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## The genus *Brucella* and clinical manifestations of brucellosis

### O gênero *Brucella* e as manifestações clínicas de brucelose

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#### - REVIEW -

#### ABSTRACT

Infection with bacteria of the genus *Brucella* results in major economic and political impact by causing reproductive diseases in a significant number of domestic animal species. Moreover, it has a great social significance, since many species are capable of causing human infection, with severe consequences. Dissemination of knowledge on a specific disease is an essential step for its control. Considering that brucellosis is still the most prevalent zoonosis in the world, information about taxonomy, clinical signs in domestic animals and humans are crucial for attempting to reduce the prevalence of this disease. The recent isolation and characterization of non-classical species of *Brucella* indicates that a lot remains to be discovered about this genus. Nevertheless, due to the social-economic importance of brucellosis, this review aims to clarify points related to taxonomy of the genus and describe the clinical relevance of infection in humans and domestic animals.

**Key word:** Brucellosis, *Brucella*, taxonomy.

#### RESUMO

A infecção por bactérias do gênero *Brucella* apresenta grande importância econômica e política por causar doenças com impacto reprodutivo em um número significativo de espécies de animais domésticos. Além disso, possui grande importância social, já que várias espécies são capazes de causar infecção humana, com graves consequências. A difusão do conhecimento em relação a uma determinada doença é um passo essencial para o seu controle. Considerando-se que a brucelose ainda é a zoonose mais prevalente no mundo, informações sobre a taxonomia, os principais sinais clínicos nas diferentes espécies domésticas e os diferentes aspectos da doença humana são de importância crucial para a tentativa

de diminuir a prevalência dessa enfermidade. O recente isolamento e a caracterização de espécies não clássicas de *Brucella* demonstram que ainda há muito a ser descoberto sobre esse gênero. Tendo em vista a importância socioeconômica da infecção por *Brucella* spp., esta revisão tem como objetivos esclarecer pontos relacionados à taxonomia do gênero, bem como descrever aspectos clínicos relevantes na infecção humana e nas diferentes espécies domésticas.

**Palavras-chave:** Brucelose, *Brucella*, taxonomia.

#### INTRODUCTION

*Brucella* spp. are Gram-negative, facultative intracellular pathogens. In nature, *Brucella* spp. are pathogens that do not multiply in the environment, but usually are transmitted directly from host to host. (GORVEL & MORENO, 2002). These organisms belong to the genus *Brucella* and cause brucellosis, which has variable clinical features that are strongly dependent on the bacterium and host species. Some of these organism can potentially cause human infections, resulting in one of the most important and widespread bacterial zoonosis in the world (SANTOS et al., 2005).

The genus *Brucella* was named after David Bruce, who first isolated the organism (then named *Micrococcus melitensis*) in 1887 from the spleen of a soldier suffering from a disease that was called Malta

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Fever (NICOLETTI, 2002; SANTOS et al., 2005). The zoonotic nature of brucellosis was demonstrated in 1905 by isolating *Brucella* from goat milk (NICOLETTI, 2002). Importantly, even as late as 1955, over 200 cases of brucellosis were caused by ingestion of a special cheese from Maltese goats (WYATT, 1999). In 1895, 1914, and 1966, *Brucella* species were isolated from aborted bovine, swine, and canine fetuses, respectively. In 1953, *Brucella ovis* was identified as a cause of epididymitis in rams (NICOLETTI, 2002). In the last 15 years 3 new non-classical species of *Brucella* has been identified (ROSS et al., 1994; FOSTER et al., 1996; SCHOLZ et al 2008a). The recent isolation and characterization of non-classical species of *Brucella* demonstrates that in spite of brucellosis being an old disease, there is still several aspects of these organisms and their associated diseases that remain unknown.

#### Taxonomy

Taxonomy is important to identify and classify in logical order the great diversity of living beings (MORENO et al., 2002). The genus *Brucella* belongs phylogenetically to the  $\alpha$ -proteobacteria, a group that contains bacterial species with a wide variety of lifestyles, including symbionts of animals and plants (*Wolbachia*, *Sinorhizobium*), as well as obligate or facultative intracellular and extracellular pathogens, such as *Rickettsia*, *Brucella* and *Agrobacterium* (TSOLIS, 2002).

Six species are currently recognized within the genus *Brucella*: *B. melitensis*, *B. abortus*, *B. suis*, *B. ovis*, *B. canis*, and *B. neotomae*. This classification is mainly based on differences in biochemical characteristics, pathogenicity and host preferences (Table 1). Each of these species of *Brucella* is adapted to a specific host, but not exclusively (ALTON et al, 1975; ALTON 1990).

