MAJOR ARTICLE

Q Fever, Spotted Fever Group, and Typhus Group Rickettsioses Among Hospitalized Febrile Patients in Northern Tanzania

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Background. The importance of Q fever, spotted fever group rickettsiosis (SFGR), and typhus group rickettsiosis (TGR) as causes of febrile illness in sub-Saharan Africa is unknown; the putative role of Q fever as a human immunodeficiency virus (HIV) coinfection is unclear.

Methods. We identified febrile inpatients in Moshi, Tanzania, from September 2007 through August 2008 and collected acute- and convalescent-phase serum samples. A $\geq$4-fold increase in immunoglobulin (Ig) G immunfluorescence assay (IFA) titer to *Coxiella burnetii* phase II antigen defined acute Q fever. A $\geq$4-fold increase in IgG IFA titer to *Rickettsia conorii* or *Rickettsia typhi* antigen defined SFGR and TGR, respectively.

Results. Among 870 patients, 483 (55.5%) were tested for acute Q fever, and 450 (51.7%) were tested for acute SFGR and TGR. Results suggested acute Q fever in 24 (5.0%) patients and SFGR and TGR in 36 (8.0%) and 2 (0.5%) patients, respectively. Acute Q fever was associated with hepato- or splenomegaly (odds ratio [OR], 3.1; $P = .028$), anemia (OR, 3.0; $P = .009$), leukopenia (OR, 3.9; $P = .013$), jaundice (OR, 7.1; $P = .007$), and onset during the dry season (OR, 2.7; $P = .021$). HIV infection was not associated with acute Q fever (OR, 1.7; $P = .231$). Acute SFGR was associated with leukopenia (OR, 4.1; $P = .003$) and with evidence of other zoonoses (OR, 2.2; $P = .045$).

Conclusions. Despite being common causes of febrile illness in northern Tanzania, Q fever and SFGR are not diagnosed or managed with targeted antimicrobials. *C. burnetii* does not appear to be an HIV-associated co-infection.

Q fever, spotted fever group rickettsiosis (SFGR), and typhus group rickettsiosis (TGR) commonly present as nonspecific febrile illnesses that are difficult to diagnose clinically. Furthermore, laboratory capacity to diagnose these infections is often lacking in developing countries. Consequently, the importance of Q fever, SFGR, and TGR as causes of acute febrile illness in sub-Saharan Africa is poorly characterized.

Although studies identifying Q fever [1], SFGR [2], and TGR [3] as etiologies of fever are limited in sub-Saharan Africa, human seroprevalence studies confirm the presence of their causative organisms. The seroprevalence of antibodies to *Coxiella burnetii*, the cause of Q fever, ranges from 5% in urban Tanzania to 37% in Zimbabwe [4–6]. Furthermore, antibodies to *C. burnetii* have been documented in 7%–17% of agricultural animals in Tanzania [5, 7], consistent with their likely role as reservoirs for human infection via environmental contamination [8]. The seroprevalence of antibodies to SFGR ranges from 25% in urban Tanzania to >50% in Zimbabwe and Kenya [4, 9, 10]. Cattle and wild

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ungulates are the primary mammalian reservoirs of *Rickettsia africae*, the agent of African tick bite fever, and *Amblyomma* ticks, up to 75% of which are infected, serve as both reservoirs and vectors [11–14]. *Amblyomma variegatum*, an important vector in Tanzania, is particularly prevalent during rainy seasons and in rural areas because of its association with animals [11, 15, 16]. The seroprevalence of antibodies to *Rickettsia typhi*, the cause of murine typhus, has been reported to be low in many African studies, although seroprevalence was 28% in urban Tanzania [4, 9]. Rodents are reservoirs for *R. typhi*, and the rat flea, *Xenopsylla cheopis*, is the primary vector mediating human transmission [17].

To understand the role of Q fever and rickettsial diseases as causes of febrile illness in northern Tanzania, we investigated the prevalence, characteristics, and correlates among adult and pediatric febrile inpatients with Q fever, SFGR, and TGR.

METHODS

Participants and Setting

Febrile patients admitted to Kilimanjaro Christian Medical Centre (KCMC) or Mawenzi Regional Hospital (MRH) in Moshi, Tanzania, from 17 September 2007 through 25 August 2008 were eligible for enrollment. Complete study methods have been described elsewhere [18, 19]. MRH is a 300-bed government hospital serving the Kilimanjaro Region; KCMC is a 458-bed government referral hospital serving several regions of northern Tanzania.

