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The effect of *C. burnetii* infection on the quality of life of patients following an outbreak of Q fever

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SUMMARY

Sixty-six cases of Q fever were diagnosed in people affiliated with a goat-farming co-operative in rural Newfoundland in the spring of 1999. Follow-up studies which included administration of the Short Form 36 Health Survey (SF-36) were conducted 3 and 27 months after the initial outbreak to prospectively follow the effects of acute Q fever on the quality of life of the participants. Twenty-seven months after the outbreak 51% of those who had Q fever reported persistent symptoms including seven participants whose symptoms had initially resolved 3 months after the outbreak. Individuals with Q fever had significantly lower scores on five of the eight scales in the SF-36 and lower scores in the mental and physical summary scales compared to uninfected controls. Although this supports the hypothesis of a 'post Q fever fatigue syndrome' (QFFS), further study is warranted.

INTRODUCTION

Q fever is a worldwide zoonosis due to the obligate intracellular bacterium *Coxiella burnetii* [1]. This highly infectious pathogen has been isolated from many wild and domestic animals where it is shed in the milk, urine, feces, and is found in particularly high concentrations in the products of conception [2–7]. Human infection usually results from exposure to infected domestic ungulates or cats and may be asymptomatic or may manifest as pneumonia, hepatitis or a nonspecific febrile illness [8–12]. Most infections are self-limiting. However, chronic manifestations such as endocarditis, osteomyelitis and hepatitis have been well documented [12, 13]. Although most patients suffering from acute Q fever have an 'uneventful' recovery, there is evidence that *C. burnetii* infection can lead to a protracted state of fatigue similar to that seen with chronic fatigue syndrome [14–17]. Although the questionnaires used to measure fatigue by Marmion et al. [14] and Ayers et al. [15, 16] were similar, they were not widely standardized and correlation between healthy individuals or those with other chronic illness cannot be made.

In the spring of 1999 farmers and workers on a newly formed goat farm cooperative on a small rural peninsula in Newfoundland, Canada were diagnosed with Q fever. An epidemiological investigation revealed that 66/179 (36·9%) farmers, workers and contacts had developed acute *C. burnetii* infection [11]. As part of the follow-up, we used the Medical Outcomes Study 36-item Short Form Health Survey (SF-36), a standardized quality of life instrument to prospectively follow members of this outbreak cohort to examine the impact of acute Q fever on the quality of life 3 months and 27 months after the initial diagnosis.

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METHODS

In the spring of 1999, serum samples and epidemiologic data were collected as part of an outbreak investigation of Q fever among workers belonging to a goat-farming co-operative in rural Newfoundland, at which time a diagnosis of Q fever was made serologically by indirect immunofluorescence as previously described [11]. In July 1999 (3 months after the original outbreak) the cohort was again contacted to participate in a follow-up investigation. A questionnaire was administered which consisted of two parts: questions regarding the nature and duration of persistent symptoms and the SF-36 quality-of-life measurement.

The SF-36 contains 36 items which measure different domains of participants health including: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (V), social functioning (SF), role emotion (RE), mental health (MH) [18]. In addition the data generated can be further summarized into physical and mental scores. The domains are scored on a scale of 1–100, with lower scores reflecting poorer health [18]. This instrument has been well validated and found to be more responsive to changes in participants' health than other quality of life measures [18–20]. The SF-36 has been administered to healthy subjects as well as to individuals with a variety of illness to generate standardized data for comparison, including normative data for American, British, Australian and Canadian populations [18, 21–24]. The SF-36 Health Survey Scores of the outbreak cohort were compared with published Canadian normative data as well as standardized values from American patients with recent angina, and type 2 diabetes and British patients who report 'long standing illness' [18, 23, 24]. A second follow-up investigation was conducted in the summer of 2000 (27 months after the outbreak). Participants who filled out the first questionnaire in July 1999 were contacted and the same outcome measures were collected.

Data analysis

Participants were subgrouped in both studies based on whether they had *C. burnetii* infection during the outbreak, and whether they continued to report symptoms or whether their complaints had been resolved. Those who did not have Q fever were considered a control population to which the patients with Q fever were compared. Differences between infected and uninfected participants were tested for statistical significance using the χ^2 test for proportions and Student's *t*-test for means. All data were analysed using SPSS for Windows version 8.0 (SPSS Inc. 1989–1999) and results were considered significant when $P<0{\cdot}05$.

