Acta Scientific MEDICAL SCIENCES (ISSN: 2582-0931)

Volume 5 Issue 6 June 2021

Review Article

# Brucellosis and Public Health

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**Received:** April 12, 2021

**Published:** May 05, 2021

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## Abstract

This paper aims to present the major significance of early diagnosis and treatment of brucellosis at a primary healthcare level, so as to prevent the risk to public health that may occur from the spread of the disease. It initially introduces the epidemiological features of the disease and information regarding the ways it spreads, as well as its symptomatology, diagnosis and treatment. It then focuses on preventive measures to stop the wide-scale spread of brucellosis, mainly in Greece. Finally, it refers to the cost and effectiveness of these measures in practice and analyses the conclusions.

**Keywords:** B. *Melitensis; B. abortus;* Public Health

## Introduction

Brucellosis is an anthropozoonotic disease caused by Gram-negative bacteria of the *Brucella* genus. The *Brucella* genus is composed of pathogenic potentially anaerobic intracellular bacteria. A total of seven *Brucella* species have been identified: *B. melitensis* (sheep and goats), *B. abortus* (cattle), *B. canis* (dog), B. *suis* (pig), B. *maris* (marine mammals), *B. ovis* (sheep), B. *neotomae* (rat). In humans, the disease may be caused by the species B. *melitensis*, B. abortus and B. *suis* and to a lesser extent by *B. canis*. In Greece, nearly all cases are attributed to B. *melitensis*, with sporadic reports regarding B. abortus and B. *suis*. The disease has been known since Roman times and is endemic to Mediterranean countries. Its significance for public health lies in the fact that it is related to immediate and long-term manifestations, such as endocarditis and infertility. However, there is an approved treatment that is widely available to the general public, but also protective measures that can eliminate the risk of the disease spreading, provided they are strictly followed [1,2].

## Background

Brucellosis is one of the most contagious anthropozoonotic disease, linked to infertility and increased mortality rates. The disease is known by many other names, including Crimean fever and Neapolitan fever. It is believed to have been first diagnosed in the late Roman era. The first reports of the disease possibly date back 2.8 million years, on a Pliocene skeleton, which showed lesions that could be attributed to bone disease caused by brucellosis. In addition, DNA testing on a medieval human skeleton found in Italy revealed presence of B. *melitensis* genetic material. The disease was linked to military campaigns, mainly in the Mediterranean region. The first scientific documentation of the disease was made by David Bruce, who isolated the aetiologic agent, then named *Micrococcus melitensis*, in the liver of a deceased soldier on Malta. The term *Brucella* was named in his honour [2]. That is the reason why Malta fever, a term used for brucellosis accompanied by fever, is mainly due to the B. *melitensis* and B. abortus subspecies. As a matter of fact, the B. abortus subspecies, has been aetiologically linked to preterm birth in cattle and intermittent fever in humans [3].

## Epidemiology

Brucellosis is the most common anthropozoonotic disease worldwide. It is endemic to the Mediterranean, Middle East, India, Mexico and South America. The annual mean incidence in the 2005-2015 decade was 5-10 per 100,000 population. (1) Even though it is the most common anthropozoonotic disease, brucellosis is classified as a rare disease by the US National Institutes of Health. This is the case for developed countries, where the incidence of the disease is less than 1 per 100,000 population (USA: 0.40/1,000,000). On the other hand, the highest rate has been recorded in Syria (1,603/1,000,000), followed by Mongolia, Iraq and Tajikistan. A major drop has been recorded in the last decade in Turkey and Kyrgyzstan in terms of recorded cases of the disease. Of course, it must be taken into account that brucellosis is the disease with the lowest diagnosis rates globally, not just due to the existing methods, but mainly due, on the one hand, to the variety of symptoms, which do not often lead patients to see a doctor, and, on the other hand, to the type of population affected by the disease, mainly farmers, livestock farmers and tannery workers, who are not often adequately informed on the consequences of the disease. (2) It is believed that direct contact with domestic farm animals, but also consumption of unpasteurised dairy products are the most common risk factors, at a rate of 65% and 59% respectively.

