Brucellosis in low-income and middle-income countries

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Purpose of review
Human brucellosis is a neglected, underrecognized infection of widespread geographic distribution. It causes acute febrile illness and a potentially debilitating chronic infection in humans, and livestock infection has substantial socioeconomic impact. This review describes new information regarding the epidemiology of brucellosis in the developing world and advances in diagnosis and treatment.

Recent findings
The highest recorded incidence of human brucellosis occurs in the Middle East and Central Asia. Fever etiology studies demonstrate brucellosis as a cause of undifferentiated febrile illness in the developing world. Brucellosis is a rare cause of fever among returning travelers, but is more common among travelers returning from the Middle East and North Africa. Sensitive and specific rapid diagnostic tests appropriate for resource-limited settings have been validated. Randomized controlled trials demonstrate that optimal treatment for human brucellosis consists of doxycycline and an aminoglycoside. Decreasing the burden of human brucellosis requires control of animal brucellosis, but evidence to inform the design of control programs in the developing world is needed.

Summary
Brucellosis causes substantial morbidity in human and animal populations. While improvements in diagnostic options for resource-limited settings and stronger evidence for optimal therapy should enhance identification and treatment of human brucellosis, prevention of human disease through control in animals remains paramount.

Keywords
brucellosis, epidemiology, neglected diseases, zoonoses

INTRODUCTION

As a geographically widespread bacterial zoonotic infection that causes substantial morbidity in both human and livestock populations, brucellosis is a disease of global importance [1]. Brucellosis is caused by *Brucella* species, which are small, Gram-negative, unencapsulated coccobacilli first isolated by Bruce in 1887 [2]. Four species, *B. melitensis*, *B. abortus*, *B. suis,* and *B. canis*, are the main pathogens of human and livestock populations [3]. Similar to tuberculosis, brucellosis is a granulomatous disease that can affect any organ and requires long-term chemotherapeutics to achieve clinical cure. Infections with *Brucella* species are rarely fatal [4], but nonetheless can cause substantial morbidity in humans. Clinical presentation varies from an acute, nonspecific febrile illness to chronic, debilitating forms whose features may include osteoarticular involvement and neuropsychiatric abnormalities [4,5▪▪]. Although illnesses among returning travelers and among deployed military personnel underscore the relevance of brucellosis to practitioners in the developed world [6,7], the impacts of brucellosis are incurred largely in the developing world [8].

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KEY POINTS

- Brucellosis is a neglected, underrecognized zoonotic infection in the developing world that can present as an acute undifferentiated fever syndrome and progress to chronic, focal forms.
- Brucellosis requires a unique treatment regimen not likely to be addressed by empiric regimens for other causes of acute undifferentiated fever syndromes: 6 weeks of doxycycline with a parenteral aminoglycoside administered concurrently during the first 1–2 weeks of therapy is the most effective regimen.
- The effects of brucellosis in human populations include the direct, sometimes debilitating morbidity from infection as well as substantial socioeconomic impact mediated by abortion and reduced productivity among livestock.
- Control of livestock brucellosis is the most effective means of reducing human brucellosis burden, but more research, including cost-effectiveness studies, is needed to demonstrate optimal control strategies in the developing world.

Fully capturing these impacts, however, is constrained by underrecognition on the part of healthcare providers, limited availability of appropriate laboratory diagnostics, and healthcare seeking behaviors and access among those most at risk for brucellosis.

With the exception of infections acquired by laboratory personnel [9▪] and the potential use of *Brucella* as a bioterrorism agent [10], human infection is acquired through contact, ingestion, or inhalation of organisms from infected animals, principally cattle, goats, and sheep. Seroprevalence studies conducted throughout the developing world demonstrate that when one looks, *Brucella* infection is frequently found among sampled livestock populations [11–15,16▪▪].

In addition to transmitting the infection to humans, animal brucellosis impacts livestock productivity, which can have socioeconomic and indirect health effects on humans, especially vulnerable livestock-keeping populations in resource-limited settings that rely on livestock for food security and income [17,18]. The impacts of brucellosis in livestock include abortion and death as well as decreased milk production and reduced reproductive efficiency [13,19–21]. Control of brucellosis is accordingly a target for economic development set forth by the WHO and development agencies [22].

