Brucellosis in India – a review

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Brucellosis is an important re-emerging zoonosis with a worldwide distribution. It is still an uncontrolled serious public health problem in many developing countries including India. Brucellosis in India is yet a very common but often neglected disease. Currently, *Brucella melitensis* accounts for most recorded cases globally with cattle emerging as a important reservoir with the few cases of *B. suis*. Isolated cases of non-terrestrial brucellosis and continuing transmission from wild animals have raised important epidemiological issues. Routine serological surveillance along with high clinical suspicion and screening of family members of index cases would be essential in delineating the real magnitude of human brucellosis in endemic countries. Increased business and leisure travel to endemic countries have led to diagnostic challenge in non-endemic areas. Laboratory testing is indispensable for diagnosis. Advances in newer rapid, sensitive, and specific testing methodologies and alternate treatment strategies are urgently needed. A safe and effective vaccine in human is not yet available. Prevention is dependent upon increasing public awareness through health education programmes and safe livestock practices. Active co-operation between health and veterinary services should be promoted. This review collates world literature and its impact to the discovery, isolation and diagnosis and epidemiology along with the control measures adapted in the Indian scenario.

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1. Introduction

Brucellosis is an important re-emerging infectious disease. The disease is closely associated with the evolution of mankind as an agrarian society linked to the practice of shepherding and popularization of animal husbandry. Brucellosis was predominant in the Mediterranean region and its history has been associated with military campaigns. Brucellosis has undoubtedly evolved as a disease since man first domesticated animals. Brucellosis was recognized as a clinical entity from the times of Crimean war. This disease was fully elucidated by Sir David Bruce, Hughes, and Zammit working in Malta. Bang discovered *Brucella abortus*, the cause of abortion in cattle and of brucellosis (undulant fever) in human beings. *B. suis* was recovered from swine by Traum and implicated as an agent of brucellosis in man by Huddleson. Evans showed that *M.melitensis*, isolates of cows and pigs belonged to one genus and generic name *Brucella* in honour of Sir David Bruce was suggested. Buddle and Boyce discovered *B. ovis*. Stoenner and Lackman isolated *B. neotomae* from rat. Carmicheal and Bruner discovered *B. canis* from dogs. Human infections due to *B. canis* are reported. *Brucella pinnipediae* and *cetaceae* are newly recognized marine mammal *Brucellae* that may also be human pathogens (Sohn *et al* 2003; McDonald *et al* 2006). These data re-emphasize the zoonotic concern of *Brucellae* throughout history. *B. abortus* strain 19 and RB51 are effective live attenuated vaccines against *B. abortus* infection in cattle. An effective *B. melitensis* Rev1 vaccine has been developed for sheep and goats.

Keywords. *Brucella* spp.; epidemiology; protean manifestations; serological surveillance; livestock vaccination

Abbreviations used: ELISA, enzyme linked immunosorbent assay; LPS, lipopolysaccharide; 2ME, 2 mercaptoethanol; PCR, polymerase chain reaction; PUO, pyrexia of unknown origin; RBPT, rose Bengal plate agglutination test; SAT, Standard tube agglutination test; S-LPS, smooth-lipopolysaccharide; TMP/SMX, trimethoprim/sulfamethoxazole

2. The bacterium

Brucellae belong to α–2 subdivision of *proteobacteria.* They are Gram-negative, partially acid fast, aerobic, facultative intracellular coccobacilli or short rods. They are oxidase, catalase, nitrate reductase and urease positive. *B. abortus* preferentially infects cattle, *B.melitensis* sheep and goats, *B. suis* pigs and *B. canis* dogs. Above species infect humans with *B.melitensis* being the most common.

2.1 *Genome*

The genome contains two circular chromosomes of 2.1 Mb and 1.5 Mb except *B.suis* biovar 3, which has a single chromosome of 3.1 Mb.

2.2 *Antigenic determinants*

There are two types of smooth lipopolysaccharide (S-LPS) surface antigens, designated A and M. A antigen predominates in *B. abortus* and *B. suis*, while M is the major antigen in *B. melitensis*. Numerous outer and inner membrane, cytoplasmic, and periplasmic proteins have also been characterized.

