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Acute Q Fever Case Detection among Acute Febrile Illness Patients, Thailand, 2002–2005

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Abstract. Acute Q fever cases were identified from a hospital-based acute febrile illness study conducted in six community hospitals in rural north and northeast Thailand from 2002 to 2005. Of 1,784 participants that underwent *Coxiella burnetii* testing, nine (0.5%) participants were identified in this case-series as acute Q fever cases. Eight case-patients were located in one province. Four case-patients were hospitalized. Median age was 13 years (range: 7–69); five were male. The proportion of children with acute Q fever infection was similar to adults ($P = 0.17$). This previously unrecognized at-risk group, school-age children, indicates that future studies and prevention interventions should target this population. The heterogeneity of disease burden across Thailand and milder clinical presentations found in this case-series should be considered in future studies. As diagnosis based on serology is limited during the acute phase of the disease, other diagnostic options, such as polymerase chain reaction, should be explored to improve acute case detection.

BACKGROUND

Q fever is caused by the intracellular, gram negative bacteria, *Coxiella burnetii*.¹ Transmission primarily occurs through the inhalation of aerosolized spore-like particles originating from animal blood, birthing fluids, and/or excreta.² Although commonly asymptomatic or occasionally marked by reproductive issues in the ruminant reservoir, it can be present in humans as an influenza-like illness, pneumonia, and/or hepatitis, with a case fatality rate below 2%.^{3,4} Most (> 90%) patients promptly eradicate the bacterium. However, months to years later, persistent focalized infections (previously referred to as chronic Q fever) can be diagnosed in 1–5% of those having presented with primary infection.^{5–8} Persistent focalized infections primarily include cardiovascular infections, which can be fatal if not treated with appropriate antibiotics as well as surgery in aortic infections.^{1,9–11}

Although variable antibody kinetics have been described, seroconversion for *C. burnetii* occurs around 7–15 days but can be delayed for as long as 6 weeks.^{1,3} Diagnosis is most commonly made by serology using indirect immunofluorescence assay (IFA) and detection of immunoglobulin G (IgG) antibodies against phase II antigens.¹

Since Q fever's first detection in Thailand in 1966, limited studies have been conducted and overall prevalence and incidence in the country is still unknown.¹² One study estimated a 1.3% prevalence of Q fever among patients presenting with fever at four hospitals in northeastern Thailand.¹³ In 2012, the first cases of Q fever endocarditis in Thailand were identified.¹⁴ With the recent identification of cases with persistent focalized infection, it is essential to elucidate the epidemiology and risk factors underlying the acute form of the disease to prevent serious chronic sequelae. Thus, we retrospectively analyzed acute Q fever cases identified from an acute febrile illness (AFI) study in north and northeast Thailand from 2002 to 2005.

The objective of our investigation was to determine the frequency of serologically confirmed acute Q fever infection among febrile patients presenting to district hospitals in rural Thailand and identify at-risk groups. The secondary objective was to assess the utility of different serological criteria for diagnosing acute Q fever to better understand potential limitations of existing diagnostic testing options and to inform future Q fever studies and clinical efforts in Thailand.

METHODS

From 2002 to 2005, an AFI study, as a part of a broader U.S. Centers for Disease Control and Prevention Global Disease Detection AFI network, was conducted in three provinces in north and northeast Thailand: Chiang Rai (2002–2005), Khon Kaen (2002–2004), and Nakhon Phanom (2004–2005), in two community hospitals in each province. Study staff enrolled outpatients and inpatients using the following criteria: age greater than 6 years, presenting within 2 weeks of fever onset, confirmed temperature > 38°C, and resident of the study site province. Exclusion criteria included recent vaccination (< 48 hours) for any disease, receipt of blood products in the previous 6 months, severe illness requiring transfer to another hospital, or an obvious sign of infection (e.g., pharyngitis, meningitis, urinary tract infection, mumps, croup, varicella, parvovirus, measles, and rubella). Study staff received written informed consent from all eligible febrile patients. No personal identifying information was included. Standard questionnaires, originally designed to capture primarily leptospirosis related factors, were used to collect demographic, clinical characteristics, laboratory data, and animal exposure. Blood was drawn from participants on enrollment, defined as an acute serum specimen, and 3–5 weeks later, defined as a convalescent serum specimen.