This review focuses on the epidemiology of brucellosis in low- and middle-income countries (LMICs). Recent data on brucellosis in returning travelers and advances in diagnosis, therapy, and control are also provided. For information on the immunology and pathogenesis of *Brucella* species infection, the reader is directed to other reviews [23–25].

EPIDEMIOLOGY OF HUMAN BRUCELLOSIS

Assessing the burden of disease due to human brucellosis – incidence, attributed disability, and case fatality rates – is challenging. Although prospective population-based surveillance of brucellosis has been conducted in several countries [26–30], none of these studies utilized active disease surveillance to estimate incidence and none reported mortality. Estimates of disability and mortality are also hindered by the proportion of cases presenting with febrile illness in brucellosis endemic areas that may be misdiagnosed [27], and by a limited understanding of the proportion of infections that progress to chronic disease. The majority of human brucellosis illnesses in endemic areas are attributed to *B. melitensis*, but disease due to other species may be underappreciated [31,32].

These limitations notwithstanding, it is well established that brucellosis is endemic throughout the Mediterranean rim and the Middle East, with incidence estimates more than 100 cases per 100 000 person-years in Iraq, Jordan, and Saudi Arabia [33–35]. Recent publications indicate that the incidence of brucellosis in central Asian countries, such as Kyrgyzstan and Azerbaijan, is similarly high [36,37].

The incidence data we present below draw largely from a systematic review of brucellosis, which provides a concise presentation of incidence and seroprevalence studies conducted throughout the world since 1990 [38▪▪]. Given the difficulties of establishing a laboratory-confirmed case and the poor quality of data from sub-Saharan Africa, the only incidence data from sub-Saharan Africa included in this systematic review were from Chad [39]. From this study in Chad, an incidence of 35 cases per 100 000 person-years was derived from a seroprevalence of 3.8%, assuming a fixed proportion of clinical cases among seropositives (10%) and a fixed duration of seropositivity [38▪▪]. Robust disease incidence data are lacking in other regions of the world as well: whereas seroprevalence studies in China and Korea indicate brucellosis is endemic in some regions [40–42], we are unaware of incidence estimates in East Asia.

As for Oceania, a study conducted in the Polynesian islands of Wallis and Futuna demonstrated *B. suis* incidence of 19 cases per 100 000 person-years attributed to the high prevalence of pig husbandry in these island cultures [31].

In the Western Hemisphere, brucellosis incidence in Mexico has been estimated at 25.7 cases per 100 000 person-years, compared to 0.02 cases per 100 000 person-years in the United States [43]. Of note, the rates of brucellosis in United States counties along the US–Mexico border were substantially higher at 0.18 cases per 100 000 person-years compared to nonborder regions of the United States. In Argentina, one study found an incidence of 12.8 per 100 000 person-years [44]. Elsewhere in Latin America, brucellosis is thought to be endemic [1,8].

Although a broader survey of brucellosis incidence in LMICs is lacking, several cohort studies conducted in resource-limited settings demonstrate brucellosis as a cause of acute febrile illness. A meta-analysis of cohort studies that identified causative pathogens of community-acquired bloodstream infections in Africa found that *Brucella* species accounted for 275 (5%) of 5578 bloodstream infections [45,46]. All 275 cases of *Brucella* bacteremia were derived from a hospital-based fever etiology study in Egypt, where *Brucella* was the second most common cause of bloodstream infection, behind *Salmonella enterica* serotype Typhi [46]. A hospital-based fever etiology study in northern Tanzania found 16 (3.5%) of 455 febrile hospital admissions met the US Centers for Disease Control and Prevention (CDC) confirmed case definition for acute brucellosis [47,48▪]. Although relatively few cases were identified, laboratory-confirmed brucellosis was a more common cause of fever in this cohort than laboratory-confirmed malaria (3.5 vs. 1.8%), and none of the 16 patients received a clinical diagnosis of brucellosis. A fever etiology study in northwestern Ethiopia also found a low proportion of febrile disease attributed to brucellosis, 17 (2.6%) of 653 patients [49]. A study in the Ecuadorian Amazon basin identified brucellosis as the cause of undifferentiated febrile illness in four (1.3%) of 304 patients [50]. In a systematic review of the etiology of fever of unknown origin (FUO) in children, 97 (10%) of 989 cases from the developing world were attributed to brucellosis, the most common infectious cause [51]. A prospective, single-center FUO study in Egyptian adults similarly found brucellosis to be the most common infectious cause [52].

