
Q FEVER CASES IN THE NORTHERN TERRITORY OF AUSTRALIA FROM 1991 TO 2006

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Abstract

Q fever (infection with *Coxiella burnetii*) has been uncommon in Australia's Northern Territory, with no reported cases until 2002. Since then, twelve cases of Q fever have been reported, representing a much lower notification rate than in surrounding Australian states. Three cases were identified in Central Australia during 2006, prompting this review of clinical and epidemiological features of all notified Northern Territory cases. Three patients required Intensive Care admission, 1 died, 5 had moderately severe illness, 2 were treated as out-patients and 2 were excluded as unlikely Q fever cases on clinical grounds. Hospital stays were long (median length of stay 9.5 days), and diagnosis and definitive therapy were generally delayed. Although macrolides and quinolones have some reported efficacy against *C. burnetii*, 2 patients experienced prolonged fever (5 and 9 days respectively) despite azithromycin, and the fatality occurred in a patient treated with multiple antibiotics including ciprofloxacin. Four patients were Aboriginal, 3 were tested for HTLV-I and 2 were positive. The patient who died was diabetic. None had valvular heart disease. Greater awareness

of acute and chronic manifestations of Q fever is required in the Northern Territory. Early institution of doxycycline in suspected cases is recommended, and more rapid diagnostic methods including polymerase chain reaction testing should be considered. Host risk factors for chronicity, which may be of particular importance in Indigenous patients, merit attention. Given the lack of occupational exposure in these cases, there seems little reason to change the current Northern Territory policy of opting out of the National Q Fever Vaccination Program. Recognised alternative exposures, such as non-occupational livestock and domestic animal contact, require consideration as local Q fever sources. *Commun Dis Intell* 2007;31:222-227.

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Introduction

Documented cases of infection with *Coxiella burnetii* (Q fever), a notifiable zoonotic disease, have been uncommon in the Northern Territory. *C. burnetii* is found in every country except New Zealand,¹ and in multiple animal hosts including wild and

domestic mammals, birds and ticks. Human cases are predominantly due to occupational exposure in livestock industries, but sporadic cases after minimal contact are increasingly recognised.² Under-diagnosis is common, despite exhortations to physicians to consider, investigate and treat Q fever where appropriate.

Acute Q fever ranges from asymptomatic to fulminant. A detailed review of Q fever in an Australian case series is provided by Spelman.³ Asymptomatic infections (identified serologically or from skin testing) are estimated to represent the majority (60%) of cases; chronic manifestations (including endocarditis and osteoarticular infections) comprise around 0.2% of cases.^{2,4} Up to 40% of patients with acute Q fever may develop endocarditis if they have pre-existing valvular disease.^{5,6}

Q fever is notifiable in Australia if there is definitive laboratory evidence, or suggestive laboratory evidence with compatible clinical illness (Box). Australian national notification rates have fallen from 4.99 cases per 100,000 population in 1993⁷ to 2.2 cases per 100,000 in 2004, probably due to the National Q Fever Management Program established in 2001,⁸ with the majority of cases occurring in Queensland and New South Wales. The first

notified Northern Territory case since commencement of electronic record keeping in 1991 was reported in 2002.⁹ The report made note of several cases occurring over previous decades recalled by local physicians. It has been assumed that Q fever is uncommon in the Northern Territory, despite a moderately sized and growing pastoral industry with traffic of people and stock across territory/state borders.¹⁰ Because of the lack of industry-associated cases, the Northern Territory has not been part of the National Q Fever Management Program.

When 3 cases of acute Q fever were identified in 2006 in Central Australia, a re-evaluation of the burden of Q fever throughout the Northern Territory was undertaken. We present the results of a retrospective review of epidemiological and clinical features of all notified Q fever cases in the Northern Territory and discuss host risk factors, treatment regimens and strategies for ensuring timely diagnosis.