These marine mammal *Brucella* isolates have phenotypic and molecular features as well as host preferences that are clearly distinct from the six previously recognized species (JAHANS et al., 1997; CLAVAREAU et al., 1998; VERGER et al., 2000; WATSON et al., 2003; JACQUES et al., 2007). In 2000, a new species of the genus, with different features when compared to other known species, was isolated from the rodent *Microtus arvalis*, and named of *B. microti* (SCHOLZ et al., 2008a). Recently, a novel *Brucella* species has been isolated from post partum uteruses of pregnant baboons with history of stillbirth (SCHLABRITZ-LOUTSEVITCH et al., 2009).

In recent years, an important controversy has developed concerning the taxonomy of the genus *Brucella*. Although *Brucella* species can be

differentiated by conventional phenotypic tests, these species display a high degree of DNA homology in DNA-DNA hybridization assays (>90% identity), including the recently recognized marine mammal strains (VERGER et al., 1987, 1998, 2000). Therefore, it has been proposed that the genus *Brucella* should be a monospecific genus, with *B. melitensis* as the sole species and the other species should be considered as biovars (VERGER et al., 1985, 1987). Conversely, several molecular genotyping methods have been developed and applied to characterize *Brucella* species, indicating that significant DNA polymorphisms occur between species, which favor the current multi-species classification of *Brucella* (HALLING et al., 2005). Importantly, comparison of genome sequences of *B. suis* and *B. melitensis* demonstrated that exist clusters of genes that are unique in both species (designated genetic islands). It is reasonable to hypothesize that these unique genes may contribute to the differences in host specificity between *Brucella* species (TSOLIS, 2002). Furthermore, recent studies based on comparative whole genome analysis of several *Brucella* species indicate that there is limited divergence with a large number of pseudogenes. Interestingly, these genomic analyses do not clearly explain the host preferences of *Brucella* spp. (WATTAM et al., 2009; FOSTER et al., 2009). One of these studies indicates that at the *B. ovis* is the basal lineage to the rest of the *Brucella* spp., and that apparently most *Brucella* species diverged from their common *B. ovis* ancestor in the past 86,000 to 296,000 years (FOSTER et al., 2009).

It is noteworthy that the International Committee on Systematics of Prokaryotes, Subcommittee on the Taxonomy of *Brucella* has taken a clear position recommending a taxonomic classification that includes different species within the genus, either classical or new, which are still considered as individual species. Therefore, the genus currently group nine species, namely *B. melitensis*, *B. abortus*, *B. suis*, *B. ovis*, *B. canis*, *B. neotomae*, *B. ceti*, *B. pinnipedialis*, and *B. microti* (<http://www.the-icsp.org/subcoms/Brucella.htm>, Last modified 15 February 2008). The newly isolated *Brucella* species from baboons (SCHLABRITZ-LOUTSEVITCH et al., 2009) has not yet been classified nor included in the above mentioned list.

#### *Brucella melitensis*

*B. melitensis* is the most important etiologic agent of brucellosis in small ruminants, although cattle and other ruminants may also be infected. This species has three different biovars (BRICKER & HALLING, 1994) and it has the higher zoonotic potential within

Table 1 - Preferential hosts and zoonotic potential of *Brucella* species.

Species	Preferential host	Zoonotic potential
<i>Brucella melitensis</i>	Sheep, goat	+++
<i>Brucella abortus</i>	Cattle	++
<i>Brucella suis</i>	Pig	++
<i>Brucella canis</i>	Dog	+
<i>Brucella ovis</i>	Sheep	–
<i>Brucella neotomae</i>	Desert wood rat ( <i>Neotomae lepida</i> )	–
<i>Brucella ceti</i>	Cetaceans	+
<i>Brucella pinnipedialis</i>	Seals	+
<i>Brucella microti</i>	common voles ( <i>Microtus arvalis</i> )	–

the genus, and thus it is recognized as the most important agent of human brucellosis (ALTON, 1990). This pathogen is widespread in several parts of the world, particularly the biovar 3 in Mediterranean and Middle Eastern countries (BANAI, 2002). Parts of Latin America are also seriously affected with biovar 1, especially Mexico, Peru and Northern Argentina (LUCERO et al., 2008). Importantly, *B. melitensis* have never been isolated in Brazil, where it is considered a foreign disease (POESTER et al., 2002).

