

Human brucellosis in South Africa: A review for medical practitioners

K Govindasamy, BVSc, MPH

One Health, Department of Veterinary Tropical Diseases, Faculty of Veterinary Science, University of Pretoria, South Africa

Corresponding author: K Govindasamy (krpasha@gmail.com)

Brucellosis is recognised as a neglected zoonotic tropical disease of global health and economic importance. Medical practitioner unawareness of the disease is reported to contribute to the overall neglect. In South Africa (SA), human brucellosis is a notifiable medical condition and bovine brucellosis is a controlled animal disease. The overall aim of this review article is to increase medical practitioner capacity to detect, diagnose and treat brucellosis in the SA context. A brief review of the literature on human brucellosis in SA is presented, together with a discussion of current issues related to medical detection, treatment and management of brucellosis, applicable to the SA context.

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Human brucellosis is a neglected zoonotic tropical disease, caused by facultative intracellular Gram-negative *Brucella* bacteria that are transmitted directly or indirectly from animals to people.^[1] Five species, i.e. *B. abortus*, *B. suis*, *B. melitensis*, *B. canis* and *B. ovis*, have domestic animals (cattle, pigs, goats, dogs and sheep) as preferred hosts. Five *Brucella* species have been found in wildlife and sea mammals, with a further four atypical strains isolated from baboons, rodents, frogs and humans.^[2] The incubation period for brucellosis in humans is reported to range from 1 to 5 weeks, with the disease being categorised into asymptomatic or symptomatic, with the latter noted to have either an acute or an insidious onset.^[3,4] The symptomatic stage of the disease has been further classified according to the duration and severity of the symptoms as acute (lasting up to 8 weeks), subacute (lasting 8 weeks - 1 year) or chronic (lasting >1 year).^[3,5] Brucellosis is also described as either uncomplicated or focal, where focal implies localisation of the bacterium in an organ system, resulting in symptoms related to that system.^[6]

Symptomatic acute and subacute disease are typified by intermittent febrile illness that persists for 1 - 5 weeks, followed by a 2-day - 2-week remission period, when symptoms are either reduced or absent,^[5] resulting in the 'undulant fever' of brucellosis. Fever may be accompanied by malaise, anorexia, extreme physical weakness or emotional exhaustion. Clinical findings during these stages are usually fever, hepatomegaly and/or splenomegaly.^[3] If the disease is not detected or treated correctly, it may persist for weeks or months and progress to the chronic form.^[7]

Chronic brucellosis refers to symptomatic disease that has persisted for >1 year, and is usually associated with focal infection that can affect any organ system, revealing its multisystem nature.^[8-10] The most common clinical signs, although nonspecific, include relapsing fevers, chills, sweating, joint pain, depression and ongoing recurrent infection.^[4] Frequently reported focal infection include sacroiliitis, orchitis and epididymitis, while neurobrucellosis and endocarditis occur less often, but may result in death.^[11]

'Asymptomatic' or 'subclinical form of the disease' is the terminology used to describe patients who are serologically positive for brucellosis, but have no clinical symptoms. This situation

commonly occurs in veterinarians, abattoir workers, farmers or persons in endemic areas.^[12]

Human brucellosis is a global health problem, with at least 500 000 cases reported annually worldwide,^[3] and with prevalence rates >10/100 000 population in some countries.^[9] Brucellosis not only affects low- and middle-income countries, impacting poorer and more marginalised people,^[13-16] but shows an evolving epidemiology with re-emerging endemic foci in countries where the disease is controlled in livestock.^[17] Little is known about brucellosis in humans in Africa.^[17] Country data on human brucellosis in sub-Saharan Africa are sparse and the true burden of the disease in this region is unknown.^[17-19]

In South Africa (SA), bovine brucellosis is a controlled animal disease.^[20,21] Human brucellosis is a notifiable medical condition, but there is currently no surveillance programme for this condition in SA.^[21] Two cases of brucellosis in humans were reported in 2016 - 1 from Western Cape^[22] and 1 from Mpumalanga provinces.^[21] This followed a published report of *B. abortus* infective endocarditis of a prosthetic valve in a patient from KwaZulu-Natal Province.^[23] The article cites a 1962 paper by Schrire,^[24] which reports the national incidence of human brucellosis to be <0.2/100 000 population. The paucity of reported cases of brucellosis since Schrire's article is used to support the conclusion that the incidence of human brucellosis in SA is low, which could be indicative of effective vaccination against brucellosis in livestock.^[23]

More recent literature emphasises the problem of under-diagnosis and under-reporting of human brucellosis in SA, highlighting medical practitioners' unawareness of the disease.^[22] Furthermore, Frean *et al.*^[21] draw attention to the reprioritisation of *B. abortus* as a public health risk in SA and the measures being taken by government veterinary services to reduce this risk. In such papers, strong recommendation is made for clinician awareness, involvement and vigilance.

This article aims to increase practitioner awareness of brucellosis by presenting evidence of the historical importance of the disease in SA from the published literature. Clinical findings are reviewed in the context of the most pertinent challenges that clinicians face in the

detection, treatment and management of brucellosis in the current SA context.