2.3 *Pathogenicity*

The pathogenicity in human brucellosis is attributed to factors like LPS, adenine and guanine monophosphate, virB, 24 kDa protein, and urease enzyme. *Brucellae* may enter the host via ingestion or inhalation, or through conjunctiva or skin abrasions. The *Brucellae* colonize in different organs with predilection for lymphoreticular system.

2.4 *Host response*

Both antibody and cell-mediated immune responses develop in most patients, but the cellular immunity is the essential component.

3. Epidemiology

Brucellosis is the most common zoonosis in the world, accounting for the annual occurrence of more than 500,000 cases (Pappas *et al* 2006). Although brucellosis and its means of transmission were discovered over 100 years ago, the disease remains a worldwide problem, predominantly so in developing countries. Since the discovery of *B. melitensis* by Bruce, brucellosis has been an emerging disease. The transmission of *Brucella* infection and its prevalence in a region depends upon several factors like food habits, methods of processing milk and milk products, social customs, husbandry practices, climatic conditions, socioeconomic status, and environment hygiene. Environmental sanitation is particularly important in the context of air borne transmission. Brucellosis is almost invariably transmitted to man from infected domestic animals. However, it has been documented beyond doubt, the possibility of human to human transmission of *Brucella* infection (Naparstek *et al* 1982; Lubani *et al* 1988; Mantur *et al* 1996; Tikare *et al* 2008). Human brucellosis was once thought to be predominantly transmitted through animal contact. However, it is now being realized increasingly that animal products such as milk and meat products also play a important role in the disease transmission. Dairy products prepared from unpasteurized milk such as soft cheeses, yoghurts, and ice-creams may contain high concentration of the bacteria and consumption of these is an important cause of brucellosis. It is the commonest mode of transmission in case of *B.melitensis* and *B.abortus* infections in general population. Camel milk is also considered to be the important source of the infection in Middle East countries and Mongolia. Bacterial load in animal muscle tissues is low, but consumption of undercooked traditional delicacies such as liver has been implicated in human infection. Some particular food habits, such as eating aborted fetuses seen in Ecuador, may be implicated in causing human brucellosis. Crushing the umbilical cord of newborn lambs and kids with the teeth is another risky habit. Consuming fresh goat's milk combined with herbal extracts to obtain relief from chronic ailments is reported to be one more risky habit. Skinning stillborn lambs and kids and aborted fetuses, which may be heavily contaminated with *Brucella* spp., also presents a high risk of brucellosis (Awad 1998). Other means of infection include skin abrasions or inhalation of airborne animal manure particles. Contamination of skin wounds may be a problem for persons working in slaughterhouses or meat packing plants or for veterinarians. Hunters may be infected through skin wounds or by accidentally ingesting the bacteria after deer, elk, moose, or wild pigs that they have killed. Inhalation is often responsible for a significant percentage of cases in abattoir employees (Robson *et al* 1993). In addition, laboratory acquired *Brucella* infection due to accidental ingestion, inhalation and mucosal or skin contact is a major health hazard for the laboratory workers handling the cultures of the virulent or attenuated strains. The disease has been recognized as one of the common laboratory- transmitted infections and has been reported to occur in clinical, research, and production laboratories (Bouza *et al* 2005; Centre for Disease Control and Prevention [CDC] 2008). Increased business and leisure travel to endemic countries have led to diagnostic challenge in areas where brucellosis is uncommon. Although *B. melitensis* accounts for most recorded cases, *B. abortus* and *B. suis* cause substantial morbidity in countries in which

they persist in domestic animals, notably in Asia and Latin America. *B. canis* rarely causes overt human disease, and *B. neotomae* and *B. ovis* have not been identified as causes of infection in humans. The presence of brucellosis in wild animals, with a potential for continuous transfer to domestic animals and from them to humans is another epidemiological issue (Cutler *et al* 2005). Those with a professional risk of acquiring infection include livestock producers, abattoir workers, shepherds, farmers, veterinarians, and laboratory personnel. Brucellosis is common in rural areas because farmers live in close contact with their animals and often consume fresh unpasteurized dairy products. However, the vending of dairy products may also bring the disease to urban areas. Brucellosis has worldwide distribution; but nowadays the disease is rare in the United States of America and in many other industrialized nations because of routine screening of domestic livestock and animal vaccination programmes.