Surveillance studies of ill travelers returning from developing countries indicate that brucellosis was a rare cause of illness [53–56]. However, among travelers returning from the Middle East and North Africa, brucellosis was the third most common cause of febrile illness [57▪]. Compared to nonexpatriate returning travelers, returning expatriates had an overall small, but significantly higher prevalence of brucellosis (2 per 1000 persons vs. 0.4 per 1000 persons, $P<0.01$) [6]. Brucellosis was first described in the context of recurrent fevers among British soldiers in Malta [2,58], and it remains an important consideration in the evaluation of ill military personnel deployed overseas [7].

As in high-income settings, the risk factors for human brucellosis in LMICs include ingestion of unpasteurized dairy products and exposure through direct contact with infected animal body fluids or tissues, especially the placenta from aborted animals [59–63]. This is reflected in a higher risk of disease in marginalized livestock-keeping communities, as well as veterinary and abattoir workers. However, there is also evidence from cities in sub-Saharan Africa that brucellosis is a cause of febrile illness in urban settings, linked to the sale and distribution of contaminated raw milk [48▪,64,65].

The case fatality rate for brucellosis has not been derived from prospective surveillance. However, data from retrospective cohorts would indicate that death from brucellosis occurs in less than 1% of cases [1,4]. Recently proposed disability weights estimate acute brucellosis at a level comparable to acute malaria, 0.190, and the estimated disability weight for chronic, localized brucellosis was 0.150, rendered similar to osteoarticular disease, a common form of focal brucellosis [5▪▪].

CLINICAL MANIFESTATIONS

Fever in brucellosis can be acute and associated with rigors or it can be chronic, low-grade, and relapsing. A systematic review gives a comprehensive assessment of the clinical manifestations of human brucellosis [5▪▪]. Arthralgia, myalgia, and back pain occur in 65, 47, and 45% of cases, respectively. Hepatomegaly, splenomegaly, and overt arthritis are seen in approximately 25%, respiratory involvement in 20%, and vertebral spondylitis in 12% of cases. Epididymo-orchitis is present in 10% of cases in men. Endocarditis and neuropsychiatric complications occur in 1 and 4% of cases, respectively. The most common neuropsychiatric manifestation is meningoencephalitis, often chronic, but other sequelae include cranial nerve deficits, seizure, and psychological disturbance. Of note, this systematic review did not find high-quality studies from sub-Saharan Africa, Latin America, or Asia to include in their meta-analysis. Whether disease manifestations might vary by region or by infecting *Brucella* species merits further investigation. For instance, whereas hematologic abnormalities such as anemia and leukopenia are common in Mediterranean populations, thrombocytopenia is fairly uncommon [66,67]; in contrast, over 40% of the brucellosis

cases in the northern Tanzania fever cohort had thrombocytopenia [48▪]. Compared to *B. melitensis* infections, *B. suis* appears to cause marked elevation in alanine aminotransferase [31] and *B. abortus* is thought to cause more mild disease [68]; but in general, data are limited regarding species-specific manifestations.