For pediatric patients 2 months to 13 years of age, inclusion criteria were a history of fever within the previous 48 hours or a measured axillary or rectal temperature >37.5°C or ≥38°C, respectively, at admission to the hospital. For adolescent and adult (≥13 years of age) patients, the inclusion criterion was an oral temperature ≥38°C at admission to the hospital. Among those who consented for enrollment, a trained clinical officer collected standardized demographic data, clinical history, physical examination findings, and provisional diagnosis data within 24 hours of hospital admission. Chest radiography was performed. Prior to the initiation of antimicrobial treatment, blood specimens were collected for a complete blood count, culture, serologic investigation, and examination for parasites. Results were returned to clinicians as available, and patient management was performed according to the local standard of care. Information regarding treatment was captured upon discharge from the hospital or death; discharged patients were scheduled for a follow-up visit 4–6 weeks after hospital admission for collection of convalescent-phase serum samples.

Laboratory Methods

Serum samples collected for Q fever, SFGR, and TGR testing were sent to the Rickettsial Zoonoses Branch of the US Centers for Disease Control and Prevention (CDC). For Q fever, convalescent-phase serum samples were screened using *C. burnetii* immunoglobulin (Ig) G enzyme-linked immunosorbent assay (ELISA) against Phase II antigen (Inverness Medical Innovations). For samples that were either positive or equivocal by ELISA, paired serum samples were tested by indirect immunofluorescence antibody (IFA) IgG assay to *C. burnetii* (Nine Mile strain) Phase I and Phase II antigens. A fourfold or greater increase in IFA reciprocal titer to Phase II antigen defined acute Q fever; titer ≥1000 to Phase I antigen or ≥64 to Phase II antigen on either sample defined Q fever exposure among those serum samples not meeting the case definition for acute Q fever.

Serum samples were tested for SFGR and TGR by IgG IFA to *R. conorii* (Moroccan strain) and to *R. typhi* (Wilmington strain), respectively. Among paired serum samples, a fourfold or greater increase in IFA titer to *R. conorii* and *R. typhi* defined acute SFGR and TGR, respectively; among single serum samples and paired serum samples not meeting the case definitions for acute SFGR or TGR, titer to *R. conorii* or *R. typhi* ≥64 defined SFGR or TGR exposure, respectively. Laboratory methods for other examinations have been previously described [18–22].

Statistical Analysis

Data were entered using Cardiff Teleform 9.0 (Cardiff) and analyzed using Stata software, version 11 (StataCorp). Participants' village of residence was classified as urban or rural based on 2002 national census data [23]. We classified the study period into wet and dry intervals using rainfall data from the Kilimanjaro Region (personal communication, H. Pierre Noel, TPC) to explore seasonal effects. We used locally validated [24] and established [25] reference ranges for adult (≥18 years) and pediatric (<18 years) hematologic data, respectively. For continuous data, we used Mann-Whitney *U* tests; for categorical data, we used Pearson's χ^2 tests or 2-sided Fisher's exact tests and Cochran-Mantel-Haenszel tests. We performed logistic regression analysis to identify predictors of acute Q fever, including any variable significant to the $P < .10$ level in univariate analysis. Because the prevalence of simultaneous infections was statistically significantly higher among those with SFGR, compared with those without SFGR, we tested for differences in demographic characteristics between these 2 groups.

Research Ethics

This study was approved by the KCMC Research Ethics Committee, the Tanzania National Institutes for Medical Research, and Institutional Review Boards at Duke University Medical Center and the CDC. Informed consent was provided by all patients; a parent or legal guardian provided consent for patients <18 years of age.

RESULTS

In this study, 403 adults and adolescents and 467 infants and children were enrolled. Participants' characteristics have been

described elsewhere [18, 19]. Serum samples were tested for Q fever, SFGR, and TGR among participants with samples available. There were no differences in demographic characteristics between the overall cohort and the subgroup who were tested for the infections.

Acute Q Fever

Among enrollees, serum samples were tested for acute Q fever among 215 (53.2%) adult and adolescent patients and 268 (57.4%) pediatric patients. Twenty-four (5.0%) patients had results suggestive of acute Q fever, including 17 (7.9%) adults and adolescents and 7 (2.6%) infants and children (Table 1).