3.1 *Global scenario*

Brucellosis remains a major debilitating illness. It is more prevalent in western parts of Asia, India, Middle Eastern, Southern European, and Latin American countries. Human brucellosis is found to have significant presence in rural/ nomadic communities where people live in close association with animals. Worldwide, reported incidence of human brucellosis in endemic disease areas varies widely, from <0.01 to >200 per 100,000 population. For example, Egypt, the Islamic Republic of Iran, Jordan, Oman, Saudi Arabia, and Syrian Arab Republic reported a combined annual total of more than 90,000 cases of human brucellosis in 1990(Awad 1998). The low incidence reported in known brucellosis-endemic areas may reflect the absence or the low levels of surveillance and reporting (McDermott and Arimi 2002). The true incidence of human brucellosis however, is unknown for most countries including India. Human brucellosis is not considered a contagious disease. Hence, clustering could result from common-source outbreaks or time-space clustering of factors that increase the risk of infection (Chomel *et al* 1994; Fosgate *et al* 2002). The species that may infect man are *B. melitensis, B. suis, B.abortus,* and *B. canis*. *B. melitensis* colonizes ovine stock and is the frequent cause of brucellosis, globally in humans. Recent re-emergence in Malta and Oman indicates the difficulty of eradicating this infection (Amato-Gauci 1995). Sheep and goats and their products are the main sources of infection by *B. melitensis* in humans, but *B. melitensis* infection in cattle is emerging as a potential problem in some southern European countries, Israel, Kuwait, and Saudi Arabia. *B. melitensis* infection is particularly problematic because *B. abortus* vaccines do not protect effectively against *B. melitensis* infection; the *B. melitensis* Rev1 vaccine has not been fully evaluated for use in cattle. In some South American countries, particularly Brazil and Colombia *B. suis* biovar 1 has become established in cattle leading to human infections. The importance of screening of household members of acute brucellosis cases in endemic areas has recently been emphasized (Almuneef *et al* 2004; Mantur *et al* 2006). This is an important epidemiological step. This must be taken into account by the family clinicians, so that timely diagnosis and provision of therapy occur, resulting in lower morbidity. The recent isolation of distinctive strains from marine mammals and humans has extended the ecologic range of the genus and, potentially its scope as a zoonosis. Since new strains may emerge and existing types adapt to changing social and agricultural practices, the picture remains incomplete. Males are affected more commonly than females which may be due to risk of occupational exposure. Although human brucellosis affects all age groups, it is said to be rare in childhood. However, in areas, where *B. melitensis* is endemic, pediatric cases are seen (Caksen *et al* 2002; Mantur *et al* 2004a).

3.2 *Indian scenario*

Brucellosis is a significant and increasing veterinary and public health problem in India. In India 80% of the population live in approximately 575000 villages and thousands of small towns; have close contact with domestic/ wild animal population owing to their occupation. Hence, human population stand at a greater risk of acquiring zoonotic diseases including brucellosis. The disease has an added importance in countries like India, where conditions are conducive for wide-spread human infection on account of unhygienic conditions and poverty. Species of main concern in India are *B. melitensis*, and *B. abortus. B. melitensis* is the most virulent and common strain for man and it causes severe and prolonged disease with a risk of disability. *B. abortus* is the dominant species in cattle. Bovine brucellosis is widespread in India and appears to be on the increase in recent times, perhaps due to increased trade and rapid movement of livestock (Renukaradhya *et al* 2002). The preponderance of natural bull service in rural India, especially in buffalo, is perhaps yet another important factor in the maintenance and spread of infection. Free grazing and movement with frequent mixing of flocks of sheep and goats also contribute to the wide distribution of brucellosis in these animals. Chahota *et al* (2003) have reported a severe outbreak of brucellosis in an organized dairy farm leading to abortions, retained placenta and still birth in cows. The diagnosis was made by serology employing rose Bengal plate agglutination test (RBPT) and standard tube agglutination test (SAT) and confirmed by the isolation of *B. abortus* biotype1. The presence of brucellosis in India was first established early in the previous century and since then has been reported from almost all states

