

NDDB

Human brucellosis

An Indian perspective

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Human Brucellosis

Brucellosis, also known by a multitude of synonyms such as 'Undulant, Mediterranean, Malta, Rock, Gibraltar, Cyprus, Typho-malarial fever', Intermittent typhoid and Bang's disease (*Al Dahouk et al., 2003*) is a zoonosis which is almost invariably transmitted by direct or indirect contact with infected animals or their products. It affects people irrespective of age and sex.

Brucellosis is not a sustainable disease in humans. The source of human infection always resides in domestic or wild animal reservoirs. The routes of infection are multiple: food-borne, occupational or recreational or linked to travel.

It is an important human disease in many parts of the world especially in the Mediterranean countries of Europe, north and East Africa, Middle East, South and Central Asia and Central and South America. Several endemic areas have achieved control like France, Israel and most of Latin America. But on the other hand new foci have emerged particularly in central Asia and the situation in certain countries in the near East (eg. Syria) is rapidly worsening. (*Pappas et al., 2006*). There are only a few countries in the world that are officially free of the disease.

Brucellosis is one of the most widespread and economically the most ravaging of zoonoses. The occurrence of the acute, often incapacitating infection in man caused by *Brucella melitensis* usually coincides with occurrence of the infection in sheep and goats. Although the infection has been reduced by control measures to a low level of incidence in some countries of Europe and North America, its incidence in other parts of the world has actually increased because of emphasis on increased animal production and aggregation under poor hygienic conditions. This is particularly the case with dairy production units which have developed around rapidly growing urban centres in many developing countries. Although human infection with *B. abortus* may be mild, it can cause troublesome and intractable illness. (*Abdussalam, 1976*).

The disease in humans can be insidious and may be present in many atypical forms. It should be noted that even in the severe form, differential diagnosis can still be difficult.

Sources of infection

Cattle, sheep, goats and pigs are the main sources of infection for humans. Transmission to humans occurs through occupational or environmental contact with infected animals or their products. Cheese made from raw milk and unpasteurised milk is the main source of foodborne transmission. It can also be a travel associated disease. However, person to person transmission is extremely rare.

B.melitensis infection is most frequently reported and causes severe disease in humans. *B.suis* has a much more restricted occurrence but can be as severe as the first. Though *B.abortus* is the most widespread cause of infection, the severity is much less than the disease caused by *B.melitensis* or *B.suis*.

Brucellosis is one of the most common laboratory-acquired infections mostly because aerosolization is a mechanism of transmission in this setting. (Robichaud et al, 2004)

It is reported that more than 60% of the patients with brucellosis had a history of both consumption of fresh goat's milk and close animal contact. The habit of consuming fresh goat milk to obtain relief from chronic ailments was also noted. (Mantur et al., 2004)

Incidence of human brucellosis in India

Human brucellosis was recognized in India in 1942 (Renukaradhya et al., 2002) and high clinical suspicion must be made in patients especially when there is history of animal contact or consumption of unpasteurized milk. (Gokhale et al., 2003)

The disease is acute in about half the cases, with an incubation period of 2-3 weeks. In the other half, the onset is insidious, with symptoms developing over a period of weeks to months from the infection.

This zoonosis is a significant public health problem in India, the magnitude of which is not known. Paucity of clinico-epidemiologic data hampers control strategies. Persistence of animal reservoir, low

physician awareness, poor availability of diagnostic facilities, and the nonexistence of regional data bases contribute towards the perpetuation of zoonosis in India. (*Handa et al., 1998*)

It is reported that fewer than 10% of the human cases of brucellosis may be clinically recognized and treated or reported in India. (*Mantur et al., 2007*).

The details of reports on incidence of human brucellosis in India are provided in Annex-1.

Symptoms of human brucellosis reported in India

Brucellosis may often be unsuspected because of its varied clinical manifestations and may be a more important cause of fever than previously considered (*Mathai et al., 1996*). Varied symptoms affecting almost all the systems have been noticed in patients with brucellosis. However, at times, seropositive patients may remain asymptomatic. (*Handa et al., 1998*)

The various symptoms of human brucellosis reported in India have been summarized in Annex-2.