Table 1. *Comparison of the SF-36 data between infected individuals and controls 3 months following the initial outbreak* (*July 1999*)

	Q-fever ($n=33$)	No Q-fever ($n=24$)	*P*
Bodily pain	77·3 (±26·6)	85·3 (±18·6)	0·3350
General health	61·8 (±26·3)	78·0 (±15·2)	0·0280
Mental health	73·9 (±22·6)	80·5 (±15·1)	0·3853
Physical function	85·6 (±19·5)	84·7 (±25·0)	0·4705
Role emotion	77·8 (±37·0)	95·8 (±11·3)	0·0509
Role physical	72·0 (±35·2)	87·5 (±22·1)	0·0763
Social function	87·5 (±22·1)	92·7 (±14·7)	0·4533
Vitality	52·7 (±30·3)	64·4 (±24·7)	0·1632
Physical scale	48·4 (±10·3)	50·9 (±8·7)	0·3685
Mental scale	49·1 (±12·1)	54·3 (±6·8)	0·2178

Table 2. *Comparison of the SF-36 data between infected individuals and controls 27 months after the initial outbreak* (*summer 2000*)

	Q-fever ($n=33$)	No Q-fever ($n=24$)	*P*
Bodily pain	64·6 (±29·8)	74·0 (±27·5)	0·2818
General health	50·5 (±27·4)	68·7 (±19·7)	0·0107
Mental health	71·5 (±18·9)	80·0 (±16·2)	0·1031
Physical function	79·4 (±20·4)	86·2 (±23·5)	0·0294
Role emotion	70·7 (±39·8)	87·5 (±29·2)	0·0800
Role physical	51·5 (±47·2)	84·4 (±36·0)	0·0064
Social function	79·5 (±21·2)	85·9 (±26·9)	0·0360
Vitality	50·3 (±23·5)	69·6 (±23·6)	0·0040
Physical scale	42·7 (±11·3)	49·1 (±11·5)	0·0175
Mental scale	48·2 (±10·2)	53·2 (±8·8)	0·0401

RESULTS

Although 82 members of the original outbreak cohort completed questionnaires during the July 1999 follow-up, only 57/179 (32%) of the original outbreak cohort completed the questionnaires at both the follow-ups in 1999 and 2001 and were used in the subsequent data analysis. The other members of the cohort could not be contacted or declined to participate in the study.

Of these 57 participants, 58% (33/57) had been diagnosed with acute Q fever during the original outbreak; 42% (24/57) did not have Q fever during

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Table 3. *Comparison of the SF-36 data between infected individuals with persistent symptoms* (*FPS*) *and those participants whose symptoms resolved* (*FRS*) *3 months after the initial outbreak* (*July 1999*)

	QFPS ($n=13$)	QFRS ($n=13$)	*P*
Bodily pain	62·9 (±31·8)	86·3 (±16·4)	0·0577
General health	43·9 (±25·7)	70·5 (±20·9)	0·0204
Mental health	57·2 (±23·3)	85·2 (±15·0)	0·0042
Physical function	75·8 (±20·2)	90·0 (±20·0)	0·0639
Role emotion	56·4 (±43·9)	94·9 (±12·5)	0·0104
Role physical	50·0 (±40·8)	84·6 (±24·0)	0·0206
Social function	73·1 (±28·8)	97·1 (±7·5)	0·0099
Vitality	29·2 (±24·8)	64·6 (±22·1)	0·0014
Physical scale	43·1 (±10·9)	50·6 (±10·2)	0·0455
Mental scale	39·9 (±12·4)	55·5 (±5·8)	0·0015

Table 4. *Comparison of the SF-36 data between infected individuals with persistent symptoms and those participants whose symptoms resolved 27 months after the initial outbreak* (*summer 2000*)

	QFPS ($n=17$)	QFRS ($n=9$)	*P*
Bodily pain	55·1 (±26·1)	73·2 (±32·2)	0·1346
General health	34·1 (±21·3)	63·2 (±22·7)	0·0102
Mental health	61·9 (±16·9)	76·9 (±14·4)	0·0399
Physical function	71·8 (±21·9)	83·3 (±19·2)	0·1503
Role emotion	52·9 (±42·6)	81·5 (±33·8)	0·1019
Role physical	35·3 (±44·2)	66·7 (±45·1)	0·1430
Social function	75·0 (±22·1)	83·3 (±15·3)	0·3914
Vitality	37·9 (±17·9)	60·0 (±17·3)	0·0095
Physical scale	38·4 (±9·0)	46·6 (±12·6)	0·0311
Mental scale	43·2 (±10·0)	51·2 (±8·4)	0·0592

the outbreak and were used as controls. The results of the SF-36 data are presented in Tables 1–5.

Only the general health scores reported by the Q fever group were significantly different from the control group at the first follow up investigation 3 months after the outbreak (61·8 *vs.* 78·0; $P=0·03$). However 27 months after the original outbreak, participants with Q fever had significantly lower scores on five of the eight scales and the physical and mental summary scales.

Participants with Q fever could be subgrouped based on whether they continued to report symptoms they attributed to *C. burnetii* infection, whether their initial symptoms had resolved, or whether they never had symptoms at the time of the outbreak (Tables 3–5). Three months after the outbreak, 39% (13/33) of participants with *C. burnetii* infection continued to report symptoms and had significantly lower scores on all scales except for physical function compared to 39% (13/33) of the infected participants whose symptoms had resolved.