The median (range) age for patients with acute Q fever was 25.5 (0.7–72.7) years, compared with 7.3 (0.2–84.6) years for those without acute Q fever ($P = .009$). Patients ≥ 18 years of age were more likely to have acute Q fever than were their younger counterparts (odds ratio [OR], 3.0; $P = .009$). Patients ≥ 18 years of age with acute Q fever were more likely to live in urban areas than were those <18 years of age (OR, 3.9; $P = .031$). Table 2 compares demographic and clinical characteristics of patients with and patients without acute Q fever. When characteristics were examined by multivariable analysis, leukopenia (adjusted OR, 4.2; $P = .025$) was associated with acute Q fever.

Acute Q fever was not clinically diagnosed in any patient; the most common diagnoses among individuals with subsequently identified cases of acute Q fever were malaria in 8 (33.3%) and pneumonia in 5 (20.8%). Eighteen (75.0%) patients with acute Q fever received antimicrobial agents, predominantly β-lactams, and 3 (16.7%) received an antimicrobial agent (chloramphenicol) active against *C. burnetii*.

Seven (41.2%) adults and adolescents and 1 (14.3%) child with acute Q fever also had human immunodeficiency virus (HIV) infection. HIV seropositivity was not more prevalent in patients with acute Q fever, compared with patients without acute Q fever ($P = .231$). The prevalence of simultaneous infections with other organisms among patients with acute Q fever did not differ from that among those without serologic evidence of acute Q fever (Table 2).

Table 1. Prevalence of Q Fever, Spotted Fever Group Rickettsiosis (SFGR), and Typhus Group Rickettsiosis (TGR) Among Febrile Inpatients, Northern Tanzania, 2007–2008

Variable	Adult and adolescent patients *n*/*N* (%)	Pediatric patients *n*/*N* (%)
Acute Q fever	17/215 (7.9)[a]	7/268 (2.6)
Q fever exposure	8/200 (4.0)	5/264 (1.9)
Acute SFGR	18/207 (8.7)	18/243 (7.4)
SFGR exposure	99/377 (26.3)	94/415 (22.7)
Acute TGR	2/207 (1.0)	0/243 (0.0)
TGR exposure	9/395 (2.3)	14/433 (3.2)

NOTE. Denominators represent total no. of patients with serologic test results for each infection or exposure.

[a] $P < .05$.

Q Fever Exposure

Thirteen (2.8%) patients had results suggestive of Q fever exposure; 8 (4.0%) of 200 adult and adolescent patients tested and 5 (1.9%) of 264 pediatric patients tested (Table 1). The median (range) age of patients exposed to Q fever was 23.4 (0.3–48.6) years. Nine (69.2%) patients were female, and 4 (33.3%), all of whom were adults, were seropositive for HIV.

Acute Spotted Fever Group Rickettsiosis

Among enrollees, serum samples from 207 (51.4%) adult and adolescent patients and 243 (52.0%) pediatric patients were tested for acute SFGR. Thirty-six (8.0%) patients had results suggestive of acute SFGR, including 18 (8.7%) adults and adolescents and 18 (7.4%) infants and children (Table 1).

The median (range) age of patients with acute SFGR was 14.6 (0.5–76.7) years, compared with 8.4 (0.2–84.6) years for those without acute SFGR ($P = .466$). Table 3 compares demographic and clinical characteristics of patients with and patients without acute SFGR.

Acute SFGR was not clinically diagnosed in any patient; the most common diagnoses among subsequently identified cases of acute SFGR were pneumonia in 14 (38.9%) and malaria in 12 (36.6%). Among patients with acute SFGR, 24 patients (66.7%) received antimicrobial agents, predominantly β-lactams and gentamicin, 5 (20.8%) of whom received an antimicrobial agent (chloramphenicol) that was active against SFGR.

Three (16.7%) adults and 2 (11.1%) children with acute SFGR also had HIV infection. HIV seropositivity was not more prevalent among patients with acute SFGR than it was among patients without acute SFGR. Among those with information available, no HIV-seropositive patient receiving trimethoprim-sulfamethoxazole prophylaxis had acute SFGR.