In Mediterranean populations, *Brucella* is a common cause of vertebral osteomyelitis, accounting for up to a quarter of all cases [69]. To distinguish *Brucella* vertebral osteomyelitis cases from *Mycobacterium tuberculosis* infection, clinicians must undertake thorough evaluations, including serologic testing for *Brucella* antibodies as well as sampling of the involved tissue when feasible. Radiographic features can help distinguish between these two granulomatous spine infections: intervertebral disc spaces are not typically involved in tubercular spine infections, whereas they are often narrowed in brucellar spine infections [70]. Conversely, the following findings are thought to be rare in brucellar cases: involvement of the posterior spinal elements and vertebral collapse (both findings are more suggestive of tubercular cases) as well as epidural abscess formation (more suggestive of pyogenic or tubercular spondylodiscitis) [70,71].

Studies of pregnancy loss show that although there is no significant linkage between prior brucellosis exposure and abortion [72], women diagnosed with acute or chronic brucellosis during pregnancy had a high prevalence of abortion, ranging from 14 to 43% [73].

CLINICAL DIAGNOSIS AND DIAGNOSTIC ADVANCES

Although brucellosis can present with signs and symptoms that may raise clinical suspicion, acute brucellosis is often difficult to distinguish from other febrile conditions, and delayed diagnosis is common. In one large series from a high-income setting, over a third of patients had symptoms for 1–3 months prior to diagnosis [74]. The same study found that a delay in diagnosis of more than 30 days was associated with increased risk of developing complicated focal forms of brucellosis, and patients with osteoarticular involvement often experience 6 months of symptoms prior to receiving the correct diagnosis [75]. In low-income settings in Tanzania, only 22% of patients with probable brucellosis reported to health facilities within 1 month, and 20% presented after 1 year of symptoms [76].

The US CDC confirmed case definition for human brucellosis requires a clinically compatible syndrome and either isolation of *Brucella* species from culture of clinical specimens or at least a four-fold rise in *Brucella* antibody titer [measured by standard agglutination test (SAT) or microagglutination test (MAT)] between acute and convalescent sera obtained at least 14 days apart [47]. The US CDC probable case definition requires a clinically compatible syndrome and one of the following: a single SAT or MAT antibody titer at least 1 : 160; detection by PCR of *Brucella* DNA in a clinical specimen; or an epidemiologic link to a confirmed case. Neither the US CDC nor WHO has a specific definition for chronic brucellosis [47,77]. Most experts would propose more than 12 months of symptoms [1] and a single SAT or MAT titer at least 1 : 160 [77], though false-negative SAT or MAT results do occur in chronic brucellosis [78].

Conventional blood culture methods using biphasic Ruiz-Castaneda bottles require 6 weeks of incubation and the diagnostic yield varies from 40–90% in acute cases to 5–20% in chronic cases [79]. Automated blood culture systems have a 5–10% higher recovery rate than biphasic methods, and the majority of isolates are recovered within 1 week [79]. Bone marrow culture, considered the gold standard, has 15–20% higher yield than peripheral blood culture [78,79]. Given the variable yield of culture, especially in subacute and chronic disease, serologic testing is often relied upon when brucellosis is suspected.

The Rose Bengal agglutination test has a sensitivity more than 90% in most studies [80–82]. It has served as a mainstay for screening in both human and animal populations, but it lacks specificity, so confirmatory testing of positive samples is required [82]. SAT and MAT remain the reference standards for serologic confirmation of brucellosis with a specificity of 99% for acute disease in endemic settings [82,83]. Commercial ELISAs for *Brucella* IgG and IgM are available, and studies indicate they are sensitive [84]. However, due to relatively low specificity of some ELISA tests, the US CDC recommends that they should not be used to confirm brucellosis cases [85]. The antigen cross-reactivity between *Brucella* species precludes speciation by serology. The exception is *B. canis*, which does not share cross-reacting antigens with other *Brucella* species [78], and therefore, when suspected, one must select serologic testing specific for *B. canis* antigens.