In case of polyarthrititis, the possibility of brucellosis should always be kept in mind, as reported in an outbreak of brucellosis in Kanvari village, Churu district, Rajasthan, wherein 91.6% of 48 persons presented were positive by RBPT. (*Kalla et al., 2001*)

Neurobrucellosis is an uncommon but serious manifestation affecting central and peripheral nervous system. The clinical profile of the disease mimick the commonly seen neurological diseases like tubercular meningitis, viral encephalitis, aseptic meningitis, cerebral malaria and viral encephalopathy. (*Kochar et al., 2000*).

Diagnosis

Presumptive diagnosis

Presumptive diagnosis of brucellosis in humans can be done by the following tests:

- a. Rose Bengal test (RBT) for screening; positive tests to be confirmed by one of the confirmatory tests
- b. Standard agglutination test (SAT).

Confirmatory diagnosis

A confirmatory diagnosis of brucellosis can be done by the following tests:

- a. Isolation of *Brucella* spp. from blood or other clinical specimen.
- b. A *presumptive* laboratory diagnosis based on detection of agglutinating antibodies (RBT, SAT) combined with detection of non-agglutinating antibodies through:
 1. ELISA IgG test;
 2. Coombs IgG.

PCR and new rapid tests such as the lateral flow assay are yet to be accredited.

Bone marrow cultures are recommended in patients with Fever of Unknown Origin (FUO) for whom routine testing turns out to be negative. Serological tests for brucellosis can be false negative in some cases due to prozone phenomenon. (Deepak et al., 2003)

It is desirable that clinicians investigate specimens from cases of tuberculosis, bacterial endocarditis, leukemia, typhoid, rheumatoid arthritis, urogenital infections, kala azar, cirrhosis & filariasis should also be screened for brucellosis in humans. (Thakur et al, 2002)

Screening of family members of index cases of brucellosis in an endemic area will therefore help pick up additional unrecognized cases. (Almuneef et al., 2004, Mantur et al., 2007)

Prevention & Control

The new challenges purported to be faced by the medical and veterinary community in brucella control are (i) the expanding wildlife reservoir of brucellosis, with a possible impact on domestic animals (ii) emergence of *B.melitensis* infections in cattle, for which prophylactic efficacy of available vaccines has not been established, and, (iii) recent recognition of a huge animal reservoir in marine mammals, for which potential virulence for animals remains unknown (Maurin, M, 2005).

The basic components to be included in a control programme for eradication of brucellosis in humans are:

- Education to avoid consuming unpasteurized milk and milk derivatives.
- Barrier precautions for people at risk (butchers, farmers, slaughterers, veterinarians).
- Careful handling and disposal of afterbirths, especially in cases of abortion.
- Serological or other testing of animals and elimination of infected herds.
- Immunization of herds through vaccination ensuring proper coverage.

Therefore, prevention of human brucellosis should mainly focus on elimination of infection in cattle along with hygiene, vaccine and effective heating and pasteurization of dairy products and related foods (*Mudaliar et al., 2003*).

The Control activities are to be coordinated and shared between the public health and animal health sectors, which should ensure joint administrative arrangements to facilitate immediate cross-notification of cases, as well as coordination of joint investigations, control, and public health education programmes.

In countries like Czech Republic, where the disease has been eradicated, the cumulative benefit/eradication ratio reached 7:1 after ten years of eradication of the disease and averted losses of approximately USD 700 million and saved more than 2000 people from becoming affected with brucellosis (*Kouba, 2003*).

In Greece, vaccination of young sheep and goats for 15 years decreased abortions in them as well as reduced the incidence of brucellosis in humans. After vaccinations were stopped in 1994, the prevalence in animals and humans quickly increased. The human incidence decreased after an emergency mass vaccination programme was taken up for young and adult animals in 1998. It was also observed that the decrease in human incidence was not linear but decreased only when vaccination coverage of animals was above 30% (*Minas et al., 2004*).

Treatment

The cure rate of brucellosis is very high if diagnosed properly and the prescribed treatment regimen administered (*Kochar et al., 2000*).