(Sehgal and Bhatia 1990; Renukaradhya *et al* 2002) , but the brucellosis situation varies widely between states. Several published reports including recent ones indicate that human brucellosis is quiet common disease in India. Mathur (1964) reported 8.5% sero-prevalence of brucellosis among dairy personnel in contact with infected animals. In a separate study carried out by Mathur (1968) in Haryana, concluded the goats and sheep as the sources of human infection by isolating *B. melitensis* as a predominant strain from human blood as well as milk samples from goats and sheep. As many as 4.2% aborted women were seropositive for the disease (Randhawa *et al* 1974). In Gujarat, 8.5% prevalence of *Brucella* agglutinins was recorded in human cases (Panjarathinam and Jhala 1986). The study conducted by Thakur and Thapliyal (2002), revealed a prevalence rate of 4.97% in samples obtained from persons exposed to animals. The much higher seroprevalence rate has been also noted in specific risk groups such as abattoir workers (Barbuddhe *et al* 2000; Chadda *et al* 2004). These observations support the occupational risk factors.

Some workers have screened pyrexia of unknown origin (PUO) cases for evidence of brucellosis. Handa *et al* (1998), identified 4 (3.3%) cases with acute brucellosis in a group of 121 patients with PUO. Sen *et al* (2002), identified 28(6.8%) seropositive cases in a group of 414 patients with PUO and Kadri *et al* (2000), identified 28(0.8%) seropositive cases in a group of 3,532 patients with PUO.

A prevalence of 3% was observed among patients attending Karnataka Medical College, Hubli (Mantur 1988). A study by Mantur *et al* (2004a) reported 93 children with brucellosis in Bijapur with a prevalence of 1.6% by SAT (≥ 1:160). A recent publication by Mantur *et al* (2006) reported 495 adult patients in Bijapur with the prevalence of 1.8%. Subsequent continuation of the study in Bijapur, additional 111 cases were reported (Mantur *et al* 2007a, 2008a,b; Tikare *et al* 2008). In a separate study by Mantur and colleagues identified 63 cases at Belgaum Institute of Medical Sciences, Belgaum (Mantur BG and colleagues, unpublished work). In a study at Vellore, Koshi *et al* (1971) reported 10 cases of brucellosis diagnosed by serology or by isolation. In another study, 92 patients were reported from Vellore. Kochar *et al* (2007) reported 175 cases of brucellosis from Bikaner. However, the epidemiological data on this disease is frequently incomplete. This is partly explained by the absence of proper laboratory facilities, lack of awareness of endemicity, under-reporting as well as poor co-operation and exchange of information between veterinary and health services.

4. Disease spectrum

Human brucellosis is known for protean manifestations (Mantur *et al* 2004a, 2006) (table 1). However, the most common presenting symptom is fever. The symptoms and signs most commonly reported are fever, fatigue, malaise, chills, sweats, headaches, myalgia, arthralgia, and weight loss (Kochar *et al* 2007; Mantur *et al* 2007b). Brucellosis is invariably under-diagnosed, likely because of misleading clinical picture (Corbel 1997). These febrile patients may be referred to as patients with PUO or the symptoms and signs are confused with those of other diseases. Thus to an unaware physician, the clinical diagnosis becomes a challenging one.