In 2010, the paired sera from Chiang Rai and Khon Kaen study sites were sent to Unité des Rickettsies, Faculté de Médecine (Marseille, France) for *C. burnetii* antibody testing by IFA (Figure 1). Two criteria were used to define an acute Q fever case. First, the United States Centers for Disease Control and Prevention (CDC) confirmed case criteria, which included clinical evidence of infection and a 4-fold increase in

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FIGURE 1. Map of Thailand highlighting the provinces (medium gray) and the districts within each province (dark gray) where samples for acute Q fever were tested in an acute febrile illness study—Khon Kaen and Chiang Rai provinces, Thailand, 2002–2005.

IgG phase II antibody titer to *C. burnetii* antigen between paired sera collected 3–6 weeks apart.³ Second, the criteria used by the French National Reference Center for Rickettsial

Diseases (FNRCRD), which included clinical evidence of infection with the duration of symptoms less than 3 months from onset, and a single acute serum sample with an IgG phase

II \geq 1:200 and immunoglobulin M (IgM) phase II \geq 1:50 or seroconversion.^{5,15,16} For purposes of this case-series, staff at the FNRCRD and CDC reviewed the titers and kinetics of the phase II IgG and IgM antibodies between acute and convalescent samples to determine whether the specimens were true positives.

Data were extracted from the existing deidentified AFI database using Microsoft Excel (Version 2013; Microsoft Corp., Redmond, WA). Data were analyzed using Epi-Info™ (Version 7.1.14.14; CDC, Atlanta, GA). Univariate analysis was performed to assess the frequency of key variables. Bivariate analysis was conducted using the Kruskal–Wallis test to compare medians, and the Chi-Square test was used to compare proportions. Statistical significance was set at $P < 0.05$.

RESULTS

Of 1,991 participants enrolled at the Chiang Rai and Khon Kaen study sites, 1,784 (90%) underwent *C. burnetii* acute and convalescent antibody testing by IFA. Although limited reagent availability restricted *C. burnetii* testing of all participants, of the 1,768 participants who indicated a province of origin, both provinces had equal representation in the cohort tested: 896 (51%) from Chiang Rai and 872 (49%) from Khon Kaen. For those participants whose specimens were not tested for Q fever, there was no difference in gender compared with those who did receive testing ($P = 0.15$). The not tested group was older (median: 37 years, range: 7–89) than the tested group (median: 21 years, range: 7–86) ($P < 0.01$), and had a higher percentage of inpatients (55%, confidence interval [CI]: 47.8–61.8) than those that underwent testing (39%, CI: 36.5–41.1) ($P < 0.01$).

Of the 1,784 tested, 16 (0.9%) participants had Q fever antibody detected in the acute or convalescent specimen (Table 1). Of those, 11 participants had laboratory findings that were consistent with at least one diagnostic criteria for Q fever; 11 (0.6%) met FNRCRD criteria and five (0.3%) met CDC confirmed case criteria. For purposes of this case-series, all

case-patients that met at least one criteria for acute Q fever were included in analysis, except for two cases (identification number 10 and 11) with high titers on initial clinical presentation (Table 1). Review of these high titers and dynamics between the acute and convalescent periods were thought to represent persistent focalized infections rather than acute Q fever cases.¹⁷ Thus, nine (0.5%) cases were included in the analysis (Table 1).

Acute Q fever case-patients' median age was 13 years (range: 7–69) (Figure 2). The median age of patients not meeting case criteria was 21 years (range: 7–86). Among the 783 children (age < 18 years) tested, six (0.8%) had acute Q fever infection and of the 1,001 adults (age ≥ 18 years) tested, three (0.3%) had acute Q fever infection (odds ratio = 0.39, $P = 0.17$). Five case-patients were male. Four case-patients were cared for as inpatients, two children and two adults. Six case-patients identified themselves as students when asked about occupation (Table 2).

Geographic clustering was observed among case-patients. Eight of the nine case-patients were located in Kranuan district of Khon Kaen province; among 872 Khon Kaen residents enrolled in the AFI study, the proportion of serologically confirmed acute Q fever infections was 0.9% (CI: 0.5–1.8) in Khon Kaen during the study's 2 years. The Kranuan district cases were all clustered along the northeast border of the province. One acute Q fever case-patient was located in Chiang Saen district of Chiang Rai province; among 896 Chiang Rai residents enrolled in the study, the proportion of serologically confirmed acute Q fever infections among AFI cases was 0.1% (CI: 0.02–0.63) during the study period (Figure 1).