1. Treatment of uncomplicated brucellosis in adults and children eight years of age and older:

- a. Tetracyclines: Tetracycline has long been the standard treatment of human brucellosis. Doxycycline is now the preferred drug and is associated with fewer gastrointestinal side effects than tetracycline.
- b. Aminoglycosides: Because the rate of relapse when tetracycline or doxycycline are given alone remains between 10–20%, most authorities recommend an amino-glycoside to be given in addition to the tetracyclines for the first two to three weeks of therapy.

Streptomycin has long been the drug of choice when used in combination with tetracycline or doxycycline. Although gentamicin, administered in combination with doxycycline yielded good results in one study, experience with this regimen is too limited to justify its use over doxycycline plus streptomycin.

2. Principal alternative therapy: Rifampicin and doxycycline combination was recommended by the WHO Expert Committee in 1986. *Skalsky et. al., (2008)*, in a clinical trial documented that overall treatment failure was significantly higher with doxycycline-rifampicin compared to doxycycline-streptomycin, mainly due to a higher rate of relapse. An analysis of various treatment regimens concluded that overall the regimen of doxycycline plus streptomycin was likely to be the most effective.

3. Secondary alternative therapy: Quinolones combined with rifampicin were significantly less effective than doxycycline combined with rifampicin or streptomycin. Though quinolones are well absorbed after oral administration and they achieve high concentrations within phagocytic cells, a lack of bactericidal activity was found at pH levels comparable to those found within cells.

4. *Treatment of complications of brucellosis:*

- a. Spondylitis: Osteo-articular complications of brucellosis may occur in up to 40% of cases. Though sacroiliitis, do not appear to require special treatment, in contrast, spondylitis and osteomyelitis with related complications, such as para-vertebral and epidural abscesses, may require prolonged therapy. Surgical drainage is rarely necessary.
- b. Neurobrucellosis: The treatment of central nervous system complications of brucellosis poses a special problem because of the need to achieve high concentrations of drugs in the CSF. Since tetracyclines and aminoglycosides do not penetrate the blood/brain barrier well, it is recommended that drugs which achieve this, such as rifampicin or co-trimoxazole, be added to the standard regimen of doxycycline plus streptomycin.
- c. Brucella endocarditis: Although death from brucellosis occurs in less than 1% of cases, the complication most frequently leading to a fatal outcome is infective endocarditis. The treatment of brucella endocarditis poses special problems because of the need to achieve bactericidal concentrations of drugs within the valvular vegetations. The combination of doxycycline plus an aminoglycoside results in rapid killing of the bacteria, and rifampicin or co-trimoxazole are used for their ability to penetrate cell membranes. Prolonged therapy is recommended and therapy should be continued for several weeks after surgery when valve replacement is necessary.
- d. Treatment of brucellosis during pregnancy: If promptly diagnosed, antimicrobial therapy of pregnant women with brucellosis can be life-saving for the fetus. Pregnant women and nursing mothers pose special problems with regard to the selection of appropriate drugs. All drugs cross the placenta in varying degrees, thus exposing the fetus to potential adverse drug effects. Tetracyclines are contraindicated in pregnancy owing to the potential for permanent staining of fetal dentition, and the susceptibility of pregnant women to drug-induced fatty

necrosis of the liver and pancreatitis. Fetal toxicity has been reported in pregnant women treated with streptomycin; however, there are no reports of toxicity with gentamicin. Consequently, the optimal therapy for brucellosis during pregnancy has not been determined with certainty. Co-trimoxazole has been used in individual cases with reported success. Another alternative is rifampicin therapy for at least 45 days depending on the clinical outcome.

- e. Treatment of brucellosis in children less than eight years of age:
The optimal treatment for brucellosis in neonates and children less than eight years of age has not been definitively determined. Tetracyclines are contraindicated because of the potential for permanent staining of deciduous teeth and inhibition of bone growth. Doxycycline binds less to calcium than other tetracyclines, and may pose less of a risk, however, there are no studies to confirm this with certainty. Consequently, aminoglycosides, co-trimoxazole, and rifampicin are the drugs generally recommended. Cotrimoxazole and rifampicin are not recommended by the manufacturers for use in young children, and the rates of relapse are high when either agent is used alone.