4.1 *Complications*

Complications can be very diverse depending on the specific site of infection. Bone and joint involvement is the most frequent complication of brucellosis (Mousa *et al* 1987). Epididymoorchitis is the most frequent genitourinary complication in men. Brucellosis during pregnancy poses a substantial risk of spontaneous abortion or intrauterine transmission of infection to the infant. We have detected in Belgaum, three cases suffering from brucellosis during pregnancy and are under treatment. Invasion of central nervous system occurs in about 5–7% of the cases of *B. melitensis* infection. *Brucella* endocarditis occurs in less than 2% of cases but accounts for the majority of deaths.

Table1. Clinical findings in 792* patients infected with *B. melitensis*

Symptoms / signs	No. of patients (%)
Fever (> 37.5°C)	625 (78.9)
Joint pain	183 (23.1)
Low backache	118 (14.8)
Night sweats	31 (3.9)
Cough, breathlessness, haemoptysis	28 (3.5)
Testicular pain, scrotal swelling, burning micturition	16 (2)
Pain in abdomen, nausea, vomiting, anorexia, jaundice	26 (3.2)
Headache	20 (2.5)
Fatigue	14 (1.7)
Papules**, mouth ulcers	11 (1.38)
Convulsions	2 (0.25)
Splenomegaly	147 (18.5)
Hepatomegaly	90 (11.3)
Hepatosplenomegaly	121 (15.2)
Lymphadenopathy	23 (2.9)
Jerky movements of limbs	1 (0.1)
Burning feet	1 (0.1)
Swollen hand	2 (0.25)
Weakness	1 (0.1)
Weight loss	8 (1.0)

* Data of the institutions where cases were identified.

** One case was also associated with subcutaneous nodules.

Complications involving the skin although rare, are reported. Respiratory tract complications may be seen in abattoir workers. Recent reports (Pappas *et al* 2003; Mantur *et al* 2006) indicate that the pulmonary involvement is not that rare. The reports of unusual manifestations with atypical lesions are on the rise. Tsolia *et al* (2002) have noted unusual complications in two children. In our series, we reported complications (arthritis excluded) in 9.4 % (table 2) of patients with unusual manifestations like chorea, hydrocele, Stevens-Johnson syndrome, urinary tract infection (Mantur *et al* 2004a, 2006). Recently, acute panniculitis as unusual presentation of brucellosis has been reported (Tanyel *et al* 2008). We have identified in Belgaum, atypical lesions like haemorrhagic epididymo-orchitis, cellulitis, severe anemia, facial palsy with hemiplegia and infertility (table 2).

Table 2. Complications of Brucellosis

Complication	No. of Cases
Genitourinary(17)	
Epididymo-orchitis*	12
Hydrocele	02
Urinary tract infection	01
Pyonephrosis	01
Infertility	01
Neurobrucellosis(16)	
Meningitis	08
Meningoencephalitis	05
Chorea	01
Peripheral neuritis	01
Facial palsy with hemiplegia	01
Endocarditis	11
Cutaneous/ Mucous membrane lesions**	11
Gastrointestinal tract(10)	
Chronic liver disease	08
Splenic abscess	01
Ac. Cholecystitis	01
Respiratory system(09)	
Pneumonia	04
Bronchitis	05
Hematologic complication(01)	
Severe anemia	01
Total	75

* One case was haemorrhagic; one was associated with cellulitis.

** Included a case of Stevens – Johnson syndrome and a case of cellulitis.

5. Diagnosis

Brucellosis imitates variety of clinical entities. Clinicians practicing in endemic areas must be familiar with this disease and develop a high degree of clinical suspicion based on epidemiological information. Otherwise because of the deceptive nature, the disease may be easily misdiagnosed or diagnosis may be delayed thereby making clinical diagnosis a challenge.

5.1 *Laboratory diagnosis*

Diagnostic tools include isolation and identification of *Brucellae* from clinical samples, detection of antigen, genome, and antibodies.