History of human brucellosis in South Africa

In southern Africa, the first human case of brucellosis was reported in 1924; it was caused by *B. abortus*.^[25,26] Outbreaks of abortions in cattle herds, first detected in 1906, were confirmed to be the result of *B. abortus* infections in 1913. These occurred in the Johannesburg area of the then Transvaal province.^[27] Recent paleopathological evidence suggests that *Brucella* may even have been present in this area for longer, and may have been the cause of disease in the late Pliocene hominin species *Australopithecus africanus* (Stw 431) in the Sterkfontein caves complex, ~2.4 - 2.8 million years ago.^[28]

The history of prioritisation of human brucellosis in southern Africa dates back to 1919, when Malta fever (caused by *B. melitensis*) was included as a notifiable human disease in the Public Health Act of 1919. Human brucellosis, caused by *B. abortus*, was recognised as a public health risk in SA^[26,29,30] 10 years after the discovery of the zoonotic nature of the bacterium.^[31] This conclusion was based on substantial evidence of undulant fever cases in man attributed to *Brucella* spp. that did not share the morphological or culture conditions of *B. melitensis* and was not associated with direct or indirect contact with goats, but instead with direct or indirect contact with cattle.^[26] Human cases of undulant fever, caused by *B. abortus*, were notified as Malta fever, and were detected and reported from all provinces of the Union of SA (except Natal) from 1928 to 1980.^[26,30,32-35]

In 1938, clusters of cases were identified in the Transvaal.^[32] The endemic state in the north-eastern Transvaal and the then South West Africa, was highlighted in 1958,^[36] and human brucellosis was reported to be a disease more common in SA than was generally believed. In 1959, brucellosis in humans was recognised as a problem, specifically in Krugersdorp, but also in the entire Transvaal.^[37] The endemicity of this region was further supported by Schrire,^[34] who identified the northern and eastern Transvaal, the Witwatersrand and Swaziland as areas representing 66.4% ($n=77/116$) of cases reported between 1956 and 1959. Furthermore, evidence of a risk to the public through the consumption of contaminated milk was identified on the Witwatersrand^[38] and northern Highveld^[39] regions of the Transvaal in 1948 and 1962, respectively.

The importance of brucellosis as a disease in humans seems to have diminished significantly by 1980. A publication by Mauff^[35] reported 7 cases of acute brucellosis within a 9-month period, 5 of which were associated with a new abattoir plant in Johannesburg – an unusual event. The last reported annual incidence rates from an analysis by the National Department of Health in 1977 and 1984, was 0.1/100 000 and 0.3/100 000 population, respectively.^[21]

However, after 1980, interest in *Brucella* continued – research was done regarding its use as a biological weapon in SA.^[40] In this covert government programme, *B. melitensis* and *B. abortus* are mentioned on the list of pathogens available for sale by Roodeplaat Research Laboratories. On the list, *B. abortus* is identified as ‘terminating pregnancy in cows’.^[40] During this period, there was a paucity of published articles on human brucellosis.

Prevention of brucellosis caused by *Brucella abortus*

B. abortus, the cause of bovine brucellosis, is considered one of the major zoonotic species causing human brucellosis in SA.^[21] *B. abortus*

occurs in cattle and may also occur in horses, pigs, sheep, goats, Bactrian camels, dromedary camels, water buffalo and yaks,^[41] as well as wildlife species, such as the African buffalo, hippopotamus, zebra, eland and impala.^[42,43]

Brucella-infected cattle are characterised by ≥ 1 of the following symptoms: abortion, retained placenta, stillbirths, poor weight gain, orchitis, epididymitis and hygromas.^[27] In cattle, *B. abortus* causes abortions – usually in the third trimester. Bacterial concentrations in the placenta and fetal tissues can be as high as $10^9 - 10^{10}$ CFU/g and are therefore the main source of transmission to humans or uninfected bovines through aerosolised or direct mucosal contact, where a minimum dose within the $10^3 - 10^4$ CFU range is needed for infection.^[44] Infection of the reproductive system does not always lead to abortion, but can persist in a herd without any overt clinical symptoms, except for the birth of weak or non-viable calves and a reduction in milk yield.^[41,44]

Therefore, direct contact with infected reproductive material or uterine discharge or indirect contact through the ingestion of bacteria shed in the milk are the main routes of transmission of *B. abortus* to humans and to other cattle. Further sources of infection have been reported, i.e. a contaminated environment, especially if it is wet and muddy, or contact with equipment used for milking or artificial insemination.^[27]

Global evidence of the zoonotic and economic importance of bovine brucellosis resulted in the emergence of national bovine brucellosis eradication schemes.^[31,41,45] SA was among the countries that initiated such a scheme, supported by legislation and regulated by veterinary state services in response to the economic and zoonotic threat of the disease in cattle.^[46-48] At the time, such schemes were being successfully implemented in developed countries, and relied on a well co-ordinated and managed veterinary services programme to reduce cattle and herd infection levels through vaccination and subsequent cattle test and slaughter programmes.^[49-54] Since the inception of bovine brucellosis eradication schemes, the USA,^[44] Sweden, Finland, Denmark, the UK (excluding Northern Ireland), Germany, Luxembourg, Belgium, the Netherlands, Austria, Switzerland, Norway, France,^[17] Malta^[55] and Australia^[56] have achieved bovine brucellosis-free status.

Vaccination of cattle with weakened live vaccines against *B. abortus* is a critical component of bovine brucellosis eradication or control programmes.^[57] Two weakened vaccines, S19 and RB51, have been registered for use in national bovine brucellosis eradication programmes.^[42] While human infection with S19 can be treated with the recommended course of antibiotics, the attenuated live rough strain, RB51, is a rifampicin-resistant attenuated strain of the smooth *B. abortus* biovar 1 S2308 strain.^[57,58] This strain has been shown to cause infection in occupationally exposed persons at an estimated rate of 2 unintentional needle-stick injuries for every 1 000 inoculations performed,^[59] and has resulted in several outbreaks affecting consumers of milk in the USA.^[60-62] Routine serological tests are unable to detect infection with RB51,^[60,63] presenting a diagnostic challenge to clinicians suspecting brucellosis.