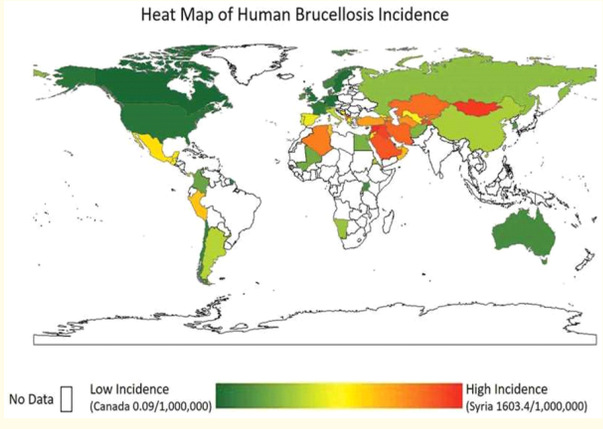


**Figure 1:** Brucellosis incidence (per 1,000,000 population). Adapted by Pappas., *et al.* 2006.

In Greece, the reported incidence is the highest in Europe. The incidence was about 2.2 per 100,000 population (5-year period 2005-2009), almost double that of other European Union countries, while it occurs twice as much in men than in women, obviously due to the fact that the former are involved in work that requires them to come into contact with domestic animals. In addition, the disease seems to fluctuate seasonally, with increased incidence in the spring months, mainly April and May, and in June. This seasonal fluctuation is possibly due to the increased exposure of livestock farmers to the pathogen during the time of parturition of goats, sheep and cattle. Besides, it is the time when flocks are taken out to graze in pastures, in which case, the risk of transmission of microorganisms between sheep increases.

The reported incidence of the disease decreased in the years 2000-2004. In the next years the average incidence was 1-3.1 per 100,000 population. The Thasos island epidemic in 2008, with 104 cases, was prompted by consumption of unpasteurised dairy products. This resulted in the increase of brucellosis incidence to 3.1 per 100,000 population. The total number of cases in the 5-year period 2005-2009 was 1,229, with an incidence of 2.2 per 100,000 population.

Out of the reported cases in the 5-year period 2005-2009, 68% were males, with an average age of 44 years. The highest average annual incidence was recorded in Thessaly, followed by East Macedonia and Thrace (9.6 per 100,000 and 7.8 per 100,000 population respectively). The lowest incidence was recorded in the Southern Aegean and Crete (0.3 per 100,000 and 0.4 per 100,000 population respectively) [2,4].

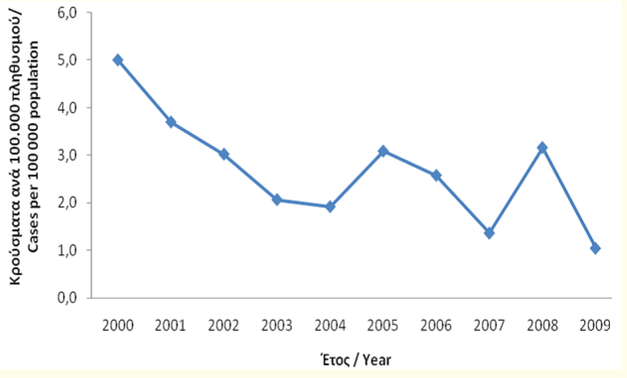


**Figure 2:** Development of brucellosis in Greece for the period 2000-2009.

Adapted from the Department of Epidemiological Surveillance and Intervention, HCDCP, "Epidemiological data on brucellosis in Greece" (Mandatory disease notification system), January 2011.