5. *Post-exposure prophylaxis:*

With increasing use of live *Brucella* vaccines to immunize cattle (*B. abortus* strain 19 and RB 51) and sheep and goats (*B. melitensis* strain Rev 1), the problem of accidental self-inoculation by veterinarians is widespread. The majority of vaccine needle-stick injuries cause puncture wounds, but usually little vaccine is injected. However, a potential risk of infection remains and it is advisable to supplement local wound care and tetanus toxoid (when indicated) with a six-week course of doxycycline. It should be noted that *B. abortus* RB 51 is resistant to rifampicin. In contrast, splashing the eyes (conjunctival inoculation) with live *Brucella* vaccines is a very effective method for transmitting brucellosis. Consequently, for

vaccine accidents involving the conjunctival route, local eye care and one or two drugs administered for the full six-week course is recommended. In addition, serum should be tested for antibodies to Brucella as soon after the accident as possible, to provide a baseline for follow-up in case symptoms occur.

Vaccination in humans

There is no convincing evidence of benefit from administering Brucella vaccines or antigen preparations, nor for the use of immune system modulators, such as levamisole, in the treatment of human brucellosis. Caution should be exercised in the use of anti-inflammatory agents to deal with local complications.

Safe and effective vaccines for the prevention of human brucellosis are not generally available. However, vaccination has played a significant role in the prevention of the disease, in conjunction with other measures, in the former USSR and China. Two live attenuated vaccine strains have been employed extensively in heavily infected areas. The vaccine was administered by skin scarification (epicutaneous route). Protection was effective for up to one year but with maximum efficacy at five to six months after vaccination. Local reactions manifested as hyperaemia and induration occurred in 76% of those immunized, whereas general reactions characterized by headache, lethargy and mild pyrexia, occurred in 3 to 7% of vaccinees. Epidemiological studies showed that the vaccine was effective in reducing morbidity in high-risk areas, with a 5 to 11-fold reduction in reported cases of acute brucellosis. However, the vaccine did induce hypersensitivity, especially with repeated doses and there were numerous contra-indications to vaccination.

The availability and use of such vaccines are now quite restricted.

More emphasis in recent years has been on the development of non-living vaccines based on sub-cellular fraction which have received fairly extensive study.

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Annex-1: Incidence (%) of brucellosis in various human populations in India

Sl. No	Source	Vets	Paravets/ Attendants	Abattoir workers	Patients with Fever of Unknown Origin (FUO)	Patients with fever and other symptoms	Occupationally exposed	General population	Remarks	Region
1	Kulshreshtha et al (1978)						18.1%		Haryana	Animal attendants
2	Sharma et al (1979)							1%		UP & Delhi
3	Kapoor et al (1984)							2.97%	101 patients .	Rajasthan
4	Rana et al (1985)	40%	51%						148 sera samples from asst.vets surgeons/paravets in Delhi	Delhi
5	Savalgi et al (1987)						20%		4 out of 20 farm staff	Brucella melitensis
6	Dessai et al (1995)						5.9%		Karnataka	Vets, paravets and shepherds
7	Kumar et al (1997)	29%							Veterinarians	Study from 165 sera samples of
				69%					Animal Handlers	
				68%					Butchers	

				57%					Sweepers	abattoir personnel in Delhi
8	Handa et al (1998)				3.3%		14%		121 cases of FUO and 50 occupationally exposed	North India
9	Mrunalini.N & Ramasastry,P(1999)						15.86%		561 sera samples from Vets, abattoir workers and farmers	AP
10	Kadri et al (2000)				0.8%				Screening of 3532 patients with FUO.	Kashmir
11	Mohanty et al (2000)					6.8%			Most of the positive reactors had history of recent or past fever, orchitis, arthritis or neuralgia	190 sera samples from Vets, paravets & attendents from farms in Odisha
12	Kalla et al (2001)					92%			Rajasthan	Acute polyarthritis
13	Sen et al (2002)				6.8%				Screening of 414 patients with FUO	Varanasi
14	Thakur,S.D & Thapliyal,D.C (2002)	17.39%					4.97	2-6%	352 sera samples	
15	Chahota et al, 2003						10%			Himachal Pradesh