Ten (27.8%) patients with acute SFGR had evidence of simultaneous infection with 1 other organism, and 1 (2.8%) patient had evidence of infection with 2 other organisms (*Leptospira* and *Salmonella* Typhi) (Table 3). Compared with those patients without acute SFGR, those with acute SFGR were more likely to have serologic evidence of another bacterial zoonosis, defined as leptospirosis, acute Q fever, brucellosis, or acute TGR. The median (range) age among patients with acute SFGR and evidence of simultaneous infection was 39.6 (3.8–70.7) years, compared with 2.5 (0.5–76.7) years for patients with acute SFGR alone ($P = .001$). There were no differences in sex, rural residence, exposure during the rainy season, or educational attainment between those with and those without evidence of simultaneous infection.

Table 2. Presenting Features of Febrile Inpatients With and Without Acute Q Fever ($n = 483$), Northern Tanzania, 2007–2008

Variable	Acute Q fever ($n = 24$)	Negative for acute Q fever ($n = 459$)	OR (95% CI); P
Demographic characteristics			
Age, median (range) years	25.5 (0.7–72.7)	7.3 (0.2–84.6)	$P = .009$
Female sex	16/24 (66.7)	214/452 (47.4)	2.2 (.92–5.3); $P = .067$
Urban	13/20 (65.0)	213/405 (52.6)	1.7 (.65–4.3); $P = .278$
Greater than primary education[a]	2/17 (11.8)	57/197 (28.9)	0.33 (.07–1.5); $P = .129$
Onset after dry season[b]	16/24 (66.7)	203/459 (44.2)	2.7 (1.1–6.3); $P = .021$
Signs and symptoms			
Days ill prior to presentation, median (IQR) days	7.0 (3.5–17.5)	4.0 (3.0–10.0)	$P = .087$
Inpatient length of stay, median (IQR) days	4.5 (3.5–10.5)	7.0 (4.0–9.0)	$P = .475$
Temperature, median (IQR) °C	38.7 (38.2–39.1)	38.4 (38.0–39.1)	$P = .125$
Systemic			
Headache[a]	14/17 (82.4)	144/197 (73.1)	1.7 (.47–6.2); $P = .406$
Chronic fever	6/24 (25.0)	87/453 (19.2)	1.4 (.54–3.6); $P = .486$
Rigors[a]	10/17 (58.8)	143/196 (73.0)	0.53 (.19–1.5); $P = .215$
Lymphadenopathy	3/23 (13.0)	38/452 (8.4)	1.6 (.46–5.8); $P = .440$
Respiratory			
Cough	18/24 (75.0)	300/457 (65.7)	1.6 (.60–4.0); $P = .346$
Chronic cough[a]	6/17 (35.3)	30/196 (15.3)	3.0 (1.0–8.9); $P = .035$
Crepitations/crackles	14/23 (60.9)	195/451 (43.2)	2.0 (.86–4.8); $P = .097$
Breathing difficulties	10/24 (41.7)	156/459 (34.0)	1.4 (.60–3.2); $P = .441$
Gastrointestinal			
Jaundice	2/23 (8.7)	6/454 (1.3)	7.1 (1.3–37.9); $P = .007$
Abdominal tenderness[a]	4/17 (23.5)	22/196 (11.2)	2.4 (.72–8.2); $P = .138$
Vomiting	8/24 (33.3)	134/457 (29.3)	1.2 (.50–2.9); $P = .675$
Diarrhea	4/24 (16.7)	43/459 (20.5)	0.78 (.26–2.3); $P = .651$
Hepato- or splenomegaly	5/23 (21.7)	38/457 (8.3)	3.1 (1.1–8.8); $P = .028$
Laboratory findings[c]			
Anemia	14/23 (60.9)	154/450 (34.2)	3.0 (1.3–7.1); $P = .009$
Leukopenia	4/23 (17.4)	23/450 (5.1)	3.9 (1.2–12.5); $P = .013$
Thrombocytopenia	1/23 (4.4)	78/450 (17.3)	0.22 (.03–1.6); $P = .104$
HIV seropositive	8/23 (34.8)	108/464 (23.3)	1.7 (.70–4.1); $P = .231$
Evidence of other infection			
Bacterial zoonoses[d]	5/24[e] (20.8)	75/459 (16.3)	1.3 (.49–3.7); $P = .564$
Malaria	0/23 (0.0)	20/455 (4.4)	NA
Bloodstream infections	2/24[f] (8.3)	45/459[g] (9.8)	0.84 (.19–3.7); $P = .813$
Other infections[h]	1/24 (4.2)	6/459 (1.3)	3.3 (.38–28.6); $P = .254$
Chest radiograph findings			
Infiltrates[a]	9/15 (60.0)	33/140 (23.6)	4.9 (1.6–15.2); $P = .003$

NOTE. Data are proportion (%) of patients, unless otherwise indicated. CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; NA, not applicable.