Twenty-seven months after the initial outbreak 52% (17/33) of the participants who had Q fever continued to report persistent symptoms. Three participants who originally had persistent symptoms had resolution of their symptoms 27 months after the outbreak. In contrast seven participants with Q fever whose symptoms initially resolved 3 months after the outbreak developed persistent symptoms they attributed to Q fever 27 months after the outbreak. Only the scores in the general health, mental health, vitality and the physical summary scales were lower in participants with persistent symptoms compared with those whose symptoms resolved. This may be a reflection of the lower scores on all scales of the SF-36 survey including the physical and mental summary

Table 5. *Changes in mental and physical summary scales for Q fever patients and control participants between July 1999 and Summer 2000*

	Controls ($n=24$)	*P*	Q-fever group ($n=33$)	*P*
Bodily pain	−11·2 (±19·7)	0·0108	−12·8 (±29·2)	0·0162
General health	−9·2 (±17·7)	0·0066	−11·3 (±21·5)	0·0059
Mental health	−0·5 (±13·7)	0·5627	−2·4 (±17·7)	0·4095
Physical function	1·6 (±22·0)	0·8379	−6·2 (±13·7)	0·0093
Role emotion	−8·3 (±28·2)	0·2656	−7·1 (±51·2)	0·3965
Role physical	−3·1 (±23·7)	0·6719	−20·5 (43·1)	0·0097
Social function	−6·8 (±24·4)	0·3623	−8·0 (±27·9)	0·1823
Vitality	5·2 (±17·1)	0·0198	−2·4 (±28·6)	0·7071
Physical scale	−1·9 (±8·0)	0·2083	−5·7 (±10·0)	0·0021
Mental scale	−1·3 (±8·1)	0·4022	−0·8 (±12·9)	0·7071

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scores recorded by both participants with Q fever and controls (Table 5). Although there was a slight increase in the physical function scores and a significant ($P=0{\cdot}02$) increase in vitality scores in the control group between the two time periods, the remainder of the scales in both groups, including the physical and mental summaries were lower, with significant decreases in the bodily pain and general health scales ($P=0{\cdot}01$; $P=0{\cdot}007$).

There were no initial symptoms that were predictive of developing persistent symptoms after acute Q fever. Antibiotic treatment at the time of acute infection was not predictive of the development of persistent symptoms. There was no obvious source of exposure that was associated with developing persistent symptoms.

DISCUSSION

The Q fever fatigue syndrome (QFFS) has been proposed to describe the protracted state of fatigue that can develop in 20% of patients who develop acute infection with *C. burnetii* [14–16]. First described in Australian abattoir workers, QFFS consists of symptoms including fatigue, headaches, sweats, arthralgias, myalgias, blurred vision, muscle fasciculations and enlarged and painful lymph nodes [14]. Subsequent studies in the United Kingdom have also supported the existence of QFFS [15, 16]. In a case–control study 5 years after a large outbreak of Q fever, Ayres et al. found that participants who were diagnosed with acute Q fever during the initial outbreak had more complaints of fatigue, sweats, blurring of vision and dyspnoea than their matched controls and that 42·3% of the infected individuals actually fulfilled the CDC criteria for chronic fatigue state [16]. In a 10-year follow-up of the same cohort Wildman et al. found that 64·8% of Q fever exposed participants had fatigue and 34·4% fulfilled the criteria for chronic fatigue syndrome, both of which were significantly higher than that seen in matched controls [17]. Although not conclusive, there is evidence to suggest that 'cytokine dysregulation and immunomodulation from persistence of *C. burnetii*' in the host may be responsible for QFFS [25, 26].

The data presented in the current study suggest that individuals infected with Q fever can have persistent symptoms >2 years after an acute outbreak, which has significant impact on their quality of life similar to British residents who report long standing illness [23] and Americans with other chronic maladies such as, type 2 diabetes mellitus, active coronary artery disease [18]. Compared to the published normalized Canadian data [24], the control 'normal' population did not differ except for higher bodily pain (BP) ($P=0{\cdot}04$) on the July 1999 survey and lower score on the mental health (MH) scale ($P=0{\cdot}04$) on the summer 2001 survey, suggesting that the members of this cohort function as well as the average Canadian and American and that the lower values seen in those individuals with Q fever who have persistent symptoms are not biased by lower 'normal' values.

This study has a number of limitations that should be considered when interpreting the results, including poor follow-up survey participation, and a potential participation bias that individuals who continued to have symptoms were more likely to participate in the study. In addition data on other co-morbidities were not available and may have impacted on the SF-36 scores reported in both the infected and uninfected cohorts. Follow-up serological data to ensure that none of the participants had serological evidence of chronic Q fever was incomplete and the statistical power of the study is limited by the low number of participants. Additional confounding variables may include socioeconomic factors. The farming cooperative was the main source of income for many of the participants and the Q fever outbreak contributed to the dissolution of the cooperative and farm closures, leaving many people without employment.

The existence of a Q fever fatigue syndrome is controversial and is difficult to prove conclusively. Wildman et al. admit that their results 'may not represent fatigue at all, but represent a biased response to questionnaires caused by the process of follow up' [17]. Although the data presented here reflect further evidence of the existence of a QFFS, the possibility that these differences reflect the socioeconomic, physiologic or psychological effects of being labelled with the diagnosis of Q fever rather than true post-infectious sequalae cannot be excluded and warrants further study.

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