INTRODUCTION

Brucellosis is a vicious disease caused by facultative intracellular extracellular pathogens of the genus *Brucella* (Moreno and Moriyón, 2002). The bacterium preferentially replicates within phagocytic cells of the reticuloendothelial system, and in the pregnant animal, inside placental trophoblasts. In domesticated animals, brucellosis is mainly manifested by abortion and epiphagocytosis of the infected cells. Under natural conditions, *Brucella* is horizontally or vertically transmitted. Horizontal transmission occurs through close contact from host to host by means of secretions, sexual intercourse, and more commonly, through licking of aborted fetuses (Figure 1). Although *Brucella* has been observed to survive for some time in open environments, the bacterium hardly divides and eventually dies (Crawford et al., 1990). Likewise, some vectors have sporadically been implicated in brucellosis transmission (Gudoshnik, 1958; Dawson et al., 2008; Neglia et al., 2013). However, neither of these two last events plays a significant role in the transmission of brucellosis and they are not of epidemiological relevance (Meyer, 1977; Moreno and Moriyón, 2006).

In humans, the disease is more severe than in domestic animals, displaying a collection of clinical symptoms (Dalrymple-Champneys, 1960; Pedro-Pons et al., 1968; Figure 2). While there are a few reports of vertical and horizontal transmission between humans (Meltzer et al., 2010; Wyatt, 2010), these are rare events. Therefore, brucellosis in humans is strongly linked to the management of infected animals and ingestion of unpasteurized dairy products (Moreno and Moriyón, 2006; Figure 1). In this regard, there is a clear connection of brucellosis with the domestication of even-toed ungulates, milking practices, and fabrication of cheese and other dairy products. It is, therefore, not accidental that lactase persistence – a genetic trait that allows adults to digest lactose from raw milk – has been traced to ungulate domestication places (Sahi, 1994; Ennattah et al., 2008; Itan et al., 2010) and in course with the persistence of brucellosis in ancient pastoral people.

At no other time in human history have the changes in technology, domestication and environment been more rapid and so extreme. For thousands of years humans have created new ways of living and social actions have emerged to minimize the effects of infectious diseases. However, domestication and clustering of wild life reservoirs with narrower genetic backgrounds have provided a steady supply of emergent pathogenic organisms. In this regard, brucellosis constitutes an utmost example of a how animal pathogens can emerge as public and veterinary health problems. Here I review how humans have fostered the illness we now call...
brucellosis that has accompanied civilization since ancient times, when the malady was recognized by its main symptoms: abortion and fever.

THE DISCOVERY OF Brucella AND BRUCELLOSIS

The seminal discovery of the causative agent of brucellosis, “Micrococcus melitensis” (later named Brucella melitensis), by the British Surgeon Captain David Bruce, his wife Mary Elizabeth Steele and the Maltese microbiologist doctor Giuseppe Caruana-Scicluna has been eagerly described in many assays (Spink, 1956; Ruiz-Castañeda, 1986; Wyatt, 2000, 2009a). These scientists isolated the bacterium from the liver of diseased soldiers in the Mediterranean island of Malta in 1887, a country that holds prominent megalithic constructions beyond 7000 years old. Following this discovery, the Maltese medical doctor Fioravanti Temistocle Archimede Laurenzo Giuseppe Sammut, better known as “Temi Zammit,” found that the causative agent of Malta fever, Mediterranean fever, Cyprus fever, Neapolitan fever, Gibraltar fever, Crimean fever, Cartagena fever, Rock fever, Barcelonan fever, Corps disease, and undulant fever – just to mention a few names used for this vicious malady – was transmitted from infected goats to humans through contaminated milk (Wyatt, 2005, 2011). Thereafter, Surgeon Captain M. Louis Hughes and Captain James Crawford Kennedy discovered significant details on the zoonotic transmission of brucellosis, including venereal transmission in both humans and animals (Wyatt, 2009b).

Ten years after the isolation of M. melitensis, the Danish scientist Bernhard Bag identified “Bacillus abortus” (later named Brucella abortus) in bovine aborted fetuses (Bang, 1897). Traum (1914) reported the isolation of another organism related to M. melitensis (later assigned as Brucella suis) from aborted pigs in United States. But the final link of these zoonotic bacteria was accomplished in 1918 by the outstanding American microbiologist Alice Catherine Evans (Evans, 1918). Her achievements helped to understand the epidemiology of brucellosis and contributed to the founding of milk pasteurization as preventive measure. Then, in 1920, Louis Meyer and Wilbur Shaw honored David Bruce and proposed to group these pathogenic bacteria within a single genus named Brucella (Meyer and Shaw, 1920).

The events that followed all these inspiring investigations have demonstrated the existence of different Brucella species (Figure 3) that cause brucellosis in domestic animals (cows, sheep, goats, pigs, camels, reindeer, and dogs), wild land animals (bison, elk, hares, muskox, caribou, foxes, and several rodents) and sea mammals (dolphin, whales, seals, and walruses; Godfroid et al., 2011; Guzmán-Verri et al., 2012). Despite of this diversity the only species that are linked to human brucellosis are...
B. melitensis, B. suis, B. abortus, and to minor extent Brucella canis (Moreno and Moriyón, 2006); this last specie being the causative agent of canine brucellosis (Carmichael and Bruner, 1968). Apart from this group there are other Brucella strains (e.g., B. inopinata) that have been rarely isolated from humans (McDonald et al., 2006; De et al., 2008; Scholz et al., 2010); however, no connection between zoonotic transmission and disease has been established.