[a] Data available for adult and adolescent patients only.

[b] Dry season defined as September–October 2007, February 2008, and June–August 2008.

[c] Reference ranges [24, 25] were as follows: Patients <1 year of age: (1) hemoglobin level, 8.1–13.2 g/dL; (2) leukocyte count, 5.0–17.3 × 10^9 cell/L; (3) lymphocyte count, 3.3–11.8 × 10^9 cell/L; and (4) platelet count, 25–708 × 10^9 cell/L. Patients 1–5 years of age: (1) hemoglobin level, 8.1–13.9 g/dL; (2) leukocyte count, 3.7–13.2 × 10^9 cell/L; (3) lymphocyte count, 2.0–8.4 × 10^9 cell/L; and (4) platelet count, 79–650 × 10^9 cell/L. Patients 6–12 years of age: (1) hemoglobin level, 10.3–14.7 g/dL; (2) leukocyte count, 3.7–9.1 × 10^9 cell/L; (3) lymphocyte count, 1.6–4.7 × 10^9 cell/L; and (4) platelet count, 94–530 × 10^9 cell/L. Patients 13–17 years of age: (1) hemoglobin level, 10.0–14.9 g/dL for females, 10.8–17.0 g/dL for males; (2) leukocyte count, 3.2–10.3 × 10^9 cell/L; (3) lymphocyte count, 1.4–4.2 × 10^9 cell/L; and (4) platelet count, 107–482 × 10^9 cell/L for females, 119–458 × 10^9 cell/L for males. Patients ≥18 years of age: (1) hemoglobin level, 11.1–15.7 g/dL for females, 13.7–17.7 g/dL for males; (2) leukocyte count, 3.0–7.9 × 10^9 cell/L; (3) lymphocyte count, 1.1–3.0 × 10^9 cell/L; and (4) platelet count, 150–395 × 10^9 cell/L.

[d] Includes spotted fever group rickettsiosis (SFGR), typhus group rickettsiosis, leptospirosis, and brucellosis.

[e] Serologic evidence for SFGR (4), brucellosis (1), and leptospirosis (1).

[f] Blood culture positive for nontuberculous mycobacteria (1) and *Salmonella* Typhi (1).

[g] Blood culture positive for *Salmonella* Typhi (18), *Streptococcus pneumoniae* (6), *Escherichia coli* (6), *Mycobacterium tuberculosis* (4), and other (14).

[h] Cryptococcal antigen positive.

Table 3. Presenting Features of Febrile Inpatients With and Without Spotted Fever Group Rickettsiosis (SFGR) (n = 450), Northern Tanzania, 2007–2008