Eight of the nine (89%, CI: 51.7–99.7%) case-patients reported animal ownership, similar to noncases at 85% (CI: 83.2–86.6) ($P = 0.74$). Of the eight reporting animal ownership, seven had dogs (88%), and six had chickens (75%); none reported ownership of buffalo or cattle.

On clinical presentation, seven (78%, CI: 39.9–97.2) case-patients reported headache and myalgia, and four (44%, CI:

TABLE 1

Paired acute and convalescent IgG and IgM antigen titers, the corresponding diagnostic criteria, and case-series inclusion among febrile participants who met at least one case definition for acute Q fever in an acute febrile illness study—Khon Kaen and Chiang Rai provinces, Thailand, 2002–2005

ID	Acute			Convalescent			CDC* confirmed criteria	FNRCRD† criteria	Case-series inclusion
	Phase II IgG	Phase II IgM	Time from illness onset to acute sera (days)	Phase II IgG	Phase II IgM	Time from illness onset to convalescent sera (days)			
1	0	0	1	3,200	400	22	X	X	X
2	0	0	3	3,200	1,600	30	X	X	X
3	0	0	3	800	3,200	28	X	X	X
4	100	50	2	400	100	23	X	X	X
5	100	200	3	400	200	29	X	X	X
6	200	0	9	200	50	31	–	X	X
7	400	50	1	400	50	31	–	X	X
8	400	50	3	400	50	39	–	X	X
9	0	0	13	100	1,600	38	–	X	X
10‡	12,800	100	1	12,800	100	36	–	X	–
11‡	25,600	800	4	51,200	3,200	28	–	X	–
12	0	50	11	0	50	22	–	–	–
13	400	0	1	400	0	27	–	–	–
14	100	0	1	100	0	16	–	–	–
15	0	0	3	0	50	28	–	–	–
16	0	50	1	0	50	26	–	–	–

IgG = immunoglobulin G; IgM = immunoglobulin M.

* United States Centers for Disease Control and Prevention.

† French National Reference Center for Rickettsial Diseases.

‡ ID 10 and 11 have a high probability of chronic endocarditis or other persistent focalized infection, which are exclusion criteria to define acute Q fever.¹⁷