Methods

We identified all notified cases of Q fever from 1991 (commencement of electronic record keeping) to 2006, using the Northern Territory Centre for Disease Control (CDC) notifiable diseases database. Clinical, laboratory and radiological data were obtained from hospital charts, general practitioner, and CDC records. Information was recorded for each patient as follows:

1. indigenous status;
2. likely Q fever exposure;
3. illness severity graded as fatal, severe (requiring admission to Intensive Care), moderately-severe (requiring hospitalisation), moderate (outpatient, significant symptoms), mild (outpatient, mild symptoms) and asymptomatic;
4. clinical features (presence or absence of documented fever, fever duration, other clinical features noted in the medical file);
5. laboratory results including *C. burnetii* serology, liver function tests, platelet count and human T-lymphotrophic virus type 1 (HTLV-I) status;
6. chest radiograph; and
7. antibiotics administered.

Results

Twelve cases of Q fever were notified to the Northern Territory CDC between 1991 and 2006; 8 in Central Australia and 4 in the Top End. A further case diagnosed in late 2006 in the Top End was not included here. No cases were reported in the Top End prior to 2002, or in Central Australia prior to 2004 (Figure 1). After discussion with treating doctors and review of clinical notes, we excluded one Top End case and

Q fever case definition

A confirmed Q fever case requires:

EITHER

1. *Laboratory definitive evidence*

OR

2. *Laboratory suggestive evidence AND clinical evidence.*

Laboratory definitive evidence

1. *Detection of *C. burnetii* by nucleic acid testing*

OR

2. *Seroconversion or significant increase in antibody level to Phase II antigen in paired sera tested in parallel in absence of recent Q fever vaccination*

OR

3. *Detection of *C. burnetii* by culture (note this practice should be strongly discouraged except where appropriate facilities and training exist.)*

Laboratory suggestive evidence

Detection of specific IgM in the absence of recent Q fever vaccination.

Clinical evidence

A clinically compatible disease.

one Central Australian case. The Top End patient remained in Intensive Care at the time of report with a protracted illness with auto-antibodies and multiple cross reactive serological results, but no Q fever-compatible illness. The Central Australian patient had atypical pneumonia without prolonged fever; Q fever Phase 1 and 2 antibodies were all elevated at low titre, and serology was also positive for *Bordetella pertussis* and *Mycoplasma pneumoniae*, the latter thought to be the more likely illness.

Of the remaining 10 cases, most were middle-aged males (Table 1). A clear exposure history was only evident in one instance (employee on live cattle export ship), but likely or possible exposures were

able to be identified in each case. No clustering of cases was noted temporally or geographically. Four patients were Indigenous; 3 of these were tested for HTLV-1 and 2 were positive. One patient had diabetes and 1 had asthma. None were noted to have valvular heart disease and none was known to be pregnant.

Clinical and demographic features are summarised in Tables 1 and 2 and Figure 2. Diagnosis and definitive treatment was significantly delayed in all but one instance. Patients received multiple broad spectrum antibiotics, including macrolides (3 patients), beta lactams (3); cephalosporins (3); meropenem (2); vancomycin (2) and ciprofloxacin (1). Despite reported anti-*C. burnetii* activity of newer macrolides and quinolone antibiotics, the patient treated with ciprofloxacin died. The 2 patients whose antibiotic regimens included azithromycin had fever durations of 5 and 9 days respectively (compared with 1 day fever duration in the patient treated early with doxycycline, and a mean of 6.8 days in untreated or delayed treatment patients). Eight patients in total were treated with doxycycline, but this was often commenced after the resolution of clinical symptoms, when serological results had become available (28 days after illness onset in one instance). Invasive investigations included 3 lumbar punctures (all normal) and 1 liver biopsy (showing granulomatous hepatitis). Patients also had multiple other serological, microbiological and radiological investigations. The median hospital length-of-stay for the 8 hospitalised patients was 9.5 days (range 5 to 21).

Figure 1. Temporal distribution of Q fever cases in Central Australia and the Top End of the Northern Territory

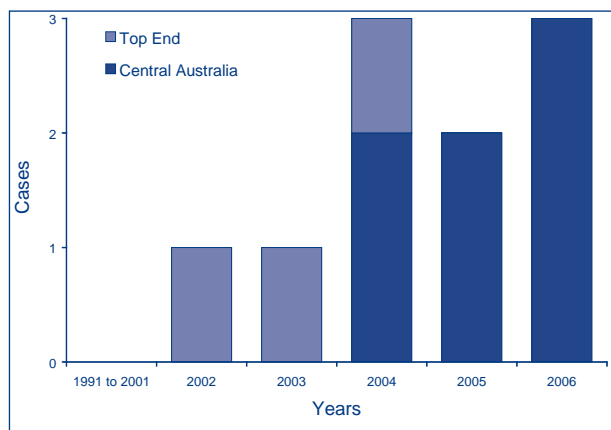


Table 1. Epidemiological and clinical data, Northern Territory Q fever cases, 1991 to 2006

