie van de resultaten, evenals aanbevelingen en implicaties die uit dit proefschrift voortkomen. Onze conclusie is dat de meeste patiënten die een Q-koortsinfectie hebben doorgemaakt herstellen. Desondanks lijdt op 24 maanden na aanvang van de ziekte meer dan één op de drie patiënten aan een ernstig aangedane gezondheidsstatus, waaronder ernstige vermoeidheid. Dit heeft een grote impact op de publieke gezondheidssector in Nederland, gezien de omvang van de Q-koortsuitbraak tussen 2007 en 2011. Aangezien een hoog percentage patiënten met veteranenziekte en patiënten met een andere lage luchtweginfectie ook een ernstig aangedane gezondheidsstatus heeft op twaalf maanden, bevelen we aan dat deze patiënten eveneens aanvullende ondersteuning hiervoor ontvangen. Gezondheidswerkers (o.a. huisartsen en

bedrijfsartsen) en de gezondheidssector moeten op de hoogte zijn van deze impact en zorgen voor adequate ondersteuning aan patiënten. Naast medische zorg op de lange termijn bevelen we ook psychologische hulp aan de groep ernstig aangedane patiënten aan, en hulp met alledaagse zaken (o.a. werk, opleiding en sociale activiteiten).

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Curriculum vitae

Joris Adriaan Frank van Loenhout was born on the 9th of June 1984 in Bergen op Zoom. After completing his secondary education at the R.K. Gymnasium Juvenaat Heilig Hart, he started his Bachelor of Science in Biological Sciences at Utrecht University in 2001. He completed this in 2004, and continued with a Master of Science in Toxicology and Environmental Health, which he finished in 2006.

After working for three months at the occupational department of the Academic Medical Center in Amsterdam, Joris joined the environmental health department of the Public Health Services Gelderland-Midden in January 2007. Within this position, he was initially responsible for the coordination of several EU-funded projects in various environmental health fields, such as transport and indoor environment (PRONET), education of environmental health physicians (PHEEDUNET and TOP) and climate change (Climate-TRAP). In 2011, a research proposal was granted for a study within the Academic Collaborative Centre of Environmental Health (AW-MMK), on heat exposure and heat stress in residences of the elderly, on which Joris worked until April 2014. Between May and September 2014, he was programme manager within AW-MMK.

Joris started combining his position at the Public Health Services Gelderland-Midden with a part-time PhD position at the Academic Collaborative Centre AMPHI at Radboud university medical center in July 2010, which resulted in this thesis on the long-term health status of Q fever patients. Since October 2014, Joris is working as a postdoctoral researcher at the Centre for Research on the Epidemiology of Disasters, within the Université Catholique de Louvain in Brussels.