CHAPTER - II

REVIEW OF LITERATURES

2.1 BRUCELLOSIS

Brucellosis is caused by members of genus *Brucella*. The ability of *Brucella* to replicate and persist in host cells is directly associated with its capacity to cause persistent disease and to circumvent innate and adaptive immunity (Fichi, 2003). The species of *Brucella* and their major hosts are *B. abortus* (cattle), *B. melitensis* (goats), *B. suis* (swine) and *B. ovis* (sheep). *B. abortus* also causes infection in horses and is commonly found in chronic bursal enlargements as a secondary invader rather than a primary pathogen (Radostits et al., 2000).

The virulence depends on survival and replication properties in different cell type, in which *Brucella* controls the maturation of its vacuole to avoid innate immune responses and to reach its replicative niche associate with the endoplasmic reticulum.

Many countries have reported a high incidence of adult and childhood Brucellosis with serious economic and public health sequelae. To date, human infection by *Brucella* organism has been caused by four species - *Brucella melitensis, B. abortus, B. suis and B. canis* (WHO., 1986).

2.2 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 the means of transmission were known over 100 years but the disease is remaining a worldwide problem, especially in all developing countries.

Several factors are affecting the prevalence of Brucella infection in a region. This includes food habits, methods of processing milk and milk products, social customs, animal husbandry practices, climatic conditions, socioeconomic status and environment hygiene. Environment hygiene is important in the contest of airborne 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 (Lubani et al., 1988; Mantur et al., 1996; Tikare et al., 2008).

Human brucellosis was once thought to be transmitted through animal contact. However, it is now being realized increasingly that animal products such as milk and meat products also play an 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.

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. 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).

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 now a day 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.

2.2.1 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 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. 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 and Mantur *et al.*, 2004).

2.2.2 Indian scenario

Brucellosis is a significant and increasing veterinary and public health problem in India. In India, 80% of the population live in approximately 575,000 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 \textit{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 reported 8.5% sero-prevalence of brucellosis among dairy personnel in contact with infected animals. In a separate study carried out by Mathur, in Haryana, concluded the goats and sheep as the sources of human infection by isolating \textit{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 \textit{Brucella} agglutinins was recorded in human cases (Panjarathinam et al., 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., (2004) 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., 2007, 2008a,b; Tikare et al., 2008).

In a study at Vellore, Koshi et al., (1971) reported 10 cases of Brucellosis diagnosed by serology or by isolation. 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.

Basappa et al., (2008) clearly stated that Brucellosis is an important re-emerging zoonosis of 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*. They also explains that 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. There are many reports in the incidence of Brucellosis in India (Mahakur and Panda, 1972).

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.

**2.3 GENERAL CHARACTERS OF BRUCELLA**

The genus Brucella consist of six classic species designated on the basis of host preference antigenic and biochemical characteristics as Brucella melitensis commonly infects goats and sheep, Brucella abortus which cause infection in cattle, Brucella suis in Pigs, Brucella canis in dogs, Brucella ovis in Sheep and Brucella neotomae in wood rats.

Brucella is an aerobic facultative intracellular pathogen. They shows certain peculiar characteristics. The bacterium does not bare classic virulence factors such as capsules, secreted proteases, Exotoxins, Endotoxins, pili and fimbriae or virulence plasmid and
its lipopolysaccharide Pathogenicity is not typical. It exhibits a tendency to invade and persist in the human host through inhibition of programmed cell death.

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

\subsection{2.3.1 Life Cycle of \textit{Brucella}}

The bacteria enter the body mainly through digestive tract, lungs or mucosal layers and intact skin. Then from the initial site they may spread from lymphatic channels or blood stream and reaches certain organs infect the tissues and causes localised infections (Lapaque \textit{et al.}, 2005). The organism escapes phagocytosis through inhibiting the phagosome-lysosome fusion and reproducing inside the macrophages (Young, 2005). After a period of few weeks to several months, non specific systemic symptoms such as fever, head ache, malaise, night sweat and arthralgia follow, resuming a flu like disease. During the early stage of the disease, patients are frequently bacteremic and organisms are seeded to multiple organ systems especially those rich in reticuloendothelial tissue such as liver, spleen, skeletal and hematopoietic system (Greenfield \textit{et al.}, 2002).

\subsection{2.3.2 Mode of Transmission}

\textit{Brucellosis} is transmitted mainly through infected animals to human. There is no evidence of transmission of the disease from human to human. Most commonly infection occurs by direct contact with infected tissues, blood, urine, Vaginal discharge, aborted fetus
and through infected placenta. Infection takes place through abraded skin, mucosa or conjunctiva.

Infection may take place indirectly by the ingestion of raw milk or dairy products from infected animals. Fresh raw vegetables can also carry infection if grown on soil containing manure from infected farms.

The environment of a cow shed may be heavily infected. Brucellae may be inhaled in aerosole form in slaughterhouse or laboratories.

### 2.3.3 Pathogenesis

The Pathogenicity in human brucellosis is attributed to factors like LPS, adenine and guanine monophosphate, virB, 24 kDa protein, and urease enzyme. Once infection is established the organisms are carried from the point of entry to the regional lymph nodes, leading to acute lymph adenitis. Bacteria multiply inside phagocytes and disseminated through systemic circulation to other organs or tissues such as the spleen, lymph nodes, uterus and the mammary glands. In male, Brucella abortus can be found mostly in the testicle where the organism cause orchitis, and accessory sex glands as well as lymphoid tissue. The bacteria can last for months, and in cases of chronic disease it can be intermittent, recurring mostly around parturition.