5.1.1 *Culture:* Blood culture provides definite proof of brucellosis but may not provide a positive result for all patients. Lysis centrifugation and blood clot culture techniques have yielded encouraging results in recent reports (Mantur and Mangalgi 2004b; Mantur *et al* 2007a) in terms of sensitivity and rapidity. The modern automated blood culture systems have somewhat improved the speed of detection. Although bone marrow cultures are considered the gold standard in some studies (Gotuzzo *et al* 1986; Mantur *et al* 2008a), results have not been universally reproducible (Shehabi *et al* 1990). In such cases, bacteremia might also be maintained from other sources of the reticulo-endothelial system (Mantur *et al* 2008a,b). Perhaps, this could be the reason for the discrepancy in the results of blood and bone marrow cultures reported in the literature.

5.1.2 *Antigen detection:* There is only one report (Al-Shamahy and Wright 1998) suggesting antigen detection by enzyme linked immunosorbent assay (ELISA) as an acceptable alternative to blood culture. Although antigen detection methods are potentially useful but have not been validated.

5.1.3 *Genome detection:* Polymerase chain reaction (PCR)has been explored for the rapid detection and confirmation of *Brucella*. Molecular characterization techniques described in the literature are very useful tools for differentiating *Brucella* spp., especially follow-up testing of unusual phenotypic results.

5.1.4 *Antibody detection:* The limitations of aforementioned tools make serology directed against antibody detection the most useful tool. Antibodies usually begin to appear in the blood at the end of the first week of the disease, IgM appearing first followed by IgG.

5.1.4.1 *Agglutination tests:* RBPT is of value as a screening test especially in high risk rural areas where it is not possible to perform SAT. Whenever possible, a serum that gives a positive result should be confirmed by a more specific test. RBPT also plays a great role in the rapid confirmation of neurobrucellosis, arthritis, epididymoorchitis, hydrocele

due to *Brucella* if the neat is positive in cerebrospinal fluid, synovial fluid, testicular fluid /semen and hydrocele fluid respectively.

SAT remains the most popular and yet used worldwide diagnostic tool. SAT measures the total quantity of agglutinating antibodies (IgM and IgG), and the quantity of specific IgG is determined by 2-mercaptoethanol (2ME). SAT titres above 1:160 are considered diagnostic in conjunction with a compatible clinical presentation. In endemic areas, a titre of 1:320 as cutoff may make the test more specific. The of type of antibody is important, as IgG antibodies are considered a better indicator of active infection and the rapid fall in the level of IgG antibodies is said to be prognostic of successful therapy. The studies by (Almuneef and Memish 2002; Mantur *et al* 2006) have shown persistence of various levels of SAT antibodies in many clinically cured patients. This emphasizes the over diagnosis and diagnostic challenges faced in an area where typhoid, malaria, tuberculosis and rheumatoid arthritis clinically mimic human brucellosis, thereby exposing/ denying patients access to specific therapy. However, study of Mantur *et al* (2006) reflected importance of the 2ME test for diagnosis in conjunction with the SAT, as well as for follow up (figure 1).

Coombs test that detects incomplete antibodies and immunocapture-agglutination tests have shown similar performances with higher sensitivity and specificity in the diagnosis.

5.1.4.2 *ELISA:* A comparison with the SAT, ELISA yields higher sensitivity and specificity (Gad El-Rab and Kambal 1998). ELISA is also reported to be the most sensitive test for the diagnosis of neurobrucellosis (Araj 1997).

5.1.4.3 *Newer rapid assays: Brucella* IgM and IgG lateral flow (Smits *et al* 2003) and latex agglutination (Abdoel and Smits 2007) assays have been found to be rapid and simple along with high sensitivity and specificity in culture confirmed cases. These tests are ideal for use as field tests in remote areas and as point of care tests in hospitals and health care centres.

The brucellosis is very often under diagnosed as shown in the data presented in table 3, where 672 (84.8%) cases would have been missed if routine serological surveillance had not been done. Alertness of clinicians and close collaboration with the microbiologist are essential even in endemic areas to correctly diagnose and treat protean human brucellosis (Mantur *et al* 2004a, 2006, 2007b). Data sharing between medical and veterinary practitioners is essential for diagnosis and eradicating this infection from public health point of view.