In SA, control of bovine brucellosis began with compulsory vaccination of cattle with S19. Testing for bovine brucellosis for maintenance and export purposes has been conducted since 1913 at the Ondesterpoort laboratory in Pretoria, SA.^[47] Further organisation of control activities began in 1978 with the introduction of the bovine brucellosis eradication scheme, which was first announced in 1968, but became effective after 1976.^[64] This scheme, which was officially nationally ratified and promulgated in 1989, was aimed at preventing

and controlling brucellosis in cattle, which would in turn reduce brucellosis in humans and increase cattle herd productivity.

SA has since undergone a political shift from an apartheid government to a democratic government over the century spanning the initial discovery of *B. melitensis* and *B. abortus*.^[31,65] The political shift resulted in the decentralisation of veterinary services in 1994. This led to implementation of the bovine brucellosis eradication programme in the mandate of the 9 provincial veterinary services^[20] to ensure an extension of such services to the previously marginalised group of mixed-race cattle farmers. Currently, a revision of the bovine brucellosis eradication scheme of 1980 is proposed to change from voluntary testing to compulsory testing of all cattle in SA.^[20,21] Vaccination of cattle herds and testing and slaughtering of infected cattle still form critical components of the strategy. Persons occupationally exposed to *Brucella*-infected cattle herds and those who routinely vaccinate, test or slaughter infected cattle, are therefore currently at risk of brucellosis.

Detection and diagnosis of brucellosis

Difficulty in detecting and diagnosing brucellosis is well described in the literature^[2,66-70] and is a major constraint in the early and accurate detection of brucellosis worldwide.^[2,66] Such difficulty is primarily due to the symptomatic phase of brucellosis being marked by nonspecific symptoms that are common to other infectious diseases, such as malaria, tuberculosis and the common flu.^[66] Fever is not always associated with a detectable bacteraemia, which reduces the sensitivity of isolation and culture of bacteria from blood or tissue during the symptomatic phase,^[2,66,71] thus limiting the use of available molecular techniques.

Serological tests are more affordable than molecular tests and have been successfully used in resource-constrained settings.^[72,73] Clinicians have relied on available serological tests to support the diagnosis of brucellosis to initiate treatment.^[19,72,73] To detect the progression of the disease or diagnose brucellosis, sequential serological tests conducted 1 - 2 weeks apart are recommended, as tests may be negative in the early stages of the disease.^[2,66,68]

However, the abovementioned articles report that brucellosis patients who have been successfully treated or who have recovered without treatment^[5] may remain seropositive for several months or years, making differentiation between patients with active disease and those with past disease – but presenting with brucellosis-like symptoms – difficult. To address this diagnostic complication, the literature recommends that the prevalence of brucellosis in healthy individuals should be measured to determine a reliable cut-off value for serological tests used by clinicians to diagnose the condition in endemic regions.^[66]

SA clinicians experienced similar difficulties in detecting and diagnosing brucellosis. They reported that serological agglutination tests were not specific or sensitive enough to differentiate between *B. melitensis*, *B. abortus* and *B. abortus* intermediate type.^[30] The low sensitivity of culture to confirm brucellosis was also a concern. This is illustrated in reports of patients who tested seropositive for brucellosis while presenting with subacute endocarditis, but who were culture negative for *Brucella* and culture positive *Streptococcus viridans*.^[30]

The most reported challenge for clinicians at that time was interpreting serological test results and determining appropriate titre cut-offs to confirm a diagnosis of brucellosis in patients with fever of unknown origin, when malaria, typhoid, paratyphoid and tuberculosis were already ruled out.^[30,32] Campbell and Greenfield,^[30]

in 1937, made use of live suspensions of *B. melitensis* and the Rhodesian strain of *B. abortus* as antigen for agglutination tests and used a minimum titre of 1:400 to diagnose brucellosis in patients with fever of unknown origin. They reported a 4.84% prevalence ($n=32/661$). The authors regarded a titre of 1:100 - 1:200 (9.36%) as probable cases or cases of brucellosis.^[30] This titre was higher than that used in a seroprevalence survey conducted by Barnetson^[32] from 1936 to 1938 to determine the frequency of *Brucella* agglutinins in SA. In this study, 1 900 blood samples routinely submitted to the SA Institute for Medical Research to test for typhoid fever, were tested for antibodies to *B. abortus* and *B. melitensis* antigens - a titre of 1:50 being indicative of brucellosis. Using this titre, the incidence of brucellosis was reported as 2.5% ($n=40/1577$) for the country during this period.

The indirect Coombs test was employed over 3 years to determine the frequency of *Brucella* antibodies in 2 393 patients.^[33] This test could detect non-agglutinating antibodies to *Brucella* and was therefore considered more sensitive to detect past or present infection. Patients who were tested were provisionally diagnosed with one of the following: arthritis, acute rheumatism, brucellosis, pyrexia of unknown origin, backache, pneumonitis, anaemia, adenitis, hepatosplenomegaly, hepatitis or tuberculosis – there was also a proportion for whom no diagnosis was provided. Twenty-one percent of these patients were seropositive to the indirect Coombs test compared with 5% of 300 randomly selected controls comprised of blood donors and antenatal patients.

