

Human Brucellosis in Rural Uganda: Clinical Manifestations, Diagnosis, and Comorbidities at Kabale Regional Referral Hospital, Kabale, Uganda

Kevin D. Dieckhaus^{1,a} and Peterson S. Kyebambe^{2,a}

¹Department of Medicine, University of Connecticut School of Medicine, Farmington; and ²China-Uganda Friendship Hospital, Naguru, Kampala

Background. Brucellosis is a zoonotic infection transmitted to humans through direct contact with infected animals, their products, or excreta such as urine or dung. Brucellosis is associated with significant morbidity in Southwestern Uganda, where cattle and goat rearing are a major economic industry. As in many settings in sub-Saharan Africa, diagnosis and management of brucellosis remain a challenge due to the presence of comorbidities and limitations in resources for diagnostic testing and therapy.

Methods. A chart review was conducted to characterize the clinical manifestations, diagnosis, comorbidities, and management of 101 patients treated for brucellosis at the Kabale Regional Referral Hospital from September 2002 to May 2010.

Results. Patients presented with substantial comorbidities. The most common manifestation of illness was osteoarticular, but disease manifestations were quite varied. A high rate of focal illness in this cohort (77%) was observed.

Conclusions. Clinicians in this setting should be cognizant of the varied presentations, comorbidities, and treatment options for this disease.

Keywords. brucellosis/complications; developing countries; global health; Uganda; zoonoses.

Brucellosis, caused by intracellular Gram-negative bacteria of the genus *Brucella*, is one of the most common zoonoses worldwide [1]. Transmission to humans most commonly occurs via consumption of insufficiently cooked meat or unpasteurized milk products. Transmission may also occur via direct contact with animals or animal secretions with breaks in the skin or via inhalation of aerosolized particles, which may occur in abattoirs or laboratories.

The annual worldwide incidence exceeds 500 000 cases per year, although it is likely underdiagnosed and underreported [2]. Brucellosis is most commonly identified in Mediterranean countries, India, the Balkans, the Middle East, Central and South America, and the Asian republics of the former Soviet Union. Disease due to *Brucella* spp is also encountered in sub-Saharan Africa, where clinical disease may coexist with or mimic other endemic illnesses such as malaria, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), and tuberculosis. One such country, Uganda, has an incidence reported as 0.9 per 100 000 population, although the true incidence may be up to 20 times the reported figure [3].

Contributing to the incidence in Uganda is endemic brucellosis in herd animals, with a prevalence as high as 55% in cattle herds [4] and 13%–43% in goat herds [5]. The potential for transmission to humans is compounded by informal milk processing, resulting in 92% of milk products passing to market unpasteurized [6]. As a consequence, *Brucella* has been identified in 12.6% to 29% of informally marketed milk in Uganda [7, 8]. The lack of herd vaccination and an informal system of milk distribution provides a ready source for *Brucella* exposure in Uganda.

Brucellosis may involve 1 or more organ systems, including musculoskeletal, hematopoietic, nervous, genitourinary, gastrointestinal, cardiovascular, hepatobiliary, pulmonary, ocular, or cutaneous, or it may manifest with nonspecific systemic symptoms or pyrexia [9]. Data on the manifestations of brucellosis is limited in sub-Saharan Africa, with one recent systemic review failing to reveal a single high-quality study from the region [10]. The purpose of the present study was to identify and report the epidemiologic and clinical features of human brucellosis identified at a regional referral hospital in rural southwestern Uganda.

MATERIALS AND METHODS

A single-center retrospective chart review was conducted at Kabale Regional Referral Hospital in Uganda. The study was approved by the Kabale Regional Referral Hospital and the Institutional Review Board at the University of Connecticut Health Center. The Kabale Regional Referral Hospital is located in the Kabale District of southwestern Uganda and is a 226-bed facility that frequently has a patient census in excess of bed capacity, with more than 12 000 inpatient admissions and

Received 6 June 2017; editorial decision 24 October 2017; accepted 26 October 2017.

^aK. D. D. and P. S. K. contributed equally to this work.

Correspondence: K. D. Dieckhaus, MD, FIDSA, Division of Infectious Diseases, UConn Health, 263 Farmington Avenue, Farmington, CT 06030-8076 (dieckhaus@uchc.edu).