Patient	Indigenous status	Age	Gender	Co-morbidities	Disease severity
Central Australian patients					
1	A	34	M	HTLV-1 positive	Moderate-severe
2	A	48	M	HTLV-1 positive, alcoholic liver disease, gastritis	Severe
3	A	37	M	Nil	Moderate-severe
4	A	27	F	Type 2 diabetes	Severe (died)
5	NA	43	M	Asthma	Moderate-severe
6	NA	48	M	Nil	Moderate
7	NA	29	M	Nil	Moderate
Top End patients					
8	NA	20	M	Nil	Moderate-severe
9†	NA	49	M	Nil	Severe
10	NA	62	F	Nil	Moderate-severe

A Aboriginal.

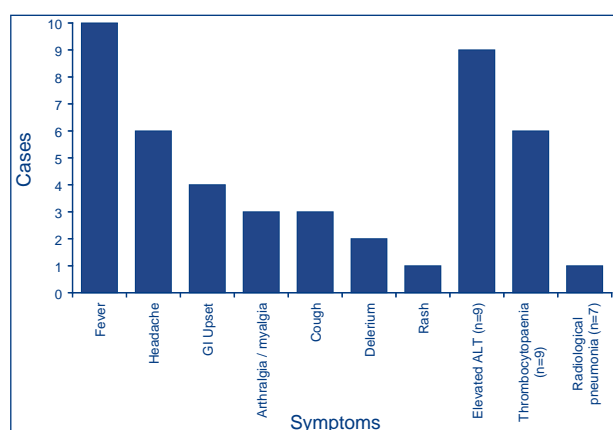
NA Non-Aboriginal.

† Patient described in case report, Reference 1.

Table 2. Possible exposure history, Northern Territory Q fever cases, 1991 to 2006

Possible exposure	Number of patients
Visited or lived in remote pastoral area	4
Non-occupational cattle slaughter	2
Minimal exposure evident, but drove in vicinity of cattle yards	2
Employee on live cattle export ship	1
Worked at cattle station	1

Figure 2. Symptom and laboratory abnormality frequency in 10 Q fever cases



GI Gastrointestinal.

ALT Alkaline phosphatase. Mean ALT=158.3 U/L.

Thrombocytopenia range: 10 to 134 x 10⁹/L.

The number of patients with results available for investigations are indicated in brackets.

Serological confirmation of Q fever was achieved using immunofluorescence assay in 9 instances, and a combination of enzyme-linked immunosorbent assay and complement fixation was done in the other instance. Five had paired serum samples demonstrating a rise in Phase 2 antibody titres, and 5 had significantly elevated Phase 2 antibodies on a single specimen. Q fever polymerase chain reaction (PCR) was not performed in any instance.

Discussion

Q fever reports from the Northern Territory since 1991 have all been acute Q fever diagnoses of at least moderate severity. The estimated financial cost to the health care system has been high due to multiple investigations, use of broad spectrum antibiotics and prolonged hospitalisation. These 10 notified cases probably represent a small proportion of all Q fever cases in the Northern Territory. European data indicate that hospitalised Q fever cases represent only 2%–4% of infected individuals.^{2,4} Even though numbers are small, there is an impression that

Q fever notification rates are rising in the Northern Territory. This may represent an increase in testing or a real increase, in contrast to the national figures.⁸ During preparation of this manuscript, a further case of acute Q fever was notified in the Top End, bringing the number of confirmed cases in 2006 to four. Hence the notification rate for the Northern Territory in 2006 (population estimate 202,793¹¹) was 2.0 cases per 100,000 population, compared with the most recently reported Australian national rate of 2.2 cases per 100 000 population.⁸

The clinical manifestations of Q fever are diverse; differences are thought to be attributable to (1) genetic differences in *C. burnetii* strains; (2) host factors such as age, sex, pregnancy, immunosuppression; (3) inoculum size; and (4) route of infection.^{2,6} The clinical presentations of the patients described here are consistent with previously reported Australian Q fever cases, including the relatively uncommon finding of pneumonia or pneumonitis (1 of 10 patients) and the infrequent occurrence of rash (1 of 10 patients).³ Although one of the 10 cases in this series died, death due to acute Q fever is uncommon, with 5 deaths recorded in Australia between 1982 to 1994.²