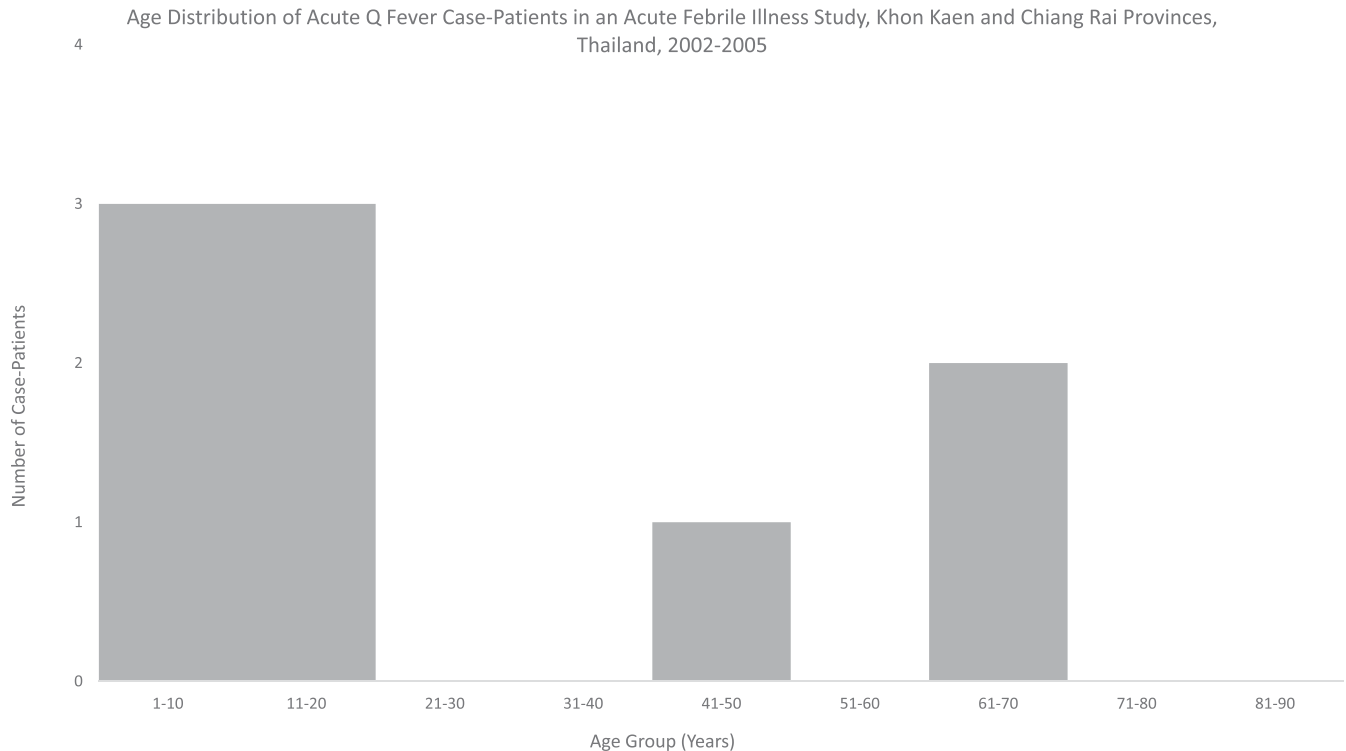


FIGURE 2. Age distribution of acute Q fever case-patients in an acute febrile illness study, Khon Kaen and Chiang Rai provinces, Thailand, 2002–2005.

13.7–78.8) reported cough. There was no statistically significant difference in signs or symptoms compared with noncases.

DISCUSSION

This case-series adds to the currently limited information available regarding Q fever in Thailand. Traditionally, Q fever has been considered to be a disease of farmers and those with an animal husbandry occupation.¹ By contrast, in this case-series, six of nine acute Q fever case-patients reported their occupation as a student. In addition, compared with

previous AFI studies, acute Q fever case-patients were notably younger.^{1,5,18} One study in the Netherlands demonstrated that only after a high-dose exposure are the attack rates of acute Q fever between children and adults similar, otherwise children have lower attack rates.¹⁹ Conversely, some African-based studies have found minimal differences in Q fever prevalence between adults and children, which may indicate differing epidemiology based on geography.^{20–22} In Thailand, specifically, previous studies that identified *C. burnetii* as a potential etiological agent for AFI were primarily limited to adult populations, thereby potentially missing Q fever as a

TABLE 2

Demographics of febrile participants among acute Q fever case-patients and non-cases presenting to district hospitals during an acute febrile illness study—Khon Kaen and Chiang Rai provinces, Thailand, 2002–2005

	Acute Q fever case-patients (N = 9)			Patients without evidence of acute Q fever infection (N = 1773)*		
	n	%	95% CI	n	%	95% CI
Median age, years (range)	13		(7–69)	21		(7–86)
Male	5	56	21.2–86.3	1,032	58	55.9–60.5
Inpatient	4	44	13.7–78.8	672‡	40	37.2–41.9
Residence						
Rural	6	67	29.9–92.5	1,038	58	56.2–60.8
Suburban	2	22	2.8–60.0	542	31	28.5–32.8
Urban	1	11	0.3–48.3	193	11	9.5–12.4
Occupation†						
Student	6	67	29.9–92.5	758	43	40.5–45.1
Farmer	1	11	0.3–48.3	589	33	31.1–35.5
Artisan	1	11	0.3–48.3	70	4	3.1–4.9
Other	1	11	0.3–48.3	382	22	19.7–23.5

CI = confidence interval.

* Does not include the two patients who met the FNRC criteria but are considered as probable persistent focalized infections.

† Multiple answers possible.

‡ Only 1,702 participants answered this question.

significant cause of disease in children in this area.^{23,24} In our study, there were more children with acute Q fever than adults. Although the low case count limited the power to determine if there was a significant difference between the age groups, our study suggests that Q fever may be an unrecognized illness in Thai youth. Future investigations need to consider the school-age population and to focus on additional environmental exposures rather than solely occupational risk. Although the risk of progression to persistent focalized infection based on age of initial infection is unknown and may differ based on location-specific prevalence of underlying valvulopathies, children can develop sequelae of Q fever infection.^{1,18} An improved understanding of Q fever exposure risks in rural Thai youth may be needed to inform future disease control guidance.