The bacteria localise in the uterus during gestation and cause ulceration of the endometrium. The initial lesions are seen on the wall of the uterus, but the organism quickly spreads to the placental cotyledons and destroys the villi. Depending on the severity of the lesions potential sequelae include abortion
especially in the second trimester (Poole et al., 2002), stillbirths and premature calves, and the animal remains infected for life.

2.3.4 Clinical Manifestations of Brucellosis

Human Brucellosis has a wide spectrum of clinical manifestation which is variable and polymorphic. It depends on the stage of the disease, and the organ and system involved. Brucella has been reported to compromise the central and peripheral nervous system, gastrointestinal, hepatobiliary, musculoskeletal, cardiovascular, and integumentary systems. There are acute, sub acute and chronic stages based on the persistence of clinical complaints. The disease starts with fever, sweat, anorexia, fatigue, low back pain, and arthralgia.

Mantur et al., (2004, 2006) reported that human brucellosis is known for protean manifestations. 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., 2007). 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.

2.3.5 Complications

Arthritis is a common complication of Brucellosis especially in young men (Ewals, 2005). There are reports of significant number of positive cases with Brucella spondulitis and sacroiliitis in the general population. Genitourinary localization has been reported in
2 % to 20% of cases involving the testicle and epididymis (Young, 1983). This can take the form of orchiepididymitis, dysuria, hematuria or rarely pyelonephritis (Soman, 1994). Prostatitis, cystitis and pyelonephritis are rare complications. Mathur reported orchitis in 18% of the cases.

Poole et al. (2002) reported a case of spontaneous abortion during the second trimester in a patient who had serological evidence of acute Brucellosis.

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 substantial risk of spontaneous abortion or intrauterine transmission of infection to the infant. In Belgaum, three cases suffering from brucellosis during pregnancy were underwent 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 (Basappa et al., 2008).

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. There are also patients with unusual manifestations like chorea, hydrocele, Stevens-Johnson syndrome, urinary tract infection (Mantur et al., 2004, 2006). Recently, acute panniculitis as unusual presentation of brucellosis has been reported (Tanyel et al., 2008).
2.3.6 Immunity in Brucellosis

Little is known about the changes in antibody concentration and the level of antibodies in persons with chronic disease, Past infection, and Occupational exposure. Gazapo et al. (1989) reported that a complete recovery from infection is normally followed by a sharp reduction in antibody levels beginning two months later.

2.4 DIAGNOSTIC METHODS

Human Brucellosis is diagnosed on the basis of clinical findings and laboratory studies that include bacteriological and serological tests. The method of isolating Brucella species from the blood of patient is successful in only 40 to 70 % of the cases (Yaguspsky, 1999). Therefore diagnosis of Brucellosis very often relies on detecting specific serum antibodies (Diaz et al., 1989). Diagnosis is not difficult if the clinical presentation is typical, but the varied manifestation of localised, acute, or chronic infection sometimes lead to misdiagnosis (Young, 1995).

A study by Foglis et al. (1999), reported the advantage of STAT for detecting the combined IgM, IgA and IgG antibodies in serum, but he has also mentioned that its diagnostic specificity is poor, especially when the titre are low. Cross reaction with other Gram negative bacteria have been observed and the diagnostic end point agglutination titre has not been satisfactorily established.

Ariza et al. (2007) have reported that most patients with persistently high titres of IgG antibody had the highest titres at admission or had focal diseases. The persistence of high titres of I
gG antibodies in patients without a high initial titre may be indicative of chronic disease.

PCR confirmation of cutaneous manifestation due to *Brucella melitensis* was done and the test was shown high sensitivity for detecting Brucella antibodies (Mutnal *et al.*, 2007).

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

### 2.4.1 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 *et al.*, 2004; Mantur *et al.*, 2007) 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.*, 2008), 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.*, 2008). Perhaps, this could be the reason for the discrepancy in the results of blood and bone marrow cultures reported in the literature.
2.4.2 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.

2.4.3 Antibody detection

The limitations of above mentioned 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.

2.4.4 Agglutination tests

RBPT is of value as a screening test especially in high risk rural areas where it is not possible to perform STAT. 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 (Basappa et al., 2008)

STAT 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 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 identifying 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.

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

### 2.4.5 Enzyme linked immunosorbant assay

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).

*Brucella* IgM and IgG lateral flow (Smits and Ficht, 1990) 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, 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., 2004, 2006, 2007). Data sharing between medical and veterinary practitioners is essential for diagnosis and eradicating this infection from public health point of view.

2.4.6 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.

2.5 TREATMENT

*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 (WHO 1986).

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 (5mg/kg/day intramuscularly) be administered concomitantly for the initial 5-7 days of therapy in order to prevent relapse (Hall, 1990; Mantur et al., 2004).

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 brucella endocarditis. However, it is generally believed that surgical intervention (valve replacement) combined with antibiotic therapy is the best approach.

2.6 PREVENTION
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.

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.

2.7 CONTROL OF BRUCELLOSIS

Vaccination and the use of test and slaughter programmes are the most frequently utilized control strategies. Precaution against the spread of Brucellosis, include the segregation of newly purchased animals and the segregation of animals when they are giving birth.

Vaccination programmes that target cattle against *B. abortus* have proved effective but attempts to control *B. melitensis* in sheep and goat is more difficult due to the difficulty in identifying, vaccinating and monitoring infected folks and in controlling their movements.

Pasteurisation of milk is another protective mechanism. All milk and other dairy products should be heat -treated to kill the bacteria. Effort can be made to improve hygiene and reduce the chance of contact between infected and non-infected animals.