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► **To cite this version:**

Georgios Pappas. The changing ecology: novel reservoirs, new threats. *International Journal of Antimicrobial Agents*, 2010, 36, 10.1016/j.ijantimicag.2010.06.013 . hal-00632724

HAL Id: hal-00632724

<https://hal.science/hal-00632724>

Submitted on 15 Oct 2011

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Accepted Manuscript

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Author: Georgios Pappas

PII: S0924-8579(10)00254-2
DOI: doi:10.1016/j.ijantimicag.2010.06.013
Reference: ANTAGE 3349



To appear in: *International Journal of Antimicrobial Agents*

Please cite this article as: Pappas G, The changing *Brucella* ecology: novel reservoirs, new threats, *International Journal of Antimicrobial Agents* (2010), doi:10.1016/j.ijantimicag.2010.06.013

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The changing *Brucella* ecology: novel reservoirs, new threats

Georgios Pappas*

Institute of Continuing Medical Education of Ioannina, H. Trikoupi 10, 45333

Ioannina, Greece

* Tel.: +30 26510 28289; fax: +30 26510 28289.

E-mail address: gpele@otenet.gr.

Abstract

Brucellosis is a zoonosis that preceded humans but continues to cause significant medical, veterinary and socioeconomic problems, mainly because its overall burden remains underestimated and neglected. Its ecology, or what we know of it, has evolved rapidly in recent years. Two novel species, *Brucella ceti* and *B. pinnipedialis*, with the potential for causing human disease have been isolated from marine mammals. Another novel species, *B. microti*, has been isolated from wildlife animals, while *B. inopinata* has been isolated from a human case. An active spillover of *Brucella* between domestic animals and wildlife is also being recognized, with elk transmitting *B. abortus* to cattle, and freshwater fish becoming infected with *B. melitensis* from waste meat. In recent years the global epidemiology of the disease has not altered drastically, apart from increased awareness of brucellosis in sub-Saharan Africa and a rapid expansion of disease endemicity in the Balkan Peninsula. Isolated stories and events underline that *Brucella* knows no borders. The modern world has offered the pathogen the ability to travel and manifest itself anywhere and has also offered scientists the ability to track these manifestations better than ever before. This may allow the disease to be neglected no longer, or at least to be recognized as neglected.

Keywords:

Brucellosis

Epidemiology

Emerging infectious disease

Zoonosis

Accepted Manuscript

1. Introduction

Brucellosis is a re-emerging zoonosis that has resurfaced at the epicentre of scientific interest and will continue to do so because of 1) its evolving epidemiology, which has seen new foci of both human and animal disease related to particular major sociopolitical events [1], 2) *Brucella*'s inclusion on all lists of potential biological weapons, although this inclusion might predominantly be of historical importance [2], 3) *Brucella*'s changing ecology, which is resulting in the recognition of new human populations at high risk of exposure, 4) the evolving scientific debate on the taxonomy of *Brucella* species and the genus as a whole [3], and 5) the recognition that human disease may mimic tuberculosis in its tendency to produce chronic, latent infection [4,5].

Yet this re-emergence is predominantly one of scientific interest and not one of the pathogen and the disease *per se*. After all, *Brucella* may actually be the oldest recognized bacterium, one that may have caused disease, recognizable even today, in hominins hundreds of thousands of years ago [6]. The disease has been perpetually present but ignored because it is a human and animal disease of the poor. Yet even for a country with moderate endemicity, such as Greece, the annual economic burden of human disease has been estimated as higher than that of influenza and other 'fashionable' diseases, and is only lower than the economic burden of tuberculosis, meningitis and hepatitis B (the latter because of costly therapies) [7]. If there is a neglected disease, brucellosis is its definition.

2. Trends in global epidemiology

Modern international travel practices have resulted in increased exposure to a series of pathogens, including brucellosis, that are not encountered in everyday clinical practice of the developed world [8]. The global epidemiology of the disease, as outlined in a 2006 review [1], has seen the emergence of Central Asia, along with the Middle East, as the primary worldwide foci. This has been the result of political changes and the evolution of free trade in countries previously under a communist regime. Open borders have resulted in a faster, often uncontrollable movement of bacteria and diseases.