Overall, case-patients presented with a nonspecific febrile illness, which is consistent with previous reports.^{1,3} This nonspecific presentation makes it difficult for physicians to consider the disease in patients based on clinical findings and improved data on risk factors for human Q fever infection in Thailand is important to improve future case detection. In addition, because of the mild symptoms and self-resolving nature of the acute illness, infected persons may not even seek healthcare; therefore, this study likely underestimates the true burden of acute Q fever infections in this population.^{1,3}

The difference in Q fever burden between the two provinces highlights the heterogeneity of the human disease based on geographic location, which is consistent with previous studies.²⁵ Even when expanding the case definition to include any person with IgG antibodies against phase II *C. burnetii* antigen, the geographic heterogeneity trend still exists with clustering within Kranuan district in Khon Kaen province. This variance in prevalence among and within provinces underscores the need to consider Q fever as an AFI etiology in other provinces of Thailand. The cluster of human cases identified in Khon Kaen province is consistent with previous studies performed in the province; animal studies performed in the same province have documented cattle and buffalo shedding of *C. burnetii*.^{13,26,27} Animal Q fever studies can help determine human risk in a region, increasing the index of suspicion among healthcare providers and lowering the threshold for Q fever testing. However, further studies are needed to determine how well the geographic heterogeneity observed in animal surveillance can predict the distribution of human disease patterns.

This study highlights differences in current criteria for the diagnosis of acute Q fever. Strictly applying the criteria, FNRC criteria identified 11 cases and CDC confirmed case criteria identified five cases. Overall, these discrepancies highlight the diagnostic challenge clinicians face when considering an acute Q fever diagnosis. The FNRC has the utility of only requiring one time testing, which can help dictate immediate case management, but may capture patients that are not true acute Q fever cases. Whereas applying the CDC confirmed case definition and waiting 3–5 weeks before convalescent results are available to make a diagnosis is not appropriate for patient care.^{1,3,5} In addition, regional differences in background positivity and variable kinetics may change the appropriate titer cutoffs and thus, the criteria's utility by geographic location.²² Overall, this study underscores the importance of considering alternative laboratory testing methods during the early stages of illness, such as polymerase chain reaction (PCR). Recent advances in this process, including lyophilization, have increased the PCR's

sensitivity to detect *C. burnetii* in the early stages of the disease.²⁸

There were several limitations in this retrospective study. First, the questionnaire used in the original study was not tailored to address *C. burnetii* transmission and clinical presentation. Thus, identification of specific risk factors most plausibly associated with acute Q fever was limited. Second, *C. burnetii* testing was not conducted until 5 years after data collection, limiting our ability to clarify survey results during analysis. In addition, the delay from data collection to analysis may limit the applicability of the data to the current population, given that the epidemiological patterns and degree of endemicity may have changed in the last 10 years. Third, antibiotic administration after enrollment was not documented, and as such, symptom resolution in participants and treatment practices could not be fully evaluated. Fourth, not all participants who were enrolled in the study had *C. burnetii* testing performed because of limited reagent availability; this may have biased the results, as the not tested group had an older median age and more inpatients, likely indicating a more severe disease presentation that may have not been captured by this analysis. Finally, the limited number of cases identified in the case-series restricted analysis and conclusions that could be made regarding acute Q fever among febrile participants in the study.

Regardless, this retrospective case-series has several strengths, which add important data to the currently limited information regarding human acute Q fever in the region. To our knowledge, this study reports the largest study population and widest age range of AFI patients tested for *C. burnetii* in Thailand to date. In addition, collected paired acute and convalescent specimens allowed acute Q fever infections to be reliably differentiated from chronic or previous infections. The surprising young age of acute Q fever infection identified in this study highlights the need to broaden understanding of acute Q fever in Thailand, taking into account mild clinical presentations of the disease, as well as the geographic heterogeneity among and within provinces of Thailand. The data can be used to tailor future investigations toward at-risk groups and the consideration of nontraditional at-risk groups, such as youth, as identified in this analysis. In addition, laboratory capacity for Q fever, including the consideration of the use of PCR to test for acute Q fever in Thailand, is needed to support diagnosis not only for case management but also for future public health surveillance efforts.

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