In goats and sheep, *B. melitensis* infection causes abortion, reduced milk yield, and orchitis. Both sexually mature genders are equally susceptible. The predominant sign of acute infection is reproductive failure with abortion and birth of weak offspring. Abortions occur mostly during the last two months of gestation. Generally, transmission in sheep and goats occurs through materials excreted from the female genital tract (ALTON, 1990).

In goats, approximately two thirds of acute natural infections during pregnancy lead to infection of the udder and milk excretion of the bacteria during the subsequent lactation. Persistent infection of the udder is accompanied by intermittent shedding of the agent in milk. Inflammation of the mammary gland reduces milk production. However, clinical signs of mastitis are seldom detectable in naturally infected goats (ALTON, 1990).

*B. melitensis* is the most virulent *Brucella* for humans with a few organisms (10 to 100) being sufficient to cause a debilitating chronic infection (FUGIER et al., 2007). Humans acquire brucellosis mainly through ingestion of contaminated milk and unpasteurized dairy products. Contact of mucosas and skin abrasions with fluids and tissues from aborted fetuses of infected animals are also important sources of *Brucella* transmission (HARTIGAN 1997; FUGIER et al., 2007). Furthermore, people may be infected by inhalation of contaminated dust or aerosols. Thus,

*Brucella* is one of the most common laboratory-acquired pathogens worldwide and is included in the potential biological weapon list (SANTOS et al., 2005).

Human infections with *B. melitensis* may have variable clinical manifestations and can become life threatening (COLMENERO et al., 2002). Although the majority of patients present with general symptoms, such as fever, malaise, sweats and lymphadenopathy and/or hepatosplenomegaly, a more severe form of the disease can be accompanied with osteo-articular signs (spondylitis, arthritis and osteomyelitis) or *genitourinary tract changes* (orchitis, epididymitis, glomerulonephritis and kidney abscesses) (HARTIGAN, 1997; COLMENERO et al., 2002). More severe complications comprise, in descending order of frequency, neurobrucellosis, liver abscesses, and endocarditis (FUGIER et al., 2007).

#### *Brucella abortus*

*B. abortus* has seven different biovars, namely biovars 1-6 and 9. Cattle is the preferential host for *B. abortus*, but the organism can be transmitted to buffaloes, camels, deer, dogs, horses, goats, sheep, and man (KUDI et al., 1997). In Brazil, bovine brucellosis due to *B. abortus* is the most prevalent *Brucella* infection (POESTER et al., 2002).

*B. abortus* causes primarily a disease in cows, being isolated from the udder, uterus, and lymphoid organs (POESTER et al., 2006). Outbreaks of brucellosis in dairy herds result in decreased milk production, increase somatic cell count in milk, occurrence of abortions and post-partum metritis (MEADOR & DEYOE, 1989). Late abortion is associated with necro-hemorrhagic placentitis (Figure 1) and fetal lesions, particularly fibrinous pleuritis and pericarditis and pneumonia (XAVIER et al., 2009). Infected cows usually abort only once, and subsequent gestations may generate calves that may be born weak or healthy. Some infected cows will not exhibit any clinical symptoms of the disease and give birth to