6. Treatment and prevention

Brucellae are inaccessible to antibiotics as they are facultative intracellular pathogens. Many antimicrobials are active against *Brucella* species; however, clinical efficacy does not always correlate with in vitro susceptibility (Hall 1990). The treatment recommended by the World Health Organization for acute brucellosis in adults is rifampicin 600 to 900mg and doxycycline100mg twice daily for a minimum of six weeks (FAO/WHO 1986). Some still claim that the

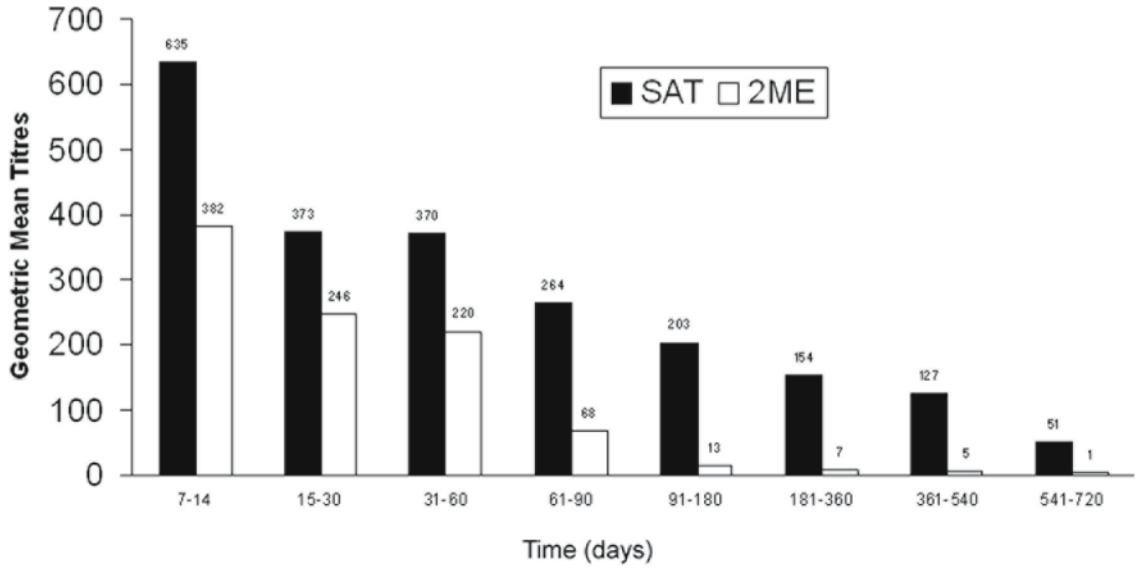

Figure 1. Results of the SAT and 2ME tests at different follow-up times in 79 cases. In most cases, in spite of falling to low levels, *Brucella* SAT titres remained measurable with significant titres despite an effective therapy and clinical cure, but there was a sustained drop in 2ME titres in 97.5% (77 / 79) of cases.

combination of intramuscular streptomycin (1 g/day for 2-3 weeks) with an oral tetracycline (2 g/day for 6 weeks) gives fewer relapses (Ariza *et al* 1985; Mantur *et al* 2006). Trimethoprim-sulfamethoxazole (TMP/SMX) is a popular compound in many areas, usually used in triple regimens. Various combinations that incorporate ciprofloxacin and ofloxacin have been tried clinically, yielding similar efficacy to that of the classic regimens (Karabay *et al* 2004). Additional experience is needed in order to determine the role of fluoroquinolones in the treatment of brucellosis. Alternatives to the classic drugs like gentamycin for streptomycin and the efficacy of alternative drug combinations have been partially explored needing further elucidation in controlled trials before they become treatment regimens. This search becomes pertinent in the view of today's treatment regimens incorporating antitubercular drugs. Childhood brucellosis can be successfully treated with a combination of two drugs; Doxycycline 4 mg / kg / day and rifampicin 10 mg/kg /day orally for six weeks. Some authors advise that gentamycin (5 mg/kg/day intramuscularly) be administered concomitantly for the initial 5-7days of therapy in order to prevent relapse (Hall 1990; Mantur *et al* 2004a). TMP/SMX 8 mg/40 mg/ kg/day can be used for children < 6 years of age. Rifampicin with or without a combination of TMP/SMX has proved safe to treat brucellosis during pregnancy. Relapses can be treated with a repeated course of the usual antibiotic regimens. Most complications of brucellosis can be adequately treated with standard regimens with few requiring longer courses. For neurobrucellosis, combination therapy with two or three drugs - that is doxycycline, rifampicin, and TMP/SMX that penetrate central nervous system is recommended (McLean *et al* 1992). The combination of doxycycline with rifampicin and trimethoprim-sulfamethoxazole has been used successfully in the treatment of brucellar endocarditis. However, it is generally believed that surgical intervention (valve replacement) combined with antibiotic therapy is the best approach.