An accepted explanation for brucellosis titres in healthy South Africans in the 1960s, was that they were exposed to the non-virulent *Brucella* antigen;^[74] therefore, positive titres do not necessarily denote active infection. This led to a deprioritisation of the possibility of disease, especially among occupationally exposed persons, such as farmers, abattoir workers and veterinarians, who showed serological titre levels without clinical symptoms of disease.^[35,74] In contrast, other literature showed that farmers and veterinarians who are frequently exposed to *Brucella* tend to display a hypersensitivity reaction that causes symptoms typical of acute brucellosis.^[12,59] Furthermore, recent international studies suggest that the absence of clinical symptoms in the presence of a high serological titre may be indicative of patients who have the subclinical or latent form of the disease – also known as the asymptomatic stage.^[9] Moreover, evidence of exposure does not imply a consistent immunity, as immunity after infection lasts for ~2 years^[5] and infection is known to be dose dependent.^[75] The development of chronic and subclinical brucellosis, marked by the temporary absence of clinical symptoms, has also been noted in these occupational groups.^[8,12,37,76]

In SA, currently, the most commonly used serological tests are the Coombs anti-*Brucella* test, the serum agglutination test (SAT), the rose Bengal test (RBT), complement fixation and the enzyme-linked immunosorbent assay (ELISA),^[21] with the Coombs anti-*Brucella* test being regarded as the most specific to diagnose brucellosis. The RBT is affordable and sensitive to sera without blocking or non-agglutinating antibodies, which is typically the situation in non-chronic cases of a short evolution of disease,^[72] and is therefore useful to detect acute cases of brucellosis. However, in endemic areas it is reported to have a low specificity^[2] and a low sensitivity to detect chronic and complicated brucellosis patients.^[2,77] The ELISA IgG has been reported to be a very sensitive serological test to detect antibodies of the IgG class, which are predominately found in the chronic phase of brucellosis, and is useful for detecting focal, complicated and chronic disease.^[77] Cut-offs for best sensitivity and

specificity in endemic areas were determined to be 10.00 IU/mL^[70] and 10.78 IU/mL, respectively.^[78] However, the most sensitive and specific test to detect complicated and chronic brucellosis in an endemic area, is reported to be the BrucellaCapt test.^[66,77,79] This serological test is regarded as more sensitive and specific than the RBT or ELISA IgG to detect chronic reinfections and persistent or relapsing cases of brucellosis.^[66,69] This commercially available immune capture serological test^[80] is based on the principles of the Coombs anti-*Brucella* test. It is cost-effective, rapid and reported to have a sensitivity and specificity of 99.2% and 96%, respectively, on samples determined positive by the Coombs test.^[81] Furthermore, BrucellaCapt titres indicate the activity of infection, regardless of the stage of disease, decreasing slowly after relapse and more distinctly after treatment.^[2] The test was, however, developed to diagnose brucellosis in non-endemic countries and needs an adjustment of the cut-off titre to detect cases if used in an endemic area.^[78]

Clinical symptoms

A multitude of symptoms affecting every body system, associated with a culture-positive or seropositive reaction to *Brucella* antigens, were reported by SA clinicians from 1935 onwards.^[12,23,29,30,34,36,37,82] Fever and chills, pyrexia of long duration, continuous fever of 6 weeks' duration, fever of some months' duration, low pyrexia, pyrexia of unknown origin and sweating have been associated with brucellosis.^[29,30,33,83]

Lesions of the skin were described in veterinarians, cattle handlers who removed placentas, farmers and abattoir workers. They presented with erythematous granulomatous lesions or a skin rash lasting 4 - 8 hours,^[29] progressing to a nodular rash lasting 3 - 4 days, usually on the forearm, which sometimes caused gross thickening of the skin. This manifestation of brucellosis was termed erythematous brucellosis by Robinson^[29] in 1935 and by Schrire in 1962.^[34] Signs of musculoskeletal involvement included arthralgia, pain in the joints, arthritis of the knee and ankle, described in a native Angolan mine worker and the wife of a medical doctor from Canada, whereas severe shoulder pain occurred in a farmer.^[30,37] Sacroiliitis and backache were described in a mine worker and an 18-year-old son of a town dairy owner,^[36,82] while a 65-year-old woman presented with *Brucella* spondylitis accompanied by radiculitis, which was referred to as 'sciatic neuritis'.^[36,37,82] Other musculoskeletal symptoms described in brucellosis cases included peripheral arthritis, osteomyelitis, muscle wasting and palmar erythema.^[29,36,37]

Hepatomegaly, cirrhosis of the liver, hepatosplenomegaly and hepatitis were also common findings in brucellosis patients. These conditions were sometimes associated with spider naevi on the chest.^[29,33,36,37] Other respiratory symptoms included pleural effusions, pneumonias, pneumonitis and bronchopneumonia.^[30] Hilar adenopathy with a non-productive cough and focal pneumonitis was described in laboratory workers.^[34] Endocarditis involving the aortic valve was described in 1937,^[30] and more recently in 2015.^[23]

Peripheral neuropathies, chorea, meningoencephalitis, cranial nerve involvement, headache, malaise, as well as psychiatric manifestations, such as depression, anxiety and neurosis, were described, indicating nervous system involvement.^[33,34,82] Many of these psychiatric symptoms were associated with a diagnosis of chronic brucellosis with an insidious onset, recorded in 17 SA patients.^[82] General practitioners referred these patients to specialists at the departments of Medicine and Microbiology, University of the Free State, Bloemfontein. The patients tested seropositive to

Brucella, with high titres on repeated serological examination. They did not present with fever, but with symptoms listed in Table 1.

Treatment and management

Late initiation of brucellosis treatment is reported to be associated with relapse and treatment failure.^[67] Currently, the recommended treatment regimens for brucellosis patients in SA is described in Table 2, and treatment dosages are given in Table 3.

Conclusions and recommendations

Brucellosis caused by *B. abortus* has been an important medical condition for more than a century in SA. Recently, however, there has been a paucity of medical literature describing the incidence of human brucellosis in SA. Even though there is an active bovine brucellosis control programme to prevent human brucellosis in the country, persons occupationally exposed to *Brucella*-infected cattle herds are still at risk of brucellosis. The public is also at risk through consumption of dairy products contaminated with the field or vaccine strain of *B. abortus*. Evidence of clinical symptoms associated with acute, chronic, uncomplicated and focal brucellosis in SA is discussed in this article.