In recent years, considerable effort has been mobilized toward the development of rapid, reliable field diagnostic assays [86] and molecular diagnostic approaches. Lateral flow assays do not require extensive laboratory infrastructure or technical expertise, and compared to the standard of SAT and/or culture, the sensitivity and specificity were 92–95 and 97%, respectively, in endemic settings [87,88]. Rapid latex agglutination tests can also be useful in areas with

limited laboratory capacity, and one study using culture-confirmed cases and negative controls demonstrated a sensitivity of 89% and a specificity of 98% [89]. PCR was effectively employed to rapidly detect *Brucella* DNA in the blood of six suspected cases which all subsequently met confirmed case definitions [90], and multiplex assays can expedite the confirmation and speciation of *Brucella* isolated by culture [91,92]. A real-time PCR assay that rapidly and accurately distinguishes *Brucella* from *M. tuberculosis* in body fluid and tissue specimens holds promise for clinical use [93].

TREATMENT

Tetracyclines and a parenteral aminoglycoside or tetracyclines and rifampin are the regimens historically recommended by the WHO for treatment of human brucellosis [94▪▪]. Combination antibacterial therapy is imperative as single-drug therapy is associated with 2.5-fold increased risk of treatment failure [95]. In the past 10 years, several clinical trials comparing regimens for the treatment of brucellosis have been conducted [96–100], and two systematic reviews of therapy for brucellosis were published in 2012 [94▪▪,101]. These studies consistently demonstrate the following principles for brucellosis therapy: 6 weeks of doxycycline with 7 days of gentamicin is as effective as 6 weeks of doxycycline with 14 days of streptomycin [96,100,101]; doxycycline along with an aminoglycoside appears to be superior to doxycycline with rifampin, and has lower rates of minor adverse events than doxycycline–rifampin regimens [94▪▪,97]; rifampin along with a fluoroquinolone is less efficacious, but remains a viable third-line regimen [95,97]. Recommended agents to treat children include rifampin, aminoglycosides, and trimethoprim–sulfamethoxazole (Table 1) [1].

Based on meta-analyses of therapeutic trials, treatment failure or relapse is 5–7% for doxycycline–streptomycin regimens and 11–17% for doxycycline–rifampin [94▪▪,101]. In observational studies, a higher proportion of relapse has been noted among patients with osteoarticular disease [4], and some experts recommend a treatment duration of 8–12 weeks for vertebral spondylodiscitis [1,102].

Given the rates of treatment failure or relapse and the geographic and antimicrobial regimen overlap that exists between brucellosis and tuberculosis, antimicrobial resistance of *Brucella* species has received attention in recent years. Both in-vitro susceptibility studies [103,104,105▪] and molecular detection methods of resistance [106,107] performed on clinical isolates of *B. melitensis* have yet to demonstrate rifampin resistance and the minimum inhibitory concentrations for other agents remain reassuringly low.

CONTROL AND PREVENTION

Brucellosis control and prevention strategies aim to minimize disease impacts and reduce animal-to-human disease transmission [1,108].

Human vaccine against brucellosis has been employed in the past, but vaccines are not widely available and concerns exist about their safety [109]. Animal vaccination campaigns followed by compulsory test-and-slaughter programs have contributed to the elimination of *B. abortus* and *B. melitensis* in some developed countries, but successful campaigns have all been expensive, long, and difficult to implement [110▪▪]. For these reasons, elimination is likely infeasible in endemic LMICs [8,111]. In such settings, the implementation of effective test-and-slaughter policies is limited by the lack of resources to compensate farmers whose animals are slaughtered [111–113]). Test-and-slaughter policies can also paradoxically contribute to the spread of infection, when identified seropositive animals are sold instead of slaughtered [114].

Vaccination of animal populations can reduce animal infection prevalence and human disease risk. The most widely used vaccines, both live-attenuated, are B. *melitensis* Rev1 (Rev1), which is used in sheep and goats, and *B. abortus* S19 (S19), which is used in cattle. Both induce good protection but both can be abortifacient if administered during pregnancy; both also interfere with serological diagnostic testing, which is required when vaccination is combined with test-and-slaughter programs [111]. A 5-year pre- and postvaccine assessment of the Rev1 vaccine among small ruminant animals in Tajikstan showed an 80% reduction in herd prevalence in areas with high vaccine uptake, 40% reduction in prevalence in areas with low coverage, and no changes in the areas where no vaccination was undertaken [115▪▪]. Cost-effectiveness modeling of a 10-year mass-vaccination campaign using Rev1 vaccine for small ruminants and S19 vaccine for cattle in Mongolia estimated that a 52% reduction in transmission between animals could be achieved and a total of 49 027 disability-adjusted life years could be averted. In a scenario wherein costs were shared between public health and livestock sectors, this study indicates that livestock vaccination would be cost-effective and result in net economic benefit [17].