Although the illegal importation of infected animals or dairy products has been acknowledged as crucial in areas as diverse as north-western Greece (from Albania) and the southern USA (from Mexico) [1,9], this trend has significantly evolved in later years. The prime example is the Balkan Peninsula. In 1990 the disease was only present in Greece and the European part of Turkey but by 1995, after a period of political and military turmoil that led to dramatic political changes, civil wars and the formation of new countries, the disease was also recognized to be alarmingly endemic in Albania and the former Yugoslav Republic of Macedonia. There have been persuasive data that, at least for Albania, the disease already existed but was not recognized because of a policy of denial or even inadequate health policy in general (Pappas, unpublished data).

By 2010 the disease had travelled over almost all the Balkans. Bosnia-Herzegovina is facing the greatest problem, with the annual incidence of

human disease rising geometrically [10]. Cases have subsequently been imported to Croatia [11] and the disease has been reintroduced to a brucellosis-free country, Bulgaria, in two ways – through the illegal importation of animals and animal products to the southern Muslim areas of Bulgaria from Turkey [12], but also through Bulgarian workers contracting the disease in farms in north-eastern Greece and returning to their homeland for treatment. Thus, at present, four Balkan countries are leading the map of European endemicity for *Brucella*, and we are not counting in the region of Kosovo, where the burden of the disease has yet to be adequately quantified.

Importation of the disease because of illegal practices is not limited to neighbouring countries. Animal disease has been recognized in sheep and goats exported to Vietnam from the United Arab Emirates under a cooperative programme that would have seen the animals bred in Vietnam and their meat subsequently returned to the Emirates [13]. There is ongoing emergence of animal brucellosis in the Fiji Islands [14], with extensive animal slaughter performed as a control measure. The actual mode of introduction of the disease to a place one would certainly not expect to find it remains unknown, but shows how easily the disease can travel nowadays.

Increasing recognition of the disease in sub-Saharan Africa is promising [15], although public health policies in these settings would be extremely difficult to implement. A brucellosis outbreak in a region of Uganda was recognized and epidemiologically linked to infected cattle, yet the authorities reported that people continued to consume meat from infected animals, despite warnings [16]. One can imagine that in countries of sub-Saharan Africa there are other

public health priorities and that people at risk may consider infected food as 'food, nevertheless', but such approaches only serve to accentuate the problem instead of solving it.

Thus the global map remains practically unchanged in 2010, although hot spots are continuously added, even where least expected. South Korea is an example with a relatively massive increase in annual human cases [17] and the background of this surprising epidemiological evolution cannot be adequately explained.

3. *Brucella* taxonomy: more and more new entries

For many decades the *Brucella* genus included six species, four of which were pathogenic for humans (Table 1). Biovars were recognized for certain of these species and the classification has remained relatively unchanged since the recognition of *B. neotomae* in the late 1960s. However, in the 1990s, pathogens categorized as *Brucella* spp. were recognized in marine mammals [18,19]. These novel species were eventually categorized as *B. ceti* (affecting predominantly porpoises and dolphins) and *B. pinnipedialis* (affecting predominantly seals) [20]. The classification is tentative and phylogenetic analysis may result in a further breakdown of *B. ceti* [3]. What is definite is that these new species can infect humans, and the reports are accumulating [21].

[Table 1 here]

The novel species *B. microti* has been recognized in Central Europe in common voles and red foxes, but also as a persistent soil contaminant [22]. It

has not been linked to human disease but if it does possess an anthropozoonotic risk then hunters would be a particular target group.

Two novel strains have each been isolated from a single human case. The first is tentatively named *B. inopinata* [23]. This novel strain was isolated from an infected human breast implant and is phylogenetically linked to *B. ovis*. Its natural reservoir and ecology remain unknown. The second was recently isolated from a patient with chronic lung disease [24]. The isolate's analysis showed similarity to *B. inopinata*. Thus at least two complex clinical pathologies in humans have already been correlated with this species.

Finally, another strain with typical *Brucella* characteristics but distinct from the currently described species was recently isolated from two baboons, both of which presented with stillbirth [25]. Is *Brucella*, after the oceans, also conquering the jungle?

Modern taxonomy practices have assisted in further delineating the significance of biovars of the old species. This has resulted in the exclusion of certain biovars (Fig. 1) as non-existent and a better understanding of the inter-relatedness of all currently described *Brucella* species. It has also caused controversies regarding typical taxonomy issues, two of which warrant mentioning. The first debate was whether *Brucella* is a monospecific genus, with all the species actually being biovars of *B. melitensis*. The second is whether *Brucella* is actually a genus itself or an *Ochrobactrum* species [26]. For the scientific reasoning behind these debates the reader should refer to the excellent relevant review by Whatmore [3].