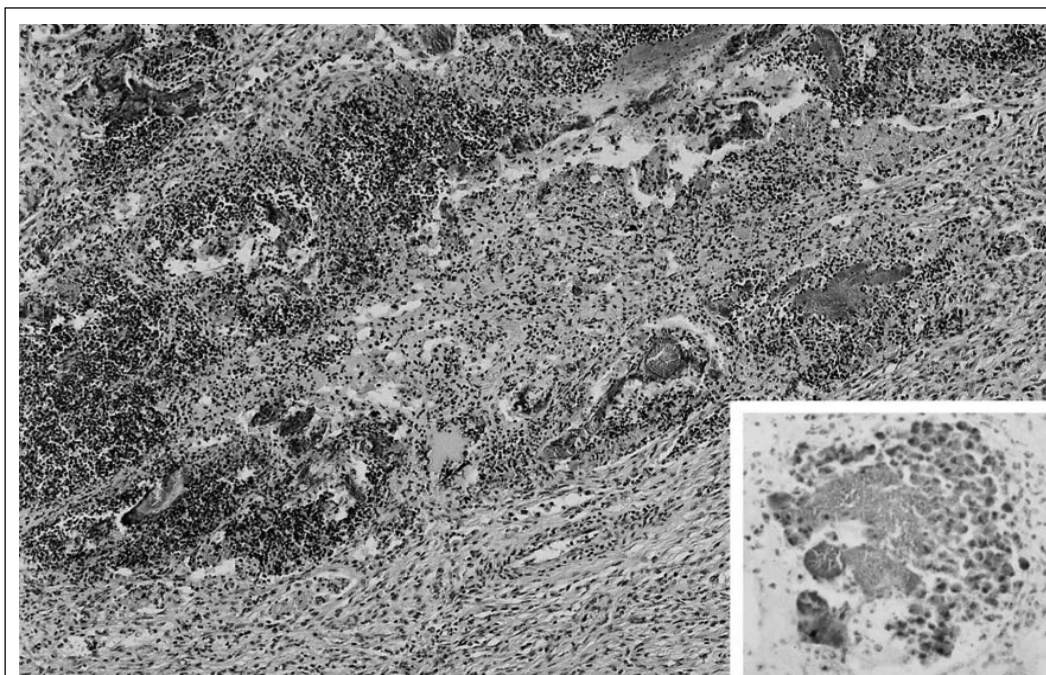


Figure 1 - Cow. Placentome. Necro-suppurative placentitis characterized for intense inflammatory infiltrate associated to cellular debris to and myriad of bacterial colonies of *Brucella abortus* within caruncular crypts. HE. 50X. Inset: caruncular crypt with several bacterial colonies and numerous cells containing intracytoplasmic immunostained *Brucella abortus*. Biotin-avidin peroxidase.

normal calves. Transmission occurs mainly after abortion or parturition of infected cows via contaminated fetus, fetal membranes, and uterine secretions (SILVA et al., 2005).

Bulls can be infected but they do not readily spread the disease. *B. abortus* is a common cause of orchitis that is often associated with a vesiculitis and epididymitis. Infection in males may result in either temporary or permanent infertility, depending on the intensity of the lesions (EAGLESOME & GARCIA, 1992).

#### *Brucella suis*

Porcine brucellosis is an emerging disease caused by *B. suis* biovars 1, 2 and 3. It is mainly a disease of domestic and wild pigs but it can also affects other species such as cattle, horses, rabbits, dogs, and humans (EWALT et al., 1997, FRETIN et al., 2008). Biovars 1 and 3, which have pathogenic potential for humans, occur in Europe, North, South and Central America, Southern Asia and Pacific islands (FRYE et al., 1991). In Brazil, only the biovar 1 has been isolated, and there are just a few reports of *B. suis* in the country, with a seroprevalence of 0.34% in recent surveys (BRAZIL, 2000). Prevalence is very low in industrial swine production systems (CARVALHO NETA et al., 2005), but it may be quite high among backyard pigs

slaughtered without sanitary inspection in Brazil (FREITAS et al., 2001).

Porcine brucellosis is a herd problem. Pigs of all ages can acquire the infection, but the disease primarily occurs in adults. *B. suis* is excreted in large numbers, for long periods in the semen and urine as well as in uterine discharges and milk being transmitted by both venereal and oral routes (ALTON, 1990).

*B. suis* infection in pigs often does not result in clinical signs, and therefore clinical diagnosis is very difficult. *B. suis* causes primarily a genital disease with abortions, but it also affects other organs, especially bones and joints (FELDMAN & OLSON, 1933). Brucellosis is the only disease in which reproductive failure in sows is accompanied by orchitis in boars and osteo-articular disorders such as arthritis, osteomyelitis, spondylitis and paralysis. The most important clinical signs in sows are infertility, irregular estrus, abortion in any stage of gestation and birth of weak piglets with a high neonatal mortality rate (DEYOE, 1967). Although orchitis and epididymitis are the most common lesions in boars, in some cases the infection is restricted to sexual glands and may not result in impaired fertility but can be an important source for shedding the organism in the semen (VANDEPLASSCHE et al 1967).

***Brucella ovis***

***B. ovis*** infection has been reported in Australia, New Zealand, North and South America, South Africa, and many countries in Europe. It occurs in most sheep-raising regions of the world (BURGUESS, 1982). In Brazil, serological surveys in the state of Rio Grande do Sul demonstrated an average seroprevalence in positive sheep flocks of 13.4% (ranging from 6.9 to 50%) (MAGALHAES NETO & GIL-TURNES, 1996), whereas a seroprevalence of 5.57% has been reported in the Northeastern part of the country (CLEMENTINO et al., 2007).