16	Mishra et al (2003)							0.5%	210 sera samples from FOU patients	Gorakhpur, UP	
17	Mudaliar et al (2003)							5.3%	Animal handlers in Pune	Maharashtra	
18	Hussain et al (2004)		11.1 %					7.69 %	Sera samples from 26 farmers, 9 attendants, 4 veterinarians, 2 laboratory workers and other people with FOU.	Assam	
19	Mrunalini et al (2004)	25 %	23%	7%	12%			45%	Farmers, shepherds and occupationally exposed	Andhra Pradesh	
20	Ajay Kumar,V.J & Nanu,E (2005)							1.6%	2.45	250 serum samples (122 from general population and rest from people associated with animals)	Kerala
21	Mantur et al, 2006								1.9%	26948 blood samples from adults above 15 years for a period of 16 years.	Karnataka
22	Agasthya et al (2007)	12%								618 sera samples	
			41%							Karnataka	Vet Inspectors

			31%							Vet assistants
			6%							Vet supervisors
							6%			Group D workers
							2%			Shepherds
				1%						Butchers
23	Appannanavar et al, 2012				9.94%				Sera samples from 1448 FUO patients	North India
24	Gemechu and Gill (2012)	17.8				26.6%		241 sera samples from occupation ally exposed groups	Ludhiana	
25	Prakash et al (2012)	37.14%			25.72%		26.6%	6%	Sera samples from FUO patients-420; Vets & milkmen-70; meat handlers-30; healthy control-50.	
26	Pathak et al, 2014				7.69%			35.89%	282 sera samples from FUO	Goa

Annex-2: Various manifestations of brucellosis in humans reported in India

S.No	Symptoms	Source
1	Neurobrucellosis: (a) Meningoencephalitis (b) Myelitis leading to spastic paraparesis (c) Polyradiculoneuropathy@ (d) Polyneuroradiculomyeloencephalopathy.	Kochar et al., 2000.
2	(a) Acute polyarthritis (b) Low grade fever of 1-2 weeks. (c) Sacroiliitis	Kalla et al., 2001.
3	(a) Spondylitis (b) Sacroiliitis	Gokhale et al., 2003.
4	(a) Persistent fever Joint pain (mainly knee) Back ache Involuntary movements of limbs. Burning sensation of feet. Pityriasis alba \$ Neurobrucellosis: Chorea#, peripheral neuritis & meningitis (h) Skin lesions (i) Carditis	(b) (c) (d) (e) (f) (g) Mantur et al., 2004.
5	(a) Arthritis (b) Abortion (c) Genito- urinary infection	Mudaliar et al., 2003.
6	Persistent fever	Deepak et al., 2003.
7	Pneumonia	Singh et al., 2005.
8	Endocarditis	Purwar et al., 2006.
9	a. Joint Pain b. Fever c. Neurobrucellosis: polyradiculoneuropathy, myeloradiculopathy, meningoencephalopathy and polyradiculomyeloencephalopathy; d. Predominant pulmonary involvement - bronchitis, pneumonia and pleural effusion; e. Epididymo-orchitis, infective endocarditis, f. Nephrotic syndrome g. Recurrent abortion.	Kochar et. el 2007
10	a. Fever , b. Joint pain, c. Genitourinary tract: Epididymo-orchitis, Hydrocele , Urinary tract infection d. Neurobrucellosis: Meningitis , Meningoencephalitis,	Mantur et. al , 2006

	<ul style="list-style-type: none"> e. Endocarditis f. Cutaneous/mucous membrane lesions g. Gastrointestinal tract: Chronic liver disease , Splenic abscess, acute Cholecystitis h. Respiratory system: Pneumonia and Bronchitis 	
11	<ul style="list-style-type: none"> a. Fever, b. Headache, c. Back pain, d. Arthralgia e. Myalgia 	Gemechu and Gill, 2012
<p>§ - Pityriasis alba is a common skin condition mostly occurring in children and usually seen as dry, fine scaled, pale patches on their faces.</p> <p>#- Chorea is an abnormal involuntary movement disorder causing quick movements of the feet or hands.</p> <p>@ - Radiculoneuropathy is not a specific condition, but rather a description of a problem in which one or more nerves (polyradiculoneuropathy) are affected and do not work properly. The nerve or nerves may be inflamed, "pinched," lack blood flow, or may be affected by a disease that is destroying it in part or totally. This can result in pain, weakness, numbness, or difficulty in controlling specific muscles.</p>		