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more than 82 000 outpatient visits per year [11]. It is located approximately 400 kilometers from the capital, Kampala, and is 1 of the 14 Regional Referral Hospitals in Uganda. The hospital serves a population of approximately 2 million people in its catchment area. It serves as the regional clinical referral hub for the Districts of Kanungu, Kisoro, and Rukungiri, some parts of Ntungamo, as well as serving people from parts of the neighboring countries of Rwanda and the Democratic Republic of Congo. Typical of many hospitals in rural sub-Saharan Africa, the site has limited diagnostic testing and therapeutic options.

A review of available hospital records from the general adult medical ward from September 28, 2002 through May 17, 2010 was performed. All records with a diagnosis indicating brucellosis on the discharge face sheet were selected for detailed chart audit. A standard case definition for brucellosis was established. This included a recorded discharge diagnosis of brucellosis, laboratory data demonstrating a *Brucella* agglutinin titer of $\geq 1:160$, and implementation of a treatment plan to complete an antibiotic treatment course specific to *Brucella* spp. *Brucella* antibody testing was performed using somatic antigens to *Brucella abortus* (Cypress Diagnostics, Lonadorp, Belgium).

Features of presenting complaints were obtained from available admission medical records. Manifestations of disease spectrum were then classified based upon the organ system involved including osteoarticular, neurologic, cardiovascular, hepatobiliary, gastrointestinal, respiratory, genitourinary, cutaneous, ocular, or nonfocal involvement, as noted by the treating physician. Charts were reviewed for additional comorbidities. Results of all available testing including radiology and serology were reviewed, including hepatitis B surface antigen, rapid plasma reagin (RPR), *Treponema pallidum* hemagglutination assay (TPHA), HIV antibody rapid test, HIV p24 antigen, Widal test, urinalyses, and cerebrospinal fluid analyses. Patient demographics, occupation, documented exposure to cattle or goats, urban or rural residence, and consumption of unboiled milk were identified, when available, through chart review. Furthermore, clinical presentations were compared in those with and without laboratory-confirmed coinfection with HIV. Human immunodeficiency virus infection was identified by either (1) a reported past medical history or (2) laboratory testing confirming a positive HIV antibody or p24 antigen.

Data were entered onsite into Microsoft Excel (2013) and imported into IBM SPSS Statistics for Windows, version 22.0. (IBM Corp, Armonk, NY). For measures of a continuous nature, sample sizes, means, medians, and standard deviations were produced. For nominal measures, sample sizes and percentages were produced. Relationships between variables were evaluated using χ^2 or Student's *t* test as appropriate.

RESULTS

Patient Demographics

Two hundred forty-six chart audits were performed. One hundred twenty-eight (52%) did not meet the required laboratory

definition, and 17 (7%) were not prescribed antimicrobial therapy directed at *Brucella* at time of hospital discharge. Of these, 6 had inadequate documentation, and 11 had alternative diagnoses established in lieu of brucellosis including hepatitis (1), pelvic inflammatory disease (1), tuberculosis (1), urinary tract infection (1), and syphilis ([7] 4 of which were neurosyphilis). One hundred one patients were identified who met the strict case definition of brucellosis.

Of the 101 patients with who met the strict case definition, the mean age was 44.7 years (range, 13–90) and 55 (54%) were male. There were no age differences between male and females. Occupational history was obtained in 65 (64%), 58 (90%) of whom were noted to be peasants or peasant farmers. Thirty-three patients (33%) were identified as having direct contact with cattle, and 6 patients (6%) were identified as having direct contact with goats. Four patients (4%) reported direct exposure to both goats and cattle. Four patients (4%) reported unpasteurized milk consumption.

Comorbidities were identified in 45 patients (45%). Fourteen patients (14%) had multiple comorbidities (Table 1). Human immunodeficiency virus coinfection with *Brucella* occurred in 16 patients (16%). Syphilis coinfection occurred in 12 patients (12%), and tuberculosis occurred in 3 patients (3%). Other comorbidities were identified in smaller numbers.