Poor semen quality associated with decreased sperm motility and concentration as well as sperm abnormalities is often associated with early infection (CAMERON & LAUERMAN, 1976). ***B. ovis*** causes primarily epididymitis in sexually mature rams, and occasionally abortion in ewes (LAWRENCE, 1961). Later on, palpable lesions may develop in the epididymis, which may be unilaterally (Figure 2) or, occasionally, bilaterally affected (LAWRENCE, 1961). Conversely, some infected rams not develop palpable lesions (CARDOSO et al., 1989). In addition, a considerable number of infected rams may shed ***B. ovis*** in the semen for long periods, without any clinical sign of infection. Asymptomatic rams may develop only a mild subfertility or retain normal fertility, thus increasing the risk of spreading the infection in the herd. The

transmission can occur by direct contact between rams kept in the same premises for prolonged periods of time (HUGHES et al., 1972; BROWN et al., 1973).

In ewes, ***B. ovis*** can uncommonly cause abortion associated with placentitis beginning at 30 days of gestation. Infected ewes may give birth to weak lambs with a high neonatal mortality rate (MEINERSHAGEN et al., 1974).

***Brucella canis***

Canine brucellosis is caused by ***B. canis*** that infects domestic dogs, wild carnivores and rarely other domestic animals (CARMICHAEL, 1990). It is especially common in Central and South America (MIRANDA et al., 2005). Infection of dogs with ***B. canis*** is widespread in Brazil, with prevalence ranging between 0.84 to 58.3% and it is concentrated mostly in the Southeast and South regions of the country (AZEVEDO et al., 2003; KEID et al., 2004; MIRANDA et al., 2005). Humans are susceptible to ***B. canis***, but infections are uncommon and they are usually mild. Most natural human infections have been acquired through close contact with infected dogs. Laboratory infections have also been reported (CARMICHAEL, 1990).

Natural infections occur most commonly after ingestion of contaminated placental tissues or aborted fetuses, vaginal secretions from infected

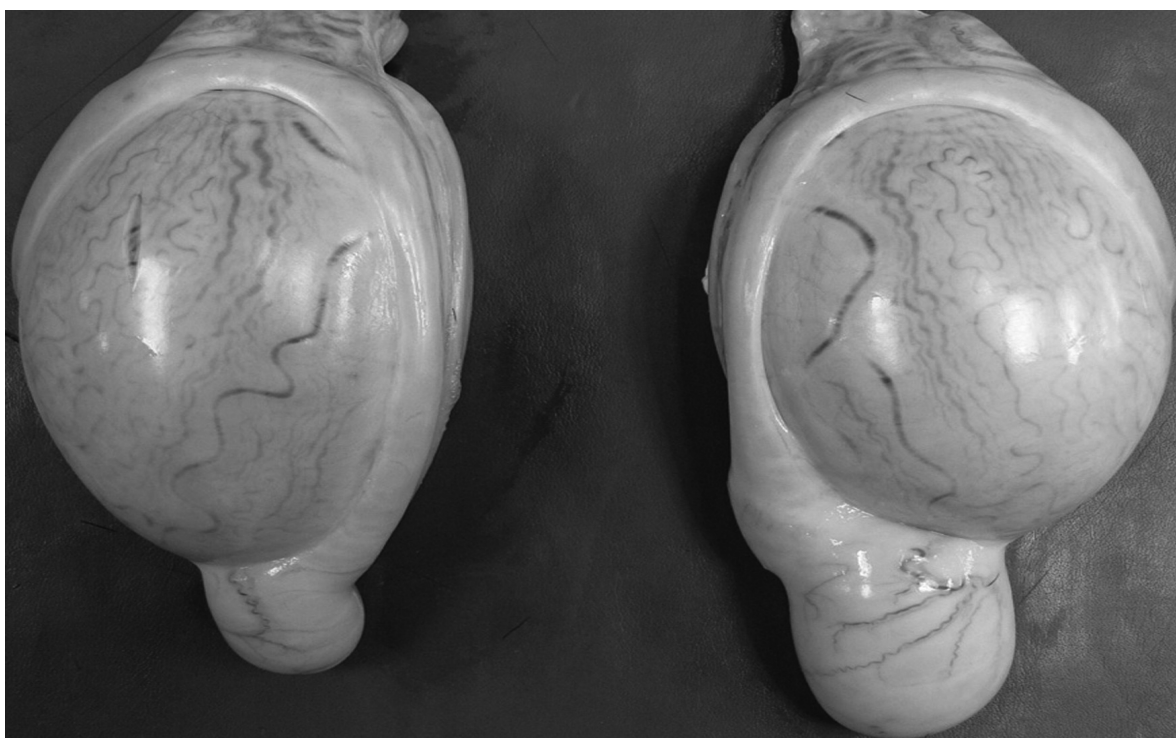


Figure 2 - Ram. Epididymitis by *Brucella ovis*. The tail of right epididymis is markedly enlarged.

