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ORIGINAL ARTICLES

Surveillance report

CASE-CONTROL STUDY FOR RISK FACTORS FOR Q FEVER IN SOUTHWEST ENGLAND AND NORTHERN IRELAND

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Q fever (*Coxiella burnetti*) is thought to account for 1% (700 cases) of community acquired pneumonia in the United Kingdom each year, and can result in serious complications such as endocarditis. Although outbreaks have frequently been reported worldwide, the causes are often not clearly identified and there have been few studies of risk factors in sporadic cases.

We conducted a matched case-control study. Cases of acute Q fever in people aged over 15 years in southwest England and Northern Ireland were identified from January 2002 to December 2004. Controls were matched for age, sex and the general practice at which they were registered. Questionnaires asking about contact with animals, and leisure and work activities, were posted to cases and controls.

Questionnaires were completed by 39/50 (78%) of the cases and 90/180 (50%) of the controls. In the single variable analysis, occupational exposure to animals or animal products was the only risk factor associated with cases at the 5% level (P=0.05, odds ratio (OR) 3.4). Long term illness appeared to be significantly protective (P=0.03, OR 0.3). In multivariable analysis the strength of association between occupational exposure and illness remained high (OR 3.6, 95% confidence interval (CI) 0.9 to 14.8) and smoking emerged as a possible risk factor.

This is the first case-control study to identify occupational exposure to animals or animal products as the most likely route of infection in sporadic cases as opposed to outbreaks.

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Introduction

Q fever is a zoonotic infection caused by the rickettsial organism *Coxiella burnetii*. In the United Kingdom it is most commonly carried, often asymptomatically, in sheep, cattle and goats, and is transmitted to humans by inhalation of aerosols. High concentrations of the organism are found in the placenta/placental fluids. Coxiellae can remain viable for months in the environment. The disease occurs most frequently in humans exposed to farm animals or in areas where animal products are handled [1]. Retrospective serological studies have shown evidence of high rates of past infection in farm workers, which suggests that many cases are often not identified at the time of illness [2].

The major clinical manifestations of Q fever are respiratory, cardiac and hepatic, although symptoms are often non-specific. *C. burnetii* is thought to account for 1% (700 cases) of community-acquired pneumonia in the UK each year, and although more serious complications such as endocarditis are rare, they do represent a significant burden of disease [3].

Although outbreaks have frequently been reported worldwide, the causes have often not been identified [4] and we have only been able to

find one previous case-control study in the literature determining risk factors in sporadic cases [5]. The highest incidence of cases in England is consistently reported from the southwest and in an epidemiological review this rural region reported one third of all cases in England and Wales [3]. Northern Ireland reports even higher rates of Q fever per 100 000 population, with between 21 and 75 cases per year since 1990 [6].

Methods

We collaborated with laboratories in southwest England and Northern Ireland to identify cases of Q fever for a matched case-control study to determine risk factors for sporadic infection. A required sample size of 43 cases was estimated using Epi Info. This size was based on a case-control ratio of 1:3, with 95% confidence and 80% power to detect an OR of 3.

Cases in patients resident in southwest England and Northern Ireland aged 16 years and over between 1 January 2002 and 31 December 2004 were identified by local laboratories and confirmed as acute by the Health Protection Agency Regional Laboratory in Bristol on the basis of a history of acute illness and the detection of specific immunoglobulins to *C. burnetii* phase 2 antigens in human sera (Coxiella burneti-Spot IF, bioMerieux® sa, France, using sheep anti-human IgG and IgM conjugates supplied by The Binding Site Ltd,UK), to detect either a fourfold rise in IgM and/or IgG on paired sera, or IgM and IgG titres ≥ 640.

Initially, three controls of the nearest age, same sex and registered with the same general practice were selected for each case (general practices in the UK cover an average population of 6000 people in the same geographical area). In 2003, the study duration was extended from two to three years and the number of controls per case increased to five, because case numbers had been lower than expected and there had been poor response rates, especially from controls.

Postal questionnaires, including questions about contact with animals, consumption of pasteurised/unpasteurised milk, and leisure and work activities within the four weeks before illness (past four weeks for controls), were sent to cases and controls. Non-responders were sent one reminder after four weeks. Data were entered onto a Microsoft Access database. Where responses were not received and there was evidence of individuals only responding where the answer was 'yes', a 'no' response was entered for data that were missing. 'Don't know' responses were excluded from the analysis. Single variable conditional logistic regression was carried out using Stata (v8.2). Variables with P<0.2 in the single variable analysis were then included in a multivariable conditional logistic regression analysis. The study received approval from the appropriate local ethics committees.

Results

Questionnaires were returned by 39/50 (78%) of the cases identified with acute Q fever and 90/180 (50%) of the controls. After excluding records without case or control matches, data from 34 cases and 77 controls were available for analysis, a ratio of 1:2.3. The age range for both cases and controls was 20-73 years (mean 47 and 48 years respectively). Twenty five (73.5%) of the case patients were men, and 9 (26.5%) were women. Over the three year study period, the majority of cases (63.6%) were reported between the months of March and June and were from a rural location (29/34 cases lived on a farm or within 3 miles of farmland). There was a clustering of four cases within a 10 mile (16 km) radius in one rural area. Further investigation did not identify any specific exposure common to these cases.

All cases reported sweating and/or a fever, 28 (82.4%) had a headache, 27 (79.4%) had respiratory symptoms (shortness of breath and/or cough), 27 (79.4%) experienced weight loss, 23 (67.7%) had joint pain and 20 (58.8%) had chest pain. Three (8.8%) had jaundice and 8 (28.6%) patients experienced other symptoms including vomiting, blurred vision, dizziness, extreme thirst, 'sore kidneys' and increased sensitivity of senses (taste and smell). The median duration of illness was 21 days. Twelve patients (35.2%) said they were still unwell at the time of completing the questionnaire.