## Brucellosis definition

Brucellosis or Malta fever is an infectious disease transmitted to humans from animals, mainly productive animals (cattle,

sheep, goats and pigs) and to a lesser extent wild animals (wild boars, hares and deer). The symptomatology may start gradually or abruptly and includes fever, which is undulating and does not recede easily, as well as sweating, headache, arthralgia, weakness and fatigue [5,6].

## Main pathogens

- *B. abortus*, biotypes 1-6 and 9
- *B. melitensis*, biotypes 1-3
- *B. suis*, biotypes 1-5
- B. *canis*, with no reported cases of infection in Greece.

## Reservoirs

Sheep and goats are a natural reservoir for *B. melitensis*, in which brucellosis manifests in a chronic or latent form, lasting months or years. The micro-organism lives in the breasts and is excreted in the milk for a long period of time, while it is also excreted through urine. The main reservoir of B. abortus is cattle. It lives in the breasts and lymph nodes and is excreted through the milk, faeces, urine and vaginal secretions of the animal. Respectively, pigs are reservoirs of B. *suis*. In Greece, *B. suis* infection is less common. Usually, the male pigs are the reservoirs. On the other hand, dogs are reservoirs of B. *canis*. Dogs in puppy farms, stray dogs and to a lesser extent pets are mainly infected. B. *canis* infection is not endemic to Greece [7].

## Transmission to humans

Brucellosis is transmitted to humans through consumption of food from infected animals, mainly dairy products, which has not undergone proper processing. Cheese products are considered less dangerous than milk because, due to fermentation, the *Brucella* bacteria survive just a few days or weeks. *At least three months should have passed from the date of production for dairy products to be considered safe.* Through unprotected contact with infected animals. *Brucella* bacteria can enter the human body through injured parts of the skin. Contact with contaminated animal fluids, such as blood, urine, vaginal secretions and placenta, and, of course, consumption of unpasteurised milk are the main sources of infection for humans. It is important to note that the *Brucella* bacteria may potentially survive for months in animal environments and conditions that favour their survival. Therefore, professions that involve working in livestock farms, slaughterhouses and tanneries are considered high-risk, especially when there is no compliance to the required standards and precautions when exercising these professions [7].

## Incubation time

It ranges from 1 week to 6 months. B. *melitensis* has a shorter incubation time to B. abortus, around 10-30 days.

## Transmission time

There are no indications regarding direct human-to-human transmission [7].

## Clinical presentation

After incubation, which may last from 1 week to several months, the patient manifests undulating fever, night sweats, fatigue, loss of appetite and apathy. In addition, general symptoms may develop, such as headache, myalgia, osphyalgia, constipation, dry cough and angina. The most common signs affect the musculoskeletal system, and include musculoskeletal pain, and involvement of the peripheral and axial skeleton. In addition, lymphadenopathy, hepatosplenomegaly and even focal abscess may also appear. The most significant complications include endocarditis, meningoencephalitis, vertebral osteomyelitis and septic arthritis (febrile and acute onset monoarthritis, mainly of the hip or knee). Furthermore, the risk of orchitis has been known since Roman times, with the ultimate outcome even being infertility. Other less common complications include hepatitis and cholecystitis [2,6].

## Diagnosis

Diagnosis may be achieved by isolating the micro-organism in blood cultures or cultures of other bodily fluids, such as cerebrospinal fluid, urine and bone marrow. The sensitivity of the blood culture may reach 90% and ranges from 15% to 94%. It is usually negative in the localised and chronic forms of the disease.

The serological tests include:

- Wright reaction
- Coombs-Wright reaction
- Rose-Bengal reaction
- ELISA
- Complement fixation.

The molecular tests include:

- Conventional PCR
- Real-time PCR.

Wright agglutination is the one most often used, with sensitivity ranging from 77% to 92%. The ELISA test determines the IgG, IgA and IgM immunoglobulins and is useful for diagnosing neurobrucellosis, but also for monitoring patients, given that a drop in IgG antibodies is observed after treatment and a rise in the event of relapse. On the other hand, the Rose-Bengal test is used as a screening test.