It is recommended that an occupational history, including contact with infected cattle herds, be considered by general practitioners when diagnosing and treating fever or symptoms of unknown origin. Treatment regimens for persons occupationally exposed to RB51 should be adjusted to exclude rifampicin. Communication between clinicians and veterinarians is recommended to strengthen risk-mitigation strategies for individual brucellosis patients as part of the management strategy. This has been shown to be integral in the formulation of targeted mitigation and risk-reduction strategies of public health or government veterinary services.^[55,84] Further study

Table 1. Symptoms and clinical signs in patients (N=17) with chronic brucellosis of insidious onset^[66]

Symptoms and signs	n (%)
Symptom	
Tiredness*	16 (94.1)
Fatigue†	16 (94.1)
Arthralgia	14 (82.3)
Depression	12 (70.6)
Muscular pain	11 (64.7)
Abdominal pain	7 (41.2)
Headache	7 (41.2)
Sweating	4 (23.5)
Anxiety	3 (17.7)
Agitated pain	2 (11.8)
Clinical sign	
Lymphadenopathy	9 (52.9)
Cervical adenopathy	6 (35.3)
Axillary adenopathy	6 (35.3)
Inguinal adenopathy	2 (11.8)
Splenomegaly	7 (41.2)
Hepatomegaly	4 (23.5)
Pyrexia	4 (23.5)
Joint involvement	1 (5.9)

*Physiological decreased ability of an organism or one of its parts to function because of prolonged exertion, which causes toxic decomposition in the muscle and nerve.

†Feeling of weariness but continuing normal activity. The weariness may be physical or mental in nature.

Table 2. Recommended treatment regimens for brucellosis*

Form of brucellosis infection	Patients	Recommended antibiotic regimen	Duration, weeks [†]
In adults	Uncomplicated	Doxycycline	6
		Doxycycline plus streptomycin or gentamicin	1 - 2
		<i>or</i>	
		Doxycycline plus rifampicin	6
	Children, years		
	<8	Co-trimoxazole plus rifampicin	4 - 6
	≥8	Doxycycline plus rifampicin	
Focal	Adults		
	Spondylitis	Doxycycline	12
		Doxycycline plus streptomycin or gentamicin	2
		<i>or</i>	
		Doxycycline plus rifampicin	12
		<i>or</i>	
		Doxycycline plus ciprofloxacin	12
	Neurobrucellosis	Doxycycline plus rifampicin plus (ceftriaxone <i>or</i> co-trimoxazole)	Prolonged until CSF normalises
	Endocarditis	Doxycycline plus rifampicin plus streptomycin or gentamicin	6 weeks - 6 months, depending on clinical response
		Surgery if indicated	
Children, years	<8	Co-trimoxazole plus streptomycin or gentamicin	6 (at least)
			2
	≥8	Doxycycline	6 (at least)
		Doxycycline plus streptomycin or gentamicin	2
	Rifampicin can be added to either regimen	6 (at least)	
		Rifampicin with/without co-trimoxazole	6

*From Frean *et al.*,^[21] with permission.
[†]Unless otherwise indicated.

Table 3. Recommended antibiotics and dosages for brucellosis treatment*

Antibiotic	Dosage
Co-trimoxazole	Trimethoprim 10 mg/kg/d (max. 480 mg/d) (2 doses/d)
	Sulfamethoxazole 50 mg/kg/d (max. 2 g/d)
Doxycycline	2 - 4 mg/kg/d (max. 200 mg/d) (2 doses/d)
Rifampicin	15 - 20 mg/kg/d (max. 2 g/d) (1 or 2 doses/d)
Gentamicin	5 mg/kg/d
Streptomycin	20 - 40 mg/kg/d (max. 1 g/d) (2 doses/d)
Ciprofloxacin	1 g/d (2 doses/d)
Ofloxacin	400 mg/d (2 doses/d)

Max. = maximum.
 *From Frean *et al.*,^[21] with permission.

is needed to determine the incidence of *Brucella* seropositivity in the healthy population, especially in bovine brucellosis endemic areas, as well as the true burden of human brucellosis in these areas. However, routine submission of samples by clinicians suspecting brucellosis will help to address the abovementioned information gap.

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- McDermott JJ, Arimi SM. Brucellosis in sub-Saharan Africa: Epidemiology, control and impact. *Vet Microbiol* 2002;90(1):111-134. [https://doi.org/10.1016/s0378-1135\(02\)00249-3](https://doi.org/10.1016/s0378-1135(02)00249-3)
- Al Dahouk S, Sprague L, Neubauer H. New developments in the diagnostic procedures for zoonotic brucellosis in humans. *Rev Sci Tech* 2013;32(1):177-188. <https://doi.org/10.20506/rst.32.1.2204>
- Doganay M, Aygen B. Human brucellosis: An overview. *Int J Infect Dis* 2003;7(3):173-182. [https://doi.org/10.1016/s1201-9712\(03\)90049-x](https://doi.org/10.1016/s1201-9712(03)90049-x)
- Glynn KDD. Brucellosis. In: Heymann DL, ed. *Control of Communicable Diseases Manual*. 19th ed. Washington, DC: American Public Health Association, 2008:87-90. <https://doi.org/10.1086/605668>
- Bush LM, Perez MT. Brucellosis. 2019. <https://www.msmanuals.com/professional/infectious-diseases/gram-negative-bacilli/brucellosis> (accessed 4 November 2019).
- Bosilkovski M. Clinical manifestations, diagnosis, and treatment of brucellosis. *UpToDate* 2016. <https://www.uptodate.com/contents/brucellosis-epidemiology-microbiology-clinical-manifestations-and-diagnosis> (accessed 5 November 2019).
- Corbel MJ. Food and Agriculture Organization of the United Nations, World Health Organization and World Organization for Animal Health. *Brucellosis in Humans and Animals*. Geneva: WHO, 2006:89.
- Mantur BG. Protean clinical manifestations and diagnostic challenges of human brucellosis in adults: 16 years' experience in an endemic area. *J Med Microbiol* 2006;55(7):897-903. <https://doi.org/10.1099/jmm.0.46097-0>
- Franco MP, Mulder M, Gilman RH, Smits HL. Human brucellosis. *Lancet Infect Dis* 2007;7(12):775-786. [https://dx.doi.org/10.1016/s1473-3099\(07\)70286-4](https://dx.doi.org/10.1016/s1473-3099(07)70286-4)