Variable	Acute SFGR (n = 36)	Negative for acute SFGR (n = 414)	OR (95% CI); P
Demographic characteristics			
Age, median (range) years	14.6 (0.5–76.7)	8.4 (0.2–84.6)	P = .466
Female sex	17/36 (47.2)	202/414 (48.8)	0.94 (.47–1.9); P = .857
Urban	13/32 (40.6)	195/362 (53.9)	0.59 (.28–1.2); P = .151
Greater than primary education[a]	3/15 (16.7)	52/188 (27.7)	0.52 (.14–1.9); P = .315
Probable exposure during rainy season[b]	12/36 (33.3)	132/414 (31.9)	1.1 (.52–2.2); P = .858
Signs and symptoms			
Days ill prior to presentation, median (IQR) days	5.5 (3.0–7.5)	4.0 (3.0–10.0)	P = .609
Inpatient length of stay, median (IQR) days	5.0 (3.0–8.0)	7.0 (4.0–10.0)	P = .104
Temperature, median (IQR) °C	38.4 (38.0–39.2)	38.5 (38.0–39.1)	P = .910
Systemic			
Headache[a]	12/18 (66.7)	141/188 (75.0)	0.67 (.24–1.9); P = .441
Chronic fever	9/36 (25.0)	74/408 (18.1)	1.5 (.68–3.3); P = .312
Rigors[a]	12/18 (66.7)	114/161 (70.8)	0.76 (.27–2.2); P = .610
Lymphadenopathy	2/36 (5.6)	37/407 (9.1)	0.59 (.14–2.6); P = .474
Respiratory			
Cough	22/36 (61.1)	270/412 (65.5)	0.83 (.41–1.7); P = .594
Chronic cough[a]	3/18 (16.7)	30/187 (16.0)	1.05 (.28–3.9); P = .945
Crepitations/crackles	19/34 (55.9)	172/407 (42.3)	1.7 (.85–3.5); P = .124
Breathing difficulties	10/36 (27.8)	142/414 (34.3)	0.74 (.35–1.6); P = .428
Gastrointestinal			
Jaundice	0/36 (0.0)	8/408 (2.0)	NA
Abdominal tenderness[a]	1/17 (5.9)	25/188 (13.3)	0.41 (.05–3.2); P = .380
Vomiting	12/36 (33.3)	119/412 (28.9)	1.2 (.60–2.5); P = .574
Diarrhea	8/36 (22.2)	82/414 (19.8)	1.2 (.51–2.6); P = .729
Hepato- or splenomegaly	3/36 (8.3)	36/411 (8.8)	0.95 (.28–3.2); P = .981
Laboratory findings[c]			
Anemia	13/36 (36.1)	146/406 (36.0)	1.0 (.49–2.0); P = .986
Leukopenia	6/36 (16.7)	19/406 (4.7)	4.1 (1.5–11.1); P = .003
Lymphopenia	11/36 (30.6)	124/403 (30.8)	0.99 (.47–2.1); P = .979
Thrombocytopenia	8/36 (22.2)	67/406 (16.5)	1.4 (.63–3.3); P = .381
HIV seropositive	5/31 (13.9)	99/409 (24.2)	0.51 (.19–1.4); P = .161
Evidence of other infection			
Bacterial zoonoses[d]	10/36[e] (27.8)	62/414 (15.0)	2.2 (1.0–4.8); P = .045
Malaria	0/36 (0.0)	19/410 (4.6)	NA
Bloodstream infections	1/36[f] (2.8)	45/414[g] (10.9)	0.23 (.03–1.8); P = .125
Other infections[h]	1/36 (2.8)	5/414 (1.2)	2.3 (.26–20.6); P = .431

NOTE. Data are proportion (%) of patients, unless otherwise indicated. CI, confidence interval; HIV, human immunodeficiency virus; IQR, interquartile range; OR, odds ratio; NA, not applicable.

[a] Data available for adult and adolescent patients only.

[b] Rainy season defined as November–December 2007 and March–April 2008.

[c] Reference ranges [24, 25] were as follows: Patients <1 year of age: (1) hemoglobin level, 8.1–13.2 g/dL; (2) leukocyte count, 5.0–17.3 × 10^9 cell/L; (3) lymphocyte count, 3.3–11.8 × 10^9 cell/L; and (4) platelet count, 25–708 × 10^9 cell/L. Patients 1–5 years of age: (1) hemoglobin level, 8.1–13.9 g/dL; (2) leukocyte count, 3.7–13.2 × 10^9 cell/L; (3) lymphocyte count, 2.0–8.4 × 10^9 cell/L; and (4) platelet count, 79–650 × 10^9 cell/L. Patients 6–12 years of age: (1) hemoglobin level, 10.3–14.7 g/dL; (2) leukocyte count, 3.7–9.1 × 10^9 cell/L; (3) lymphocyte count, 1.6–4.7 × 10^9 cell/L; and (4) platelet count, 94–530 × 10^9 cell/L. Patients 13–17 years of age: (1) hemoglobin level, 10.0–14.9 g/dL for females, 10.8–17.0 g/dL for males; (2) leukocyte count, 3.2–10.3 × 10^9 cell/L; (3) lymphocyte count, 1.4–4.2 × 10^9 cell/L; and (4) platelet count, 107–482 × 10^9 cell/L for females, 119–458 × 10^9 cell/L for males. Patients ≥18 years of age: (1) hemoglobin level, 11.1–15.7 g/dL for females, 13.7–17.7 g/dL for males; (2) leukocyte count, 3.0–7.9 × 10^9 cell/L; (3) lymphocyte count, 1.1–3.0 × 10^9 cell/L; and (4) platelet count, 150–395 × 10^9 cell/L.

[d] Includes acute Q fever, chronic Q fever, leptospirosis, brucellosis, and typhus group rickettsiosis (TGR).