T-cell immunity is the primary mode of Q fever control by the infected host. Impaired T-cell immunity in HIV, cancers, lymphoma and pregnancy has been associated with failure to eradicate *C. burnetii*, and progression to chronic disease.^{2,6,12} HTLV-1, which is endemic in Aboriginal Central Australians at up to 13.9% seroprevalence,¹³ was positive in 2 patients in this series. While there are no previous reports of an association between HTLV-1 and Q fever, it is possible that the T-cell deficits associated with HTLV-1 may predispose to impaired clearance of intracellularly sequestered *C. burnetii* and a greater risk of chronic infection. The association of HTLV-1 and acute Q fever in the 2 patients reported is probably due to chance, but highlights the potential problems of the concurrence of endemic HTLV-1 with Q fever. Since assiduous serological follow-up and prolonged therapy to reduce the risk of progression to chronic Q fever is recommended in other recognised risk groups (people with valvular heart disease or pregnancy)⁶ after an episode of acute Q fever, such approaches may also be warranted in HTLV-1 positive individuals.

High rates of rheumatic heart disease in the Northern Territory^{14,15} should also be cause for heightened Q fever awareness, since Q fever endocarditis is more likely to occur on previously damaged valves, especially if combined with T-cell immunosuppression.² A case of Q fever endocarditis is recalled from Alice Springs in the 1980s (Dr Nadarajah Rajabalendran, Alice Springs Hospital, personal communication), but details are unavailable.

Timely diagnosis and management of Q fever is required. This can be achieved through greater health staff awareness of this infection in the Northern Territory, with earlier testing and institution of effective antibiotic therapy. Q fever PCR tests are in development, which may facilitate early diagnosis. In an Australian cohort of 27 patients with acute Q fever, Q fever PCR assays (one or both of COM1 and IS1111 PCR) were positive in blood in 63% of patients overall, and in 89% of samples collected early in the illness prior to development of Phase 2 IgM antibody.¹⁶

Recommended first line treatment for acute Q fever is doxycycline 100 mg twice daily for 14 days,¹⁷ or (debatably) co-trimoxazole 160 mg/800 mg twice daily in pregnant patients,¹⁸ commenced within the first 3 days of illness to achieve reduction in fever duration.² The 2 patients described here who were treated from early in their illness with azithromycin remained febrile for 5 and 9 days compared with a mean of 6.8 days for untreated patients, and 1 day for the patient in whom doxycycline was administered early, suggesting lack of potency of azithromycin in these patients. This contrasts with a retrospective Greek study, where patients treated with clarithromycin were febrile for a mean of 3.9 days (only one day longer than those treated with doxycycline).¹⁹ Heterogeneity in antibiotic resistance in different *C. burnetii* strains may explain such variable responses.² Because of the potential for late sequelae of *C. burnetii* infection, some recommend commencing treatment even after apparent symptom resolution if the initial opportunity for treatment was missed. Evidence for this approach in patients without risk factors for chronicity is lacking; nevertheless, all but 3 of the patients described here were treated in this manner as the diagnosis had not been made earlier in the course of the illness.

Even though Q fever might exist in the Northern Territory at higher rates than so far predicted, the lack of occupational exposure in this case series suggests that the current policy in the Northern Territory of opting out of the national vaccination program is appropriate, but this may require revision at a later date. The small inoculum required means that minimal exposure such as being in the vicinity of infected animals (as postulated for some patients in this series) may provide sufficient exposure for infection. Contact with other potential Q fever hosts (domestic dogs and cats, native bandicoots) may have been overlooked as possible exposures.

In conclusion, the occurrence or recognition of Q fever in the Northern Territory could be increasing, and under-diagnosis is likely. Small numbers prevent conclusions being drawn. Increased awareness, early testing and institution of effective anti-Q fever therapy may effect a decrease in morbidity

and costs of the disease. While no cases of chronic Q fever were identified during this 15 year period, the risk factors for chronicity, especially in the Indigenous population, call for heightened awareness of this infection.

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