Patient Presentations

Patients presented with a wide variety of initial symptoms (Table 2). The most common complaints were osteoarticular pain ($n = 46$, 46%), fever ($n = 36$, 36%), abdominal pain ($n = 31$, 31%), cough ($n = 28$, 28%), anorexia ($n = 26$, 26%), and headache ($n = 23$, 23%). Of those with osteoarticular complaints, 23 (50%) noted pain in the lower back, 14 (30%) noted pain in the sacroiliac region, 19 (41%) noted pain in other specific

Table 1. Comorbidities Among the Study Cohort^a

Comorbidities	Patients (%)
Any comorbidity	45 (45)
≥ 2 comorbidities	14 (14)
Syphilis	12 (12)
HIV/AIDS	16 (16)
Alcohol abuse	6 (6)
Cryptosporidium	4 (4)
Diabetes	3 (3)
Hypertension	3 (3)
Tuberculosis	3 (3)
Congestive cardiac failure	2 (2)
Epilepsy	2 (2)
Hepatitis B	2 (2)
Reactive arthritis	2 (2)

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

^aOne each (1%) of bipolar disorder, chlamydia, cryptococcal meningitis, coronary artery disease, malignancy, orthopedic injury, rheumatic heart disease, and urinary tract infection.

Table 2. Presenting Symptoms

Symptom	Number (%)
Osteoarticular pain	46 (46)
Lower back	23 (50)
Sacroiliac	14 (30)
Knees/legs	3 (7)
Shoulders	1 (2)
Hip	1 (2)
Multiple locations	20 (44)
Fever	36 (36)
Abdominal pain	31 (31)
Cough	28 (28)
Anorexia	26 (26)
Headache	23 (23)
Palpitations	16 (16)
Emesis	14 (14)
Cognitive difficulty	8 (8)
Constipation	8 (8)
Diarrhea	8 (8)
Skin changes	7 (7)

locations including hip, knee, shoulder, and 20 (44%) noted pain in more than 1 location.

Among the classified clinical syndromes, skeletal manifestations were most commonly identified, occurring in 35 (35%) of all patients, followed by nonfocal febrile illness (23%), central nervous system (19%), hepatobiliary (8%), respiratory (6%), cardiovascular (5%), gastrointestinal (2%), and genitourinary (2%) manifestations. There were no statistically significant differences in presentation between HIV-seropositive patients and HIV-seronegative/sero-unknown patients (Table 3).

Laboratory Findings

Brucella agglutination testing was available for all cases of confirmed *Brucella*. The mean titer was 1:234 ± 142, range 1:160–1:1280, with 64% of cases presenting with a titer of 1:160. Bacteriologic cultures were not available due to inherent laboratory biohazard risks and resource constraints.

Table 3. Clinical Syndromes

Clinical Syndrome	HIV Negative or Unknown		HIV Positive ^a	
	N (%)	N (%)	N (%)	N (%)
Skeletal	35 (35)	4 (25)	3 (19)	5 (31)
Nonfocal/FUO	23 (23)	3 (19)	2 (13)	2 (13)
Central Nervous System	19 (19)	2 (13)	0	0
Hepatobiliary	8 (8)	0	0	0
Respiratory	6 (7)	0	0	0
Cardiovascular	5 (5)	0	0	0
Gastrointestinal	2 (2)	0	0	0
Genitourinary	2 (2)	0	0	0
Cutaneous	1 (1)	1 (6)	0	0
Ocular	0	0	0	0

Abbreviations: FUO, fever of unknown origin; HIV, human immunodeficiency virus; NS, not significant.

^aP = NS for all values between HIV positives and HIV negative/unknowns using Bonferroni correction.

Other laboratory data were obtained in 65 patients (80%) (Table 4). A leukocyte count was obtained on 31 patients (31%) identifying neutropenia in 23% of patients and leukocytosis in 13% of patients. The mean total leukocyte count was 6.3×10^3 cells/mm³ (range, 3.2–16.2). Erythrocyte sedimentation rate was obtained in 31 patients (38%) with a mean of 73.8 mm/hour (range, 14–126 mm/hour).

Pre-existing HIV positivity was noted in 16 patients (16%), with 11 patients (11%) aware of serostatus at presentation, and an additional 5 patients were diagnosed during the course of hospitalization. Of the newly diagnosed HIV⁺ patients, antibody seropositivity was present in 2 patients, and 3 had a positive p24 antigen consistent with acute HIV infection. CD4 count was obtained in 4 HIV-infected patients (25%), with a mean of 315 cells/mm³ (range, 28–504). Fifty-eight patients (64%) were tested for syphilis, typically with a screening RPR and confirmatory TPHA, 12 (20%) of whom tested positive.