[e] Serologic evidence for leptospirosis (5), acute Q fever (4), brucellosis (3), and TGR (1).

[f] Blood cultures positive for *Salmonella* Typhi (1).

[g] Blood cultures positive for *Salmonella* Typhi (18), *Streptococcus pneumoniae* (6), *Escherichia coli* (6), *Mycobacterium tuberculosis* (4), and other (13).

[h] Cryptococcal antigen positive.

Typhus Group Rickettsiosis

Serum samples from 207 (51.4%) adult and adolescent patients and 243 (52.0%) pediatric patients were tested for acute TGR. Two (0.5%) adult patients had results suggestive of acute TGR (Table 1). Both patients had serologic evidence of simultaneous infections with HIV and brucellosis in one case and acute SFGR and leptospirosis in the other.

Spotted Fever Group and Typhus Group Rickettsiosis Exposure

Among those patients tested for SFGR and TGR exposure, 193 (24.4%) had results suggestive of SFGR exposure, including 99 (26.3%) of 377 adult and adolescent patients tested and 94 (22.7%) of 415 pediatric patients tested (Table 1). Reciprocal titers were 64 (frequency, 93; 48.2%), 128 (frequency, 52; 26.9%), 256 (frequency, 30; 15.5%), 512 (frequency, 11; 5.7%), 1024 (frequency, 4; 2.1%), 2048 (frequency, 2; 1.0%), and 4096 (frequency, 1; 0.5%).

Twenty-six (13.7%) patients with SFGR exposure had HIV infection, compared with 171 (29.0%) patients without evidence of SFGR exposure ($P < .001$). HIV-infected patients were less likely to have evidence of SFGR exposure (OR, 0.39; $P < .001$) than were those without HIV infection. Among HIV-infected adults and adolescents, the odds of SFGR exposure were 0.50 ($P = .201$) for patients receiving trimethoprim-sulfamethoxazole prophylaxis.

Twenty-three (2.8%) patients had results suggestive of TGR exposure, including 9 (2.3%) of 395 adult and adolescent patients tested and 14 (3.2%) of 433 pediatric patients tested (Table 1). Reciprocal titers were 64 (frequency, 10; 43.5%), 128 (frequency, 7; 30.4%), 256 (frequency, 3; 13.0%), 1024 (frequency, 1; 4.3%), 4096 (frequency, 1; 4.3%), and 16,384 (frequency, 1; 4.3%).

DISCUSSION

We present results from a prospective investigation of Q fever and rickettsial diseases as causes of acute febrile illness among hospitalized adult and pediatric patients in sub-Saharan Africa. We demonstrate that Q fever and SFGR, but not TGR, are common causes of febrile illness among inpatients in northern Tanzania and are likely to be endemic infections in this area. Despite their importance, these infections were difficult to recognize, and no patient was treated specifically for Q fever or SFGR. Our results suggest that greater awareness of and availability of diagnostic tests for Q fever and SFGR may improve patient outcomes in sub-Saharan Africa.

The prevalence of acute Q fever among adults and adolescents in our study was similar to that observed among febrile outpatients in Mali based on acute-phase serum samples alone [1]. The prevalence of acute SFGR was lower than that observed among febrile outpatients in Cameroon, although that study excluded patients with diagnoses of malaria or brucellosis [2]. The prevalence of TGR was low in our study, which was likely attributable to few risk factors being present in northern Tanzania [9, 26]. Evidence of Q fever and SFGR exposure also reinforces the endemicity of these infections. We identified no other comparable studies from sub-Saharan Africa reporting the prevalence of these diseases among febrile individuals.

Clinical characteristics of Q fever and SFGR in our study were nonspecific and did not clearly distinguish these infections from other etiologies for fever. Although acute Q fever typically presents as a nonspecific febrile illness, our findings suggest that clinical hepatitis may provide a useful clue [8]. Of the reported hematologic changes associated with acute SFGR [27], we found only leukopenia to be more common among patients with SFGR compared with those without SFGR. Our study did not systematically collect data on the presence of eschars, which are a common sign of acute SFGR reported among travelers but are less well examined in local populations [11, 28]. Among patients who were exposed to *C. burnetii*, 7 had a serologic picture that was consistent with chronic Q fever, although none had a murmur identified on cardiac auscultation or received a clinical diagnosis of endocarditis. Our study was not designed to comprehensively examine epidemiologic risk factors of Q fever and rickettsial diseases. However, we noticed a seasonal variation in Q fever onset that may be related to the livestock parturient season, as demonstrated in other studies, but we also noticed that males were not more likely than were females to have Q fever [8, 29–31]. We did not demonstrate an association between rural residence or rainy season and acute SFGR. Additional investigations are needed to risk-stratify febrile patients and implement public health control measures.