bitches, and during breeding. The organism may be shed for long periods in vaginal secretion after abortion and semen (CARMICHAEL & KENNEY, 1970; GEORGE et al., 1979).

In females, the most prominent clinical sign is abortion after 45-55 days of gestation in about 75% of the cases. Early embryonic death and reabsorption, or abortion 10-20 days after mating, may occur in some cases (CARMICHAEL, 1990). In males, the main sign is epididymitis and orchitis, which may be unilateral or bilateral, and often results in infertility. Semen from infected males usually contains large numbers of abnormal sperm and inflammatory cells, especially during the first three months after infection. Chronically infected males may have no sperm, or reduced numbers of immature sperm (CARMICHAEL & JOUBERT, 1988).

A particularity of *B. canis* infection is a prolonged bacteremia. Therefore, blood culture is a valuable diagnostic approach in this case (CARMICHAEL & KENNEY, 1970).

#### *Brucella ceti* and *Brucella pinnipedialis*

Since 1990, *Brucella* strains have been isolated from a variety of marine mammal species, including seal (*Phoca vitulina*), dolphins (*Tursiops truncatus*; *Delphinus delphis*; *Lagenorhynchus acutus*; *Stenella coeruleoalba*), whale (*Balaenoptera acutorostrata*), and other species (EWALT et al. 1994.; ROSS et al., 1994; FOSTER et al., 1996; CLAVAREAU et al., 1998; WYATT, 1999). These isolates have been classified as *B. ceti* and *B. pinnipedialis*, referring to isolates from cetaceans and seals, respectively (FOSTER et al., 2007). Transmission may occur by direct contact through mucosae and injured skin, oral route due to ingestion of other infected marine mammals (FOSTER et al., 2002), or by vertical or horizontal transmission to fetus since *Brucella* has been isolated in fetal tissues and in milk from dolphins (HERNANDEZ-MORA et al., 2008).

Pathological changes include skin abscesses, hepatic and splenic necrosis or/and histiocytic inflammation, meningitis, discospondylitis and abortion (FOSTER et al., 1996). Non suppurated meningoencephalitis has been described as the most consistent histological change in dolphins with neurological signs and positive serology and immunohistochemistry to *Brucella* sp. (GONZÁLEZ et al., 2002; HERNANDEZ-MORA et al., 2008). These marine *Brucella* species are capable of infecting terrestrial mammal species as demonstrated by experimental infection of cattle (RHYAN et al., 2001).

Marine *Brucella* species are capable of infecting humans causing neurological disorders

(SOHN et al., 2003; HERNANDEZ-MORA et al., 2008). Transmission to human occurs probably through direct contact with marine mammals, although there are reports of human brucellosis caused by marine isolates in which there was no evidence of contact of the patient with marine animals (SOHN et al., 2003; McDONALD et al. 2006; HERNANDEZ-MORA et al., 2008).

#### *Brucella neotomae*

*B. neotomae* was discovered by STOENNER & LACKMAN (1957) and approved as a new species of *Brucella* in 1980. *B. neotomae* is known to infect only the desert wood rat under natural conditions in the USA, and no other cases in addition to the original isolation have been reported.

#### *Brucella microti*

*B. microti* has been isolated from systemically infected common voles (*Microtus arvalis*) in South Moravia, Czech Republic in 2000 (SCHOLZ et al., 2008a). Later on, *B. microti* was isolated from mandibular lymph nodes of wild red foxes (*Vulpes vulpes*) hunted in Austria. SCHOLZ et al., 2008b). Furthermore, specific *B. microti* DNA sequences were recently detected in soil, but whether soil is the primary habitat of *B. microti* remains to be investigated (SCHOLZ et al., 2008c).

## CONCLUSION

The genus *Brucella* includes several organisms, some of which with a very significant zoonotic potential, whereas some species poses significant risk for animal health and production. In the recent past years there has been an increasing number of newly recognized species of *Brucella*.

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