Treatment and Outcomes

Prescribed treatment courses were characterized by specific agents administered and by number of antibiotics with anti-*Brucella* activity prescribed. Ninety-seven patients (96%) were treated with both doxycycline and an aminoglycoside, with gentamicin used in 8 (8%) and streptomycin in 92 (91%). Trimethoprim/sulfamethoxazole (TMP/SMX) was used in 11 cases (11%), quinolones were used in 21 cases (21%), ceftriaxone was used in 4 cases (4%), and rifampin was used in 1 case (1%) (Figure 1). Twenty-eight patients (28%) received 3 antibiotic regimens, and 3 patients (3%) received 4 antibiotic regimens. All patients had treatment courses planned for 6 weeks, except 1 who was treated for 20 weeks [12].

Six deaths (6%) were recorded during patients' hospitalizations (3 with neurologic, 2 with hepatobiliary, one with gastrointestinal disease), 2 patients (2%) were transferred to other facilities, and 93 patients (92%) were discharged from the hospital with plans to follow up in community health units or outpatient clinics. Follow-up and completion of the antibiotic course was unable to be

Table 4. Laboratory Findings

Laboratory Finding	N (%)	Mean [Range]/N (%) Positive
WBC	31 (31)	6.3 [3.2–16.2]
<4000 cells/mcL	7 (23)	
4000–11 000 cells/mcL	20 (65)	
>11 000 cells/mcL	4 (13)	
ESR	24 (24)	73.8 [14–126]
>30 mm/hour	18 (75)	
Hemoglobin	16 (16)	10.1 [5.2–16.2]
<12 mg/dL	11 (69)	
CD4 count	4 (25)	315 [28–504]
Syphilis serology	58 (57)	12 positive (20)
Blood smear (malaria)	18 (18)	1 positive (6)
<i>Brucella</i> agglutinin titer	101 (100)	1:234 [1:160–1:1280]

Abbreviations: ESR, erythrocyte sedimentation rate; WBC, white blood cells.

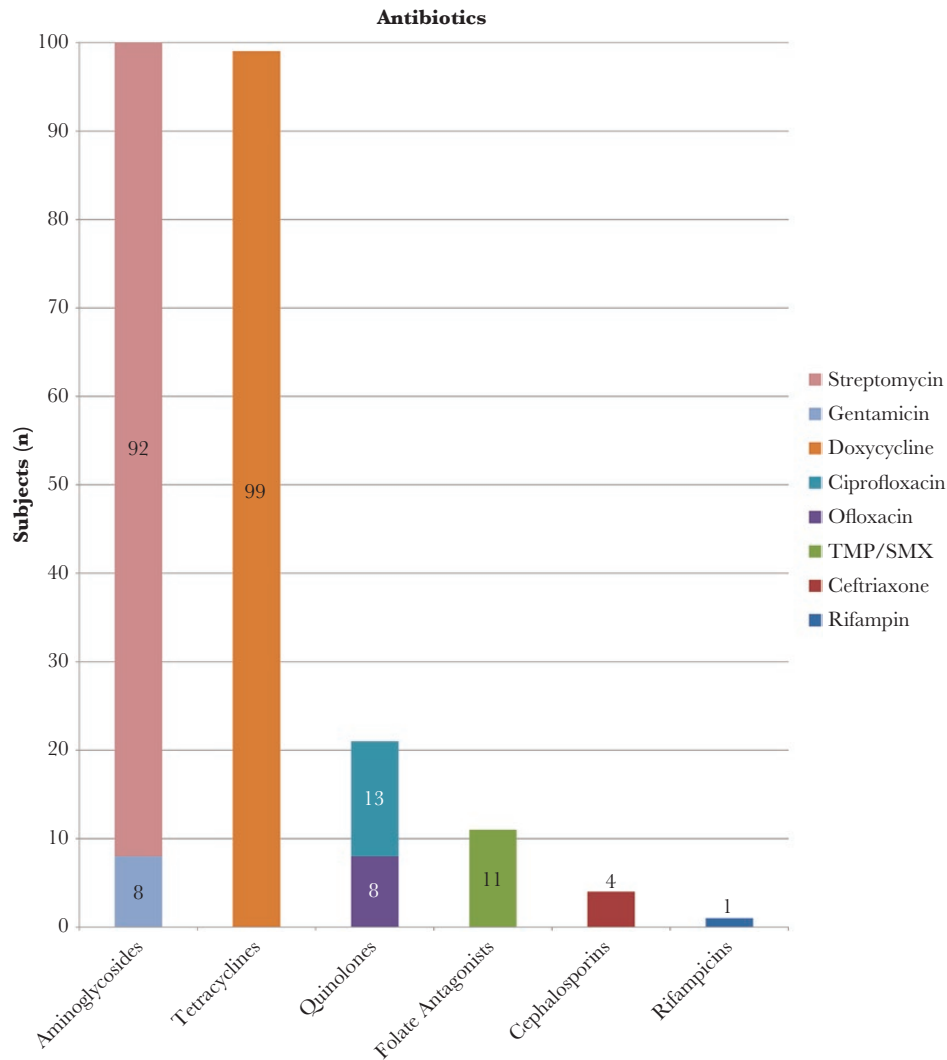


Figure 1. Antibiotic regimens. TMP/SMX, trimethoprim/sulfamethoxazole.