Table 3. Clinical diagnosis of 792* cases following initial examination

Principal / Differential diagnosis	No. of cases (%)
Enteric fever	258(32.5)
Malaria	122(15.4)
Arthritis	89 (11.2)
Brucellosis	120(15.1)
Pyrexia of unknown origin	65(8.2)
Epididymo-orchitis,**bilateral hydrocele, urinary tract infection, pyonephrosis, infertility	17(2.1)
Tuberculosis	8(1.01)
Chronic liver disease, splenic abscess, acute cholecystitis	11(1.3)
Endocarditis	11(1.3)
Bronchitis, Pneumonia	9 (1.1)
Skin rashes, Stevens-Johnson syndrome,Cellulitis	11(1.3)
Meningitis	8(1.01)
Human immunodeficiency virus infection	5 (0.6)
Encephalitis	5(0.6)
Malaria, enteric fever, brucellosis***	3(0.3)
Enteric fever, brucellosis***	44(5.5)
Pulmonary tuberculosis, brucellosis***	1(0.12)
Rheumatic arthritis, brucellosis***	1(0.12)
Chorea	1(0.12)
Peripheral neuritis	1(0.12)
Facial palsy with hemiplegia	1 (0.12)
Severe anemia	1 (0.12)

*includes
(i) 30 cases from KMC Hubli (Mantur 1988).
(ii) 699 cases from Bijapur (Mantur *et al* 2004a, 2006, 2007a, 2008a,b; Tikare *et al* 2008).
(ii) 63 cases from Belgaum Institute of Medical Sciences, Belgaum (Mantur B G and colleagues, unpublished).

**One case was haemorrhagic; one case was also associated with cellulitis.

***Differential diagnosis.

Prevention of human brucellosis is dependent on control of the disease in domestic livestock mainly by mass vaccination (Nicoletti 2001). In many countries, the use of *B.abortus* strain vaccine in cattle and *B.melitensis* strain Rev1 vaccine in goats and sheep has resulted in the elimination or near-elimination of brucellosis in these animals. A plan for the control of bovine brucellosis has already been developed in India (Renukaradhya *et al* 2002). Also, the Government of India has made it mandatory to regularly screen all the breeding bulls from artificial insemination centres for brucellosis and to use brucellosis free bulls for semen production. However, as brucellosis transmitted from small ruminants poses a significant health risk factor, efforts are urgently required to control brucellosis in goats and sheep also. Studies are ongoing to develop an effective vaccine against *B. suis*. Since the treatment of animal brucellosis is very expensive, one should encourage the mass vaccination of livestock. Animal owners should be taught about the importance of vaccination of their animals. In spite of the clinical efficacy and cost effectiveness of vaccination, the

limited availability of vaccines and lack of awareness have led to the persistence of brucellosis in most areas especially India. This has led to screening and slaughtering of infected animals causing economic burden.

The lack of human vaccines and effective control measures make it necessary for the doctors and other health care workers to take protective measures. Protective clothing / barriers while handling still births / products of conception and cultures can reduce occupation-related brucellosis (Young 1995). The avoidance of unpasteurized dairy products will prevent infection in the general population. A control programme for human brucellosis would depend to a large extent on public health education about the disease and its risk factors, good administrative arrangement and ensuring the maximum co-operation of the community, particularly between health and veterinary authorities.

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