10. Buzgan T, Karahocagil MK, Irmak H, et al. Clinical manifestations and complications in 1 028 cases of brucellosis: A retrospective evaluation and review of the literature. *Int J Infect Dis* 2010;14(6):e469-e478. <https://doi.org/10.1016/j.ijid.2009.06.031>
11. Dean AS, Crump L, Greter H, Hattendorf J, Schelling E, Zinsstag J. Clinical manifestations of human brucellosis: A systematic review and meta-analysis. *PLoS Neglect Trop Dis* 2012;6(12):e1929. <https://doi.org/10.1371/journal.pntd.0001929>
12. Henderson RJ, Hill DM. Clinical problems: Subclinical *Brucella* infection in man. *BMJ* 1972;3(5819):154-156. <https://doi.org/10.1136/bmj.3.5819.154>
13. Franc KA, Krecsek RC, Häslar BN, Arenas-Gamboia AM. Brucellosis remains a neglected disease in the developing world: A call for interdisciplinary action. *BMC Public Health* 2018;18(1). <https://doi.org/10.1186/s12889-017-5016-y>
14. Mableson HE, Okello A, Picozzi K, Welburn SC. Neglected zoonotic diseases - the long and winding road to advocacy. *PLoS Neglect Trop Dis* 2014;8(6):e2800. <https://doi.org/10.1371/journal.pntd.0002800>
15. Michael E, Madon S. Socio-ecological dynamics and challenges to the governance of neglected tropical disease control. *Infect Dis Poverty* 2017;6(1):35. <https://doi.org/10.1186/s40249-016-0235-5>
16. World Health Organization. The Control of Neglected Zoonotic Diseases: From Advocacy to Action. Geneva: WHO, 2014.
17. Pappas G, Papadimitriou P, Akritidis N, Christou L, Tsianos EV. The new global map of human brucellosis. *Lancet Infect Dis* 2006;6(2):91-99. [https://doi.org/10.1016/s1473-3099\(06\)70382-6](https://doi.org/10.1016/s1473-3099(06)70382-6)
18. Dean AS, Crump L, Greter H, Schelling E, Zinsstag J. Global burden of human brucellosis: A systematic review of disease frequency. *PLoS Neglect Trop Dis* 2012;6(10):e1865. <https://doi.org/10.1371/journal.pntd.0001865>
19. Ducrotot M, Bertu WJ, Matope G, et al. Brucellosis in sub-Saharan Africa: Current challenges for management, diagnosis and control. *Acta Tropica* 2017;165:179-193. <https://doi.org/10.1016/j.actatropica.2015.10.023>
20. Department of Agriculture, Forestry and Fisheries. Review of Bovine Brucellosis Control in South Africa. Pretoria: DAFF, 2016.
21. Frean J, Cloete A, Rossouw J, Blumberg L. Notifiable medical conditions: brucellosis. *NICD Commun Dis Surveill Bull* 2018;16(3):110-117.
22. Wojno JM, Moodley C, Pienaar J, et al. Human brucellosis in South Africa: Public health and diagnostic pitfalls. *S Afr Med J* 2016;106(9):883-885. <https://doi.org/10.7196/samj.2016.v106i9.11020>
23. Mahomed S, Mahabeer Y, Mlisana K, Bissety P. A rare case of *Brucella abortus* endocarditis in South Africa. *South Afr J Infect Dis* 2015;30(2):64-66. <https://doi.org/10.1080/23120053.2015.1054198>
24. Schrire L. Human brucellosis in South Africa. *S Afr Med J* 1962;36(18):342-349.
25. Duncan JT. The role of the domestic cow in the epidemiology of undulant fever. *Transact Roy Soc Trop Med Hyg* 1924;18(6):318-327. [https://doi.org/10.1016/s0035-9203\(24\)90496-2](https://doi.org/10.1016/s0035-9203(24)90496-2)
26. Duncan JT. The identification of *Brucella abortus* from human sources. *Transact Roy Soc Trop Med Hyg* 1928;22(3):269-280. [https://doi.org/10.1016/S0035-9203\(28\)90099-1](https://doi.org/10.1016/S0035-9203(28)90099-1)
27. Bishop GC, Bosman PP, Herr S. Bovine brucellosis. In: Coetzer JAW, Thomson GR, Tustin RC, eds. *Infectious Diseases of Livestock with Special Reference to Southern Africa*. Cape Town: Oxford University Press, 1994:1052-1072.
28. D'Anastasio R, Zipfel B, Moggi-Cecchi J, Stanyon R, Capasso L. Possible brucellosis in an early hominin skeleton from Sterkfontein, South Africa. *PLoS ONE* 2009;4(7):e6439. <https://doi.org/10.1371/journal.pone.0006439>
29. Robinson EM. Recent views on the *Brucella* group. *S Afr Med J* 1935;9(18):645-650.
30. Campbell W, Greenfield EC. The incidence of brucellosis in cases of pyrexia of uncertain origin in the Cape Province of the Union of South Africa. *S Afr Med J* 1937;11(6):192-201.
31. Evans AC. Brucellosis in the United States. *Am J Publ Health Nations Health* 1947;37(2):139-151. <https://doi.org/10.2105/ajph.37.2.139>
32. Barnettson J. Undulant fever: Its incidence in South Africa. *S Afr Med J* 1939;13(7):230-233.
33. Zoutendyk A. Incomplete antibodies in brucellosis: An indirect agglutinin (Coombs) one-tube screen test. *S Afr Med J* 1958;32(28):706-709.