[Figure 1 here]

In terms of practice, such debates are theoretical but dangerous. Categorizing everything as *B. melitensis* would result in significant misunderstanding of the accepted definitions of brucellar disease, which link tightly to specific animal reservoirs and, to a point, to the severity of human disease. Furthermore, categorizing *Brucella* with *Ochrobactrum* would result in placing a significant human pathogen under the umbrella of a plant pathogen with minimal, if any, potential for human disease.

4. Old species, new threats?

The role of *B. canis* in human disease is considered limited. Yet there are increasing reports of small outbreaks related to this species [27], which is not diagnosed with classical serology as readily as the other species pathogenic for humans.

The role of *B. suis* biovars in inducing infection has also been considered limited. However, there are increasing reports of brucellosis observed in hunters in contact with or consuming meat from wild boar [28–30]. *B. suis* was definitely implicated in the relevant US cases [28], but not in the Australian cases, where an epidemiological survey in wild boar of the region did not reveal the presence of *Brucella* (but incidentally revealed the presence of *Leptospira*) [29]. It should be noted that, at least in Europe, *B. suis* biovar 2 is a significant pathogen for wild boar but has traditionally been considered unable to infect humans. However, in a relevant report in wild boar hunters, *B. suis* biovar 2 was isolated and pathogenetically implicated [30].

Finally, an alarming report recently came from Egypt. There, *B. melitensis* was isolated from *Clarias gariepinus*, a freshwater fish of the Nile. These fish were presumably infected by the ingestion of meat waste of infected animals thrown into the river (illegally) [31]. These edible fish could serve as the port of re-entry of the pathogen to the human food chain. After the oceans and the jungle, *Brucella* is also entering the rivers.

5. Wildlife as a constant reservoir

The role of wildlife animals as a reservoir for human disease has already been outlined in the case of the risk to hunters. Wildlife species naturally infected with *Brucella* can also serve as a reservoir for animal disease. This is the case with disease transmission between wild boar and domestic pigs and, more interestingly, between elk and cattle. The latter possibility has resulted in major political debate in the USA in recent years, with elk trapping, testing and, if positive, killing in the Yellowstone National Park area to avoid transmission of *B. abortus* to domestic cattle during grazing. A recent DNA genotyping study confirmed that the origin of brucellosis affecting domestic and wildlife species in the Greater Yellowstone area was indeed the elk [32].

6. A new world likely to expand

Recognition of the ubiquitous presence of *Brucella* in the environment will most likely continue. The magnitude of marine mammal brucellosis and its clinical importance for human disease is only starting to become evident. The recognition of at least four new species in recent years will soon be followed by at least two more, doubling the number of confirmed species in less than a

decade. Furthermore, the recognition that classical species persist, re-emerge in new foci, penetrate the borders of brucellosis-free countries in unexpected modes, and find new animal reservoirs that perpetuate human risk underlines that *Brucella*, a pathogen preceding humans, will most probably continue to affect human and animal health until it is recognized that it truly is the most neglected disease in terms of morbidity, socioeconomic effects and financial support to committed researchers.

Funding: None.

Competing interests: None to declare.

Ethical approval: Not applicable.

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[Figure legend]

Fig.1. Phylogenetic relationships of the recognized *Brucella* species.

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Table 1A provisional *Brucella* taxonomy

Species	Animal host	Human disease
Old species		
<i>B. melitensis</i>	Sheep, goats, camels	The most common cause of human brucellosis
<i>B. abortus</i>	Cattle, buffalo, elk, yaks, camels	The second most common cause of human infection
<i>B. suis</i>	Domestic pigs, wild boar, reindeer, caribou, rodents	Of increasing interest in human disease, with hunters of wild boar at risk
<i>B. canis</i>	Canines	Increasing reports, particularly from South America, possibly understudied elsewhere
<i>B. ovis</i>	Sheep	Not reported
<i>B. neotomae</i>	Rodents	Not reported

Novel species

<i>B. ceti</i>	Porpoises, dolphins, whales	Reports of complicated disease
<i>B. pinnipedialis</i>	Seals	(neurobrucellosis, spondylitis) and one laboratory infection
<i>B. microti</i>	Red foxes, common voles (also isolated from soil)	Not reported
<i>B. inopinata</i>	Unknown	Isolated from a human case (prosthetic breast implant infection)

Future species

BO2	Unknown	Isolated from a human case (chronic destructive pneumonia)
Baboon isolate	Baboons	Not reported