Although milk pasteurization is a more downstream control strategy, it can reduce *Brucella* transmission to humans. A study of bulk milk samples in Kampala, Uganda modeled a 47% risk reduction in

Table 1. Treatment of human brucellosis

	Antimicrobial agent	Comments
Recommended regimens	Doxycycline 100 mg p.o. b.i.d. for 6 weeks plus	Although randomized studies monitored for adverse reactions to aminoglycosides, aminoglycoside serum levels were not performed in most studies and rates of ototoxicity and nephrotoxicity were low
	(Gentamicin 5 mg/kg/day i.v./i.m. daily for 7–10 days) or (streptomycin 1 g i.m. daily for 14–21 days)	Pediatric dosing: doxycycline relatively contraindicated, gentamicin 5 mg/kg i.m./i.v. daily, streptomycin 20 mg/kg i.m. daily
	Doxycycline 100 mg p.o. b.i.d. for 6 weeks plus	Higher rates of composite (relapse or treatment failure) as well as higher rates of adverse events compared to doxycycline and an aminoglycoside
	Rifampin 600–900 mg p.o. daily for 6 weeks	Pediatric dosing: rifampin 15 mg/kg p.o. daily
Alternative agents	Ciprofloxacin 500 mg p.o. b.i.d. for 6 weeks or Ofloxacin 200–400 mg p.o. b.i.d.	
	Trimethoprim–sulfamethoxazole (160 mg/800 mg p.o. b.i.d. or 8 mg/kg/day trimethoprim component p.o. divided every 8 hours) for 6–8 weeks	Recommended for treatment of childhood brucellosis in conjunction with an aminoglycoside or rifampin Pediatric dosing: 8 mg/kg b.i.d. trimethoprim component

b.i.d., twice daily; i.m., intramuscularly; i.v., intravenously; p.o., by mouth. Data from [1,94▪▪].

human brucellosis if pasteurization centers could be incorporated into the urban milk production chain [65]. Infection risk among persons in frequent contact with potentially infected animals can also be reduced through personal hygiene measures and adoption of safe working practices, including use of protective clothing, disinfection of protective clothing, and disinfection of potentially infected implements and premises [1]. Such measures may be untenable in LMICs due to resource limitations and animal husbandry cultural traditions.

In resource-limited settings, the control of brucellosis in animal populations can achieve substantial health and economic benefits in both animal and human sectors [17,115▪▪]. Further studies to describe the reservoir dynamics of brucellosis in endemic countries and evaluate the cost-effectiveness of control efforts are needed to inform policymakers at all levels [110▪▪,116].

CONCLUSION

Brucellosis is widespread in LMICs, most prominently in the Mediterranean rim, Middle East and Central Asia, with accurate assessments largely lacking in other regions. Brucellosis is a cause of nonspecific febrile illness in LMICs and a rare cause of febrile illness among returning travelers. An appropriate index of suspicion based on risk factors and local prevalence is required, as undifferentiated fever syndromes due to brucellosis have the potential to evolve into chronic, debilitating focal forms, and the treatment for acute brucellosis is unique compared to empiric regimens for other causes of fever in LMICs. Although mortality is low, treatment failure or relapse is not infrequent despite low levels of antimicrobial resistance. Control of brucellosis in livestock is the best strategy for decreasing the disease burden in humans, but more research on the cost-effectiveness of control strategies in LMICs is required. As much of our knowledge on the epidemiology and clinical manifestations of brucellosis is derived from the populations of the Mediterranean rim, further research is needed on the incidence, causative species, risk factors, and manifestations of brucellosis in other regions of the world.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 484–485).

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