In the single variable analysis, occupational exposure to animals or animal products was the only risk factor associated with cases at the 5% level (P=0.05, OR 3.4, 95%CI 1.0 to 11.8) [TABLE 1]. Long term illness

Table 1

Single variable analysis of risk factors for Q fever, southwest England and Northern Ireland, January 2002 - December 2004

Risk factor		Cases exposed (%) (n=34)	Controls exposed (%) (n=77)	Matched OR (95% CI)	P value
Close contact with sheep		4 (11.8)	10 (13.0)	0.8 (0.2 to 2.7)	0.66
Close contact with cows[1]		2 (6.1)	4 (5.3)	1.5 (0.3 to 8.4)	0.63
Close contact with pigs		3 (8.8)	1 (1.3)	6.9 (0.7 to 70.9)	0.11
Close contact with goats		2 (5.9)	2 (2.6)	2.8 (0.4 to 20.4)	0.32
Contact with pets (Cats, dogs, birds and other animals)		31 (91.2)	65 (84.4)	1.6 (0.4 to 6.1)	0.50
Occupational exposure to animals/animal products (e.g. veterinarian, butcher, arable farmer)		9 (26.5)	8 (10.4)	3.4 (1.0 to 11.8)	0.05
Consumption of unpasteurised dairy products (milk or cheese)		1 (2.9)	5 (6.5)	0.5 (0.1 to 4.2)	0.51
Proximity to nearest farmland[2]	0	5 (17.2)	5 (7.9)	0.6 (0.2 to 1.7)*	0.38
	0 – 1.6 km	18 (62.1)	49 (77.8)		
	1.6 – 5 km	6 (20.7)	9 (14.3)		
Handling/use of organic matter (Straw, hay, manure and/or compost)		15 (44.1)	24 (31.2)	1.8 (0.8 to 4.1)	0.18
All river/lake water contact (Swimming, water sport and other contact in a river/lake water)		9 (26.5)	15 (19.5)	1.6 (0.6 to 4.7)	0.36
Other outdoors activities (Country walking, horseriding, gardening and other outdoors activities)		27 (79.4)	56 (72.7)	1.4 (0.6 to 3.7)	0.46
Long-standing illness/medical condition[3]		8 (24.2)	34 (46.6)	0.3 (0.1 to 0.9)	0.03
Smoking status	Never smoked	7 (20.6)	35 (45.5)	1	0.11
	Ex-smoker	17 (50.0)	27 (35.1)	2.6 (1.0 to 7.1)	
	Smoker	10 (29.4)	15 (19.5)	2.4 (0.7 to 7.7)	

* For each additional increase in category

1 Case n = 33; Control n = 76 2 Case n = 29; Control n = 63 3 Case n = 33; Control n = 73

Table 2

Multivariable analysis of risk factors for Q fever, southwest England and Northern Ireland, January 2002 – December 2004

Risk factor		Matched OR (95% CI)	P value
Long-standing illness/ medical condition		0.2 (0.05 to 0.7)	0.006
Smoking status	Never smoked	1	0.03
	Ex-smoker	4.5 (1.3 to 15.2)	
	Smoker	2.5 (0.7 to 9.6)	
Occupational exposure		3.6 (0.9 to 14.8)	0.06

appeared to be significantly protective (P=0.03, OR 0.3, CI 0.1 to 0.9). In the multivariable analysis, long term illness remained significantly protective, and smoking emerged as a possible risk factor [TABLE 2]. Although the P value increased from 0.05 to 0.06 when added to the multivariable model, the strength of association between occupational exposure and illness remained high (OR 3.6, 95% CI 0.9 to 14.8).

Discussion

Occupational exposure has been documented as a risk for Q fever in case series and outbreaks since the organism was first discovered in 1937 [7]. As far as we are aware, this is the first case-control study to identify it as the most likely route of exposure in sporadic cases. The temporal distribution of Q fever cases between March and June is similar to that seen in other studies in the UK and Spain, consistent with increased exposure to *C. burnetii* after animal births in spring [3, 8].

As expected, the majority of cases reported non-specific symptoms such as fever and sweating. However, cough and shortness of breath were consistent with respiratory tract involvement, the most common manifestation of Q fever in the UK. The low proportion of cases with jaundice supports the observation that hepatitis is not a common presentation in the UK [3], although patients with mild or granulomatous hepatitis would not necessarily have been jaundiced. Other countries have reported a higher proportion of cases with hepatitis, up to 40% of acute cases in one study in France [9].

The incidence of Q fever in the study regions fell almost as soon as the study started. It is possible that this was due to the effects of foot and mouth disease that occurred in England in 2001, just before the study commenced. Also, a low response rate, especially among controls, resulted in some variables being dropped from the analysis, and misclassification bias may have been introduced into the analysis by assigning missing values to 'no'. It is also possible that other risk factors were not included in the study, such as exposure to rats, which have been identified as an important reservoir for *C. burnetii* in the UK [10].

The apparent protective effect of long term illness was surprising, but could reflect lower outdoor exposure to rural environments in people with long term illness. Apart from occupational exposure and a possible link with smoking, other risk factors studied did not reach statistical significance at the 5% level. Occupational exposure could explain at most a quarter of cases, but we did not expect to have sufficient statistical power to identify risk factors below an odds ratio of 3. Further studies to elucidate risk factors for sporadic Q fever should plan for a larger sample size. In the meantime, prevention and control measures should be directed at reducing the risk of occupational exposure [11].

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