Given that clinical management algorithms and research focus predominantly on malaria and bacterial sepsis [32, 33] and that laboratory capacity may be lacking in low-resource settings, it is not surprising that Q fever and SFGR pose a diagnostic challenge. One consequence of Q fever and SFGR being undiagnosed is that few patients receive appropriate treatment. Although Q fever and SFGR infections are often self-limited, antimicrobial treatment is necessary to shorten fever duration and to prevent morbidity and mortality, particularly from chronic Q fever. It is notable that tetracyclines are readily available and are inexpensive in many low-resource settings.

Local availability of diagnostic tests using acute-phase serum samples would have a number of advantages. Not only could patients be appropriately managed but unnecessary use of antimalarial and broad-spectrum antibacterial therapy could also be avoided. Because we relied on patients to provide convalescent-phase serum samples to confirm a diagnosis, we could not investigate deaths due to Q fever and SFGR. Nucleic acid amplification methods would aid in single-sample diagnosis of Q fever and SFGR early after symptom onset and independent of antimicrobial treatment

[12, 34–37] but may not be suited to low-resource settings, where rapid diagnostic tests are desirable.

Although some investigators have suggested that Q fever may be an HIV-associated coinfection [38, 39], our results do not support such a relationship. Because our study was prospective, identified cases of acute Q fever, and was conducted in an area of high HIV infection and Q fever prevalence, it represents a more robust investigation of a relationship between HIV infection and Q fever than is found in seroprevalence or retrospective studies [38, 39]. This, combined with other studies [4, 40–42] that have indicated no increased incidence or severity of Q fever with HIV seropositivity, suggests that a strong relationship between HIV infection and Q fever is unlikely. However, it remains possible that a weak relationship exists between HIV infection and Q fever that we lacked the statistical power to detect. Furthermore, it is possible that a relationship could be masked by trimethoprim-sulfamethoxazole prophylaxis in HIV-infected persons or if the serologic assays used to diagnose Q fever may be less reliable in HIV-infected persons. Of interest, we note a protective effect of HIV against SFGR exposure that did not appear to be mediated by trimethoprim-sulfamethoxazole prophylaxis. Although this finding is not consistent with a seroprevalence study of SFGR and HIV infection in Gabon, a protective effect has been incidentally reported with rickettsialpox in the United States and scrub typhus in Southeast Asia [43–45]. The possible protective effect of HIV infection against SFGR merits further investigation.

A substantial proportion of patients with serologic evidence of SFGR in this study also had evidence of another zoonosis. Given similar epidemiologic risk factors for several zoonoses [46], it is plausible that simultaneous infection may occur [47, 48]. Alternatively, it is possible that apparently concurrent infections actually represent false-positive results attributable to antibody cross-reactions, nonspecific antibody immunoreactivity, or the timing of sample collection in disease course. Because we did not undertake confirmatory testing, we could not resolve these instances of apparent coinfection.

Our study had a number of limitations. Not all enrolled patients had serum samples available for all testing because of limited volumes of blood collected and the need for convalescent-phase serum samples to confirm a diagnosis. A lack of data on the prevalence of Q fever, SFGR, and TGR in northern Tanzania meant that establishing serologic criteria for diagnosis was challenging. We selected rigorous criteria to minimize shortcomings of specificity, but this approach may have underestimated prevalence. Our diagnostic test for SFGR was based on *R. conorii*, despite the fact that *R. africae* is likely to be a more important pathogen in Tanzania. Although there is extensive cross-reaction between *R. conorii* and *R. africae*, SFGR diagnosis may have been improved with an *R. africae*–based assay.

In conclusion, we demonstrate that Q fever and SFGR, but not TGR, are common causes of febrile illness in northern Tanzania and are likely to be endemic. Greater awareness among clinicians and the availability of a reliable single-sample diagnostic test would improve patient management, would likely result in better patient outcomes, and would assist with estimating the disease burden for these infections. Additional research is needed to identify locally important risk factors to design prevention strategies.

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