Combining cultures and serological tests increases the sensitivity rates of disease diagnosis to 96% [1,6].

## Preventive measures

- Educating the population on the consumption of pasteurised milk and dairy products.
- Educating livestock farmers and slaughterers on the risks of handling potentially infected animals.
- Vaccinating young animals in areas with increased prevalence of the disease associated with B. *melitensis* and B. abortus.
- Disinfecting the areas where infected animals are found.
- Pasteurising milk and dairy products. If this is not possible, boiling the milk [7].

## Control of cases

The control of cases, contacts and the close environment of diseased animals and humans includes 4 stages, as follows:

- Reporting of cases to the health authorities.
- Protection from secretions of diseased animals and humans.
- Current disinfection: only in the case of purulent secretions.
- Epidemiological control to identify the source of infection [7].

The following ways are proposed to control the transmission of the disease: vaccination of animals, slaughtering of infected animals, surveillance controls or a combination thereof.

There is no human vaccine available for brucellosis. However, three vaccines have been developed for animals: RB51 and S19 for *B. abortus* in cattle, and Rev 1 for B. *melitensis* in small domestic animals. Although these vaccines do not protect the animals from *Brucella* colonisation and infection, they reduce the likelihood of abortions, which results in reduced likelihood of the disease being transmitted to healthy animals. Therefore, the healthy animals of the herd are protected.

The *B. melitensis*, *B. abortus* and *B. suis* strains are the so-called "smooth" strains, while the B. *canis* and B. *ovis* are the so-called "wild" strains. The difference lies in the fact that the cell membrane of smooth strains contains the smooth lipopolysaccharide (sLPS), which is not the case in wild strains. So the vaccine for B. *abortus* (S19) contains strains that carry the specific LPS on their cell membrane, while the vaccine for B. *melitensis* (Rev 1) contains strains that do not carry it. Vaccine RB51, which is used for B. abortus strains, is the exception, as it contains micro-organisms that do not carry the lipopolysaccharide on their membrane [2].

## Treatment

Co-administration of medications for a prolonged period is required for the treatment of brucellosis. It is necessary for the administered medications to achieve the necessary intracellular concentration, but also respond to an acidic pH.

The treatment regimens used for brucellosis include:

- Doxycycline for 6 weeks in combination with gentamicin for 1 week
- Doxycycline for 6 weeks in combination with streptomycin for 2-3 weeks
- Doxycycline in combination with rifampicin for 6 weeks
- Doxycycline in combination with rifampicin for 6 weeks and gentamicin for 2 weeks

Alternative regimens include:

- Trimethoprim-sulfamethoxazole for 6 weeks in combination with gentamicin for 2 weeks
- TMP-SMX for 6 weeks in combination with doxycycline
- Ciprofloxacin or ofloxacin in combination with doxycycline for 6 weeks

## Endocarditis

Special mention is made to endocarditis from brucellosis, which is a rare complication with a high mortality rate. It is the most common cause of death from *Brucella* bacteria. Treatment requires immediate surgery, as well as antimicrobial treatment. A combination of 3-4 antibiotics is used, e.g. doxycycline, rifampicin or streptomycin, with or without cotrimoxazole, for a period of 6 weeks to 6 months. As a rule, aminoglycosides are used for the first 2-4 weeks [1].

## Conclusion

Brucellosis is an ancient disease, which may be encountered to this day, especially in developing countries. It is the most common anthropozoonotic disease and the most frequently reported laboratory-associated infection. Although major strides have been made in its diagnosis and treatment, especially in the last two decades, the number of cases continues to be high, mainly in underdeveloped countries, but also in war-torn regions.

The challenges that need to be addressed are:

- Developing new and reliable diagnostic methods.
- Developing new, more effective vaccines.
- Containing the disease in natural animal reservoirs, resulting in reducing the chance of transmission to humans.

Cooperation among scientists and social bodies at a local, national and transnational level is required to achieved these targets [2].

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