determined in this cohort. Improvement in clinical status was noted in 73 patients (72%) at the time of discharge, and the clinical status of 21 patients (21%) was recorded as not changed or unknown.

DISCUSSION

Brucellosis remains an important zoonotic illness in developing countries, and it continues to have a significant impact on patient morbidity in the Kabale District (Kigezi region) of Uganda. Recognition and clinical management of disease due to *Brucella* spp may be challenging in rural African settings due to other concurrent comorbidities and limitations of diagnostic and therapeutic options. *Brucella abortus* has traditionally been considered the primary agent of human brucellosis in Uganda [13]. However, *Brucella melitensis* is also known to be prevalent in goats in Uganda, with 10% of goats and 43% of goat herds affected [5], thus also posing a potential risk to humans.

Limitations in medical infrastructure and social challenges common to sub-Saharan Africa have been shown to lead to

delays in diagnosis of brucellosis in other African cohorts [14]. Symptoms are classically protean in presentation, consisting most classically of joint pain, fever, weakness, diaphoresis, and lower back pain [15]. Symptoms may overlap with other highly endemic illnesses such as malaria, HIV/AIDS, and tuberculosis, which can make the clinical diagnosis challenging. Infectious comorbidities including syphilis, HIV/AIDS, malaria, and tuberculosis were commonly identified in this cohort of patients in rural Uganda.

Physical examination may be nonspecific and may reveal hepatomegaly, splenomegaly, and lymphadenopathy [16]. *Brucella* can affect nearly every organ system [10], although it involves the osteoarticular system most commonly [17]. Consistent with prior studies, the most common organ system involved in our overall patient population was osteoarticular (35%). In our cohort, 45% had concomitant comorbidities, likely increasing the difficulty in arriving at a diagnosis. Unlike other studies that report the prevalence of focal findings ranging between 27.7% and 43.2% [15, 18], the presence of focal

findings was much higher in our study at 77%. It is likely that additional cases of brucellosis infection resulting in nonfocal, systemic, or febrile illness are present in the region but are either not recognized or are misclassified as being due to other endemic infectious illnesses.

Despite *Brucella* spp having a predilection for the reticulo-endothelial system, suggesting that immunodeficiency secondary to HIV might lead to altered clinical manifestations, prior studies of HIV-positive patients with brucellosis revealed no significant differences in the clinical presentation of the disease compared with HIV-seronegative patients [19]. The present evaluation is consistent with prior studies and did not identify any significant differences in the clinical presentation of brucellosis in HIV-seropositive patients compared with seronegative patients.

Diagnostic testing may be limited to serum antibody testing in the rural sub-Saharan African setting. The present study identified *Brucella* infection on the basis of serological tests, but these are incapable of distinguishing infection with *B abortus* from that of *B melitensis*. Bacteriologic culture, polymerase chain reaction, the Rose Bengal plate agglutination test, and enzyme-linked immunosorbent assay were not available and are often limited in the rural African setting. Serum antibody testing using the serum agglutination testing is most effective when using a definition of a 4-fold or greater rise in *Brucella* agglutination titer between acute- and convalescent-phase serum specimens obtained ≥ 2 weeks apart [20]; however, this approach is not practical in many settings in sub-Saharan Africa due to difficulties in obtaining laboratory studies and limitations in patient follow up. Antibodies at a single time point may be affected by a high rate of background exposure in endemic settings and has been noted to be positive in 11% of residents of another area of western Uganda [8]. False-positive *Brucella* antibody test results can also be caused by cross-reacting antibodies to *Escherichia coli* O157, *Francisella tularensis*, *Moraxella phenylpyruvica*, *Yersinia enterocolitica*, certain *Salmonella* serotypes, and from persons vaccinated against *Vibrio cholera* [21]. Serial dilutions evaluating for a prozone phenomenon are not routinely performed, and thus testing may fail to identify symptomatic patients with very high titers of antibody. A high baseline prevalence of antibody requires a titer of at least 1:160 in endemic areas to rule out low-level background positivity in symptomatic patients [22, 23].