34. Schrire L. Human brucellosis in South Africa. *S Afr Med J* 1962;36(5):342-349.
35. Mauff AC. Acute brucellosis in Johannesburg. *S Afr Med J* 1980;58(12):477-479.
36. Ipp H. Brucellar spondylitis and hepatitis - a report on two cases with a review of the literature. *S Afr Med J* 1958;32(45):1077-1078.
37. Lewis JS. Brucellosis in Krugersdorp, with a review of the problem in southern Africa. *S Afr Med J* 1959;33(9):177-181.
38. Lewin W, Bersohn I. Brucella agglutinins: Their occurrence in Witwatersrand milk supplies and in the serum of normal persons. *S Afr Med J* 1948;22(23):763-765.
39. Erasmus JA, Floor J. Bovine brucellosis in the Highveld region: Incidence in dairy herds. *J S Afr Vet Ass* 1988;59(1):39-43.
40. Gould C, Folb P. Project Coast: Apartheid's Chemical and Biological Warfare Program. Geneva: United Nations Institute for Disarmament Research, 1990.
41. Crawford RP, Hidalgo RJ. Bovine Brucellosis: An International Symposium. College Station: Texas A & M University Press, 1977.
42. World Organisation for Animal Health. Bovine Brucellosis. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. Paris: OIE, 2016:3.
43. Godfroid J, Scholz HC, Barbier T, et al. Brucellosis at the animal/ecosystem/human interface at the beginning of the 21st century. *Prevent Vet Med* 2011;102(2):118-131. <https://doi.org/10.1016/j.prevetmed.2011.04.007>
44. Olsen S, Tatum F. Bovine brucellosis. *Vet Clinics: Food Animal Practice* 2010;26(1):15-27. <https://doi.org/10.1016/j.cvfa.2009.10.006>
45. World Organisation for Animal Health. Bovine Brucellosis. Manual of Diagnostic Tests and Vaccines for Terrestrial Animals. Paris: OIE, 2008:3.
46. Bosman PP. Scheme for the control and eventual eradication of bovine brucellosis. *J S Afr Vet Ass* 1980;51(2):75-79.
47. Drimmelen GCV. The brucellosis survey in South Africa. *J S Afr Vet Ass* 1949;20(3):178-188.
48. World Organisation for Animal Health. Brucellosis in Cattle, Sheep and Goats. Paris: OIE, 1987.
49. Alton G. The national brucellosis program of Australia. In: Crawford RP, Hidalgo RJ, eds. *Bovine Brucellosis: An international symposium*. College Station: Texas A & M University Press, 1977.
50. Becton P. The national brucellosis program of the United States. In: Crawford RP, Hidalgo RJ, eds. *Bovine Brucellosis: An international symposium*. College Station: Texas A & M University Press, 1977.
51. Brendan C. The national brucellosis programme of the Republic of Ireland. In: Crawford RP, Hidalgo RJ, eds. *Bovine Brucellosis: An international symposium*. College Station: Texas A & M University Press, 1977.
52. McKeown GR. The national brucellosis program of Canada. In: Crawford RP, Hidalgo RJ, eds. *Bovine Brucellosis: An international symposium*. College Station: Texas A & M University Press, 1977.
53. Michael P. The national brucellosis program of France. In: Crawford RP, Hidalgo RJ, eds. *Bovine Brucellosis: An international symposium*. College Station: Texas A & M University Press, 1977.
54. Morgan WJB. The national brucellosis program of Britain. In: Crawford RP, Hidalgo RJ, eds. *Bovine Brucellosis: An international symposium*. College Station: Texas A & M University Press, 1977.
55. Wyatt H. Lessons from the history of brucellosis. *Rev Sci Tech* 2013;32(1):17-25. <https://doi.org/10.20506/rst.32.1.2181>
56. Department of Agriculture. Eradication Success Story - Australia is Free of *Brucella abortus*. <https://www.agriculture.gov.au/sites/default/files/sitecollectiondocuments/animal-plant/animal-health/pet-food-safety/brucella-abortus-colour.pdf> (accessed 25 May 2020).
57. Dorneles EM, Sriranganathan N, Lage AP. Recent advances in *Brucella abortus* vaccines. *Vet Res* 2015;46(1):76. <https://doi.org/10.1186/s13567-015-0199-7>
58. World Organisation for Animal Health. Brucellosis (*Brucella abortus*, *B. melitensis* and *B. suis*) (infection with *B. abortus*, *B. melitensis* and *B. suis*). 2016. https://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/3.01.04_BRUCELLOSIS.pdf (accessed 26 May 2020).
59. Ashford DA, di Pietra J, Lingappa J, et al. Adverse events in humans associated with accidental exposure to the livestock brucellosis vaccine RB51. *Vaccine* 2004;22(25-26):3435-3439. <https://doi.org/10.1016/j.vaccine.2004.02.041>
60. Centers for Disease Control and Prevention. Exposures to drug-resistant brucellosis linked to raw milk: How to reduce risk of infection. 2019. <https://www.cdc.gov/brucellosis/exposure/drug-resistant-brucellosis-linked-raw-milk.html> (accessed 25 May 2020).
61. Negrón ME, Kharod GA, Bower WA, Walke H. Human *Brucella abortus* RB51 infections caused by consumption of unpasteurized domestic dairy products - United States, 2017 - 2019. *MMWR Morb Mortal Wkly Rep* 2019;68(7):185. <https://doi.org/10.15585/mmwr.mm6807a6>
62. Steir MM. Raw milk intake: Beware of emerging brucellosis. *J Med Microbiol* 2018;67(5):681-682. <https://doi.org/10.1099/jmm.0.000722>
63. Centers for Disease Control and Prevention. Human exposure to *Brucella abortus* strain RB51 - Kansas, 1997. *MMWR Morb Mortal Wkly Rep* 1998;47(9):172.
64. Bosman PP. Skema vir die beheer en uiteindeleike uitroeiing van beesbrucellose. *J S Afr Vet Ass* 1980;51(2):75-79.
65. Madkour MM. Madkour's Brucellosis. Berlin: Springer Science, 2012. https://doi.org/10.1007/978-3-642-59533-2_2
66. Al Dahouk S, Nöckler K. Implications of laboratory diagnosis on brucellosis therapy. *Expert Rev Anti-infect Ther* 2011;9(7):833-845. <https://doi.org/10.1586/eri.11.55>
67. Franco MP, Mulder M, Smits HL. Persistence and relapse in brucellosis and need for improved treatment. *Transact Roy Soc Trop Med Hyg* 2007;101(9):854-855. <https://doi.org/10.1016/j.trstmh.2007.05.016>
68. Gazapo E, Lahoz JG, Subiza JL, Baquero M, Gil J, de la Concha EG. Changes in IgM and IgG antibody concentrations in brucellosis over time: Importance for diagnosis and follow-up. *J Infect Dis* 1989;159(2):219-225. <https://doi.org/10.1093/infdis/159.2.219>
69. Gupte S, Kaur T. Diagnostic approach to brucellosis. *J Trop Dis* 2016;04(01):e109. <https://doi.org/10.4172/2329-891X.1000e109>
70. Hasibi M, Jafari S, Mortazavi H, Asadollahi M, Djavid GE. Determination of the accuracy and optimal cut-off point for ELISA test in diagnosis of human brucellosis in Iran. *Acta Med Iran* 2013;51(10):687-692.
71. Al Dahouk S, Tomaso H, Nöckler K, Neubauer H, Frangoulidis D. Laboratory-based diagnosis of brucellosis - a review of the literature. Part I: Techniques for direct detection and identification of *Brucella* spp. *Clin Lab* 2003;49(9-10):487-505.
72. Diar R, Casanova A, Ariza J, Moriyón I. The rose Bengal test in human brucellosis: A neglected test for the diagnosis of a neglected disease. *PLoS Neglect Trop Dis* 2011;5(4):e950. <https://doi.org/10.1371/journal.pntd.0000950>
73. Ducrotot MJ, Bardosh KL. How do you get the rose Bengal test at the point-of-care to diagnose brucellosis in Africa? The importance of a systems approach. *Acta Trop* 2017;165:33-39. <https://doi.org/10.1016/j.actatropica.2016.10.004>
74. Van Drimmelen GC. Interpretation of *Brucella* agglutinin titres. *S Afr J Sci* 1963;59(11):527-531.
75. Kahl-McDonagh M, Arenas-Gamboia A, Ficht T. Aerosol infection of BALB/c mice with *Brucella melitensis* and *Brucella abortus* and protective efficacy against aerosol challenge. *Infect Immun* 2007;75(10):4923-4932. <https://doi.org/10.1128/iai.00451-07>
76. Spink WW. What is chronic brucellosis? *Ann Intern Med* 1951;35(2):358-374. <https://doi.org/10.7326/0003-4819-35-2-358>
77. Araj GF. Update on laboratory diagnosis of human brucellosis. *Int J Antimicrob Agent* 2010;36:S12-S17. <https://doi.org/10.1016/j.ijantimicag.2010.06.014>
78. Peeridogah H, Golmohammadi MG, Pourfarzi F. Evaluation of ELISA and Brucellacapt tests for diagnosis of human brucellosis. *Iran J Microbiol* 2013;5(1):14-18.
79. Arabaci E, Oldacay M. Evaluation of serological diagnostic tests for human brucellosis in an endemic area. *J Microbiol Infect Dis* 2012;2(02):50-56. <https://doi.org/10.5799/ahinjs.02.2012.02.0042>
80. Vircell Microbiologists. Brucellacapt. 2016. <https://en.vircell.com/support/faqs/3-brucellacapt/> (accessed 18 May 2019).
81. Vircell Microbiologists. Informative dossier Brucellacapt. 2016. <https://en.vircell.com/support/faqs/3-brucellacapt/> (accessed 18 May 2019).
82. Sacks N, Van Rensburg AJ. Clinical aspects of chronic brucellosis. *S Afr Med J* 1976;50(19):725-728.
83. Robinson R, Metcalfe R. Zoonotic infections in veterinarians. *N Z Vet J* 1976;24(9):201-210. <https://doi.org/10.1080/00480169.1976.34317>
84. Hughes G, Hughes M, Matthew Louis Hughes and undulant fever. *J Roy Army Med Corps* 1969;115(4):198-203. <https://doi.org/10.1136/jramc-115-04-07>

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