Given the resource limitation of resources available at Kabale Regional Referral Hospital, supporting laboratory data with brucellosis was incomplete. All 101 patients with confirmed brucellosis had a study-defined titer of at least 1:160 (median, 1:160; range, 1:160–1:1280) and a clinical presentation consistent with brucellosis. Of the patients with further serological studies, the most common abnormalities were an elevated

erythrocyte sedimentation rate and anemia, which is consistent with prior literature [15].

Management of brucellosis is complicated by limited health infrastructure, limited antibiotic availability, requirement of parenteral administration of aminoglycosides, and the concern for development of resistance to streptomycin and/or rifampin in cases where infection with *Mycobacterium tuberculosis* may be present. Brucellosis typically requires prolonged therapy with at least 2 agents to which it is susceptible. Antibiotics active against *Brucella* spp include tetracycline, gentamicin, streptomycin, ceftriaxone, ciprofloxacin, levofloxacin, ofloxacin, and rifampin [24]. Treatment typically consists of a tetracycline plus rifampin or tetracycline plus aminoglycoside for at least 6 weeks [25]. The Uganda clinical guidelines [26] recommend that initial therapy consist of a course doxycycline for 6 weeks combined with an aminoglycoside or ciprofloxacin for 2 weeks, or treatment with TMP/SMX for 6 weeks combined with gentamicin for 2 weeks. Rifampin, ceftriaxone, and ofloxacin may be effective [16]. The addition of a third agent is recommended in some combinations and in neurologic disease [12, 16]. In this cohort, 97 (96%) met the national treatment standard, typically doxycycline combined with an aminoglycoside. Use of additional agents including TMP/SMX, ceftriaxone, rifampin, and fluoroquinolones (ciprofloxacin, ofloxacin) were frequently added to this core regimen. Thirty-one patients (31%) had 3 or more antibiotics prescribed. Duration of antimicrobial therapy was typically 6 weeks, but it was extended if there was an incomplete clinical response. The longest duration of treatment noted at this hospital was 20 weeks [12].

Contact with animals and animal products are common in this cohort. Rural patients are likely to be either raising livestock or to come in contact with livestock given the pastoral grazing practice in this region of Uganda. Seroprevalence for brucellosis in local cattle herds ranging between 55% and 100% provides a ready zoonotic reservoir for disease transmission [4, 27]. Given a high prevalence (92%) of unpasteurized milk reaching the consumer in this region, it is likely that unboiled milk consumption may also play a significant mode of transmission, and this is likely underreported in these rural patients [6]. A systematic practice of cattle herd vaccination and milk pasteurization could potentially have a large impact on the public health burden caused by this illness.

There are several limitations to this study to be noted. The study was conducted at a single clinical site and thus may not be reflective of other geographic locales. Medical documentation was sparse in this cohort, and thus many subjects had limited data documented in the available record. This may lead to potential skewing of data towards those with higher acuity levels who required more aggressive medical and laboratory evaluation that is recorded and thus available for analysis. The antibody testing criteria for study inclusion, a value of 1:160 or greater at a single time point, is imperfect. Titers

may lead to false positives in a region with high background endemicity for brucellosis and coexisting comorbid illnesses. False negatives may be seen in patients who may have acute brucellosis but have not yet mounted a significant antibody titer at the time of phlebotomy, those with chronic brucellosis, immunologic impairment, or those with the prozone phenomenon [12, 16].

CONCLUSIONS

In conclusion, brucellosis remains an important cause of morbidity and mortality in southwestern Uganda. Clinicians in this setting should be aware of brucellosis as a cause of disease in this setting that may occur in isolation or in conjunction with other comorbidities. Recognition of clinical disease due to *Brucella* spp remains challenging given a high background rate of exposure and low-level antibody positivity, limited testing modalities, and the protean nature of the illness. Clinical management may also present challenges due to a high frequency of confounding comorbidities and limited therapeutic options in sub-Saharan Africa.

Acknowledgments

We acknowledge Drs. Vishal Joshi, Ankita Kadakia, and Benjamin Busman, who contributed to project operations, chart review, and data management.

Potential conflicts of interest. All authors: No reported conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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