Members of the genus Brucella are phylogenetically related to α-Proteobacteria that live in close association with animal and plant cells (Moreno and Moriyón, 2002). From the genotypic perspective the genus is monophyletic with DNA similarity above 97% (Verger et al., 1985). In spite of this, Brucella species can be distinguished by single-nucleotide polymorphism analysis, host preference and conspicuous differences in virulence (Bossary et al., 1982; Foster et al., 2012). In addition, there are several straight forward phenotypic differences, being the most obvious the absence of surface O-polyosaccharide chain in naturally occurring rough species such as B. canis and Brucella ovis (Moreno and Moriyón, 2006). One interesting feature of the genus is the absence of plasmids and lysogenic phages, a phenomenon that precludes the horizontal transference of genes through classical routes (Moreno, 1998). Based on this, it has been proposed that the extant Brucella species expand clonally within the host environment and that genetic drift depends almost exclusively on mutation and internal genetic rearrangements (Moreno, 1998).

Brucellosis is one of the few diseases in which efficient live bacterial vaccines (e.g., B. abortus S19 and B. melitensis Rev1) have been developed (Cotton et al., 1933; Elberg and Meyer, 1958). Likewise, through history of microbiology very few diseases have more diagnostic tests than brucellosis (Moreno and Moriyón, 2006). As expected, through history of microbiology very few diseases have more diagnostic tests than brucellosis (Moreno and Moriyón, 2006). As expected, the isolation of the bacterium stands as the gold standard. However, simple techniques, such as the Rose Bengal test, have survived all challenges and are the most widely used serological assays (Díaz et al., 2011). This is not by chance, since by the combination of immunization with smooth vaccines, Rose Bengal serological diagnosis and culling of the animals, brucellosis has been controlled and eradicated in many countries of the world (Davidson, 1970; Crawford and Hidalgo, 1977; Whittem, 1978; Wise, 1980; Chamberlin, 1985; Crawford et al., 1990).
Moreno Zoonotic brucellosis

FIGURE 3 | Dispersion of *Brucella* species confronted to the phylogeny of their preferred host mammal. The dispersion of the various *Brucella* species is depicted as cones proportional to the number of strains analyzed. The numbers in the mammal phylogenetic tree represent millions of years. *B. suis* biovar 2 also has affinity for hares (lagomorphos). *B. ceti* Hum (human type) does not correspond phylogenetically to *B. ceti* group and this single isolate requires taxonomic definition. The source of the two isolates of *B. inopinata* is unknown. Notice that phylogenetic relationship between the two clades is not perfect suggesting that carnivore mammals acquire brucellosis (probably by depredation) after the initial dispersion of cetaceans and ungulates from an ancestral mesonychid, close to 65–60 million ya. Phylogenetic dendrogram was adapted from Guzmán-Verri et al. (2012).

**THE EMERGENCE OF ZOONOTIC BRUCELLOSIS**

Through coordinated measures, brucellosis was finally eradicated from the island of Malta 90 years after the discovery of the disease (Wyatt, 2009a). Unfortunately, this has not been the fate of other areas around the Mediterranean Sea, mainly in African, eastern Mediterranean, and Middle East countries, where the disease has been endemic for thousands of years and from which brucellosis was spread around the world (Figure 4).

**ZOONOTIC BRUCELLOSIS IN EURASIA AND MIDDLE EAST**

Analogous to the island of Malta, Butrint in Albania keeps valuable World Heritage Sites that give testimony on the existence of pastoral inhabitants for millennia (Ryder, 1981). Pathological studies and DNA analysis performed in human remains from graves dated 1260–1020 ya, revealed the presence of *Brucella* as the causative agent of the disease that affected these Middle Age inhabitants in the ancient city of Butrint (Mutolo et al., 2012). In addition to Albania, other Balkans countries such as Macedonia and Bosnia and Herzegovina still struggle with animal and human brucellosis; a phenomenon that was boosted by the decline of veterinary and health services in these countries during the political and armed conflicts in the 1990s (Bosilkovski et al., 2010; Puto et al., 2010; Ahmetagic et al., 2012). Human brucellosis outbreaks have also thrived in Balkan neighboring countries such as Greece, Italy, and Turkey (Minas et al., 2007; Mancini et al., 2013). Most likely the disease was endemic in these Mediterranean counties since the beginning of civilization (D’Anastasio et al., 2011). Remains of cheese buried in Pompeii and Herculaneum have been associated with the transmission of brucellosis in Roman imperial times (Capasso, 2002). Likewise, a critical analysis of Thucydides’ history regarding the plague of Athens (2430–2420 ya) suggests the presence brucellosis (Kousoulis et al., 2012). Archeological evidence from 7000 ya in the eastern Mediterranean region of Anatolia demonstrated ancient skills to transport milk and to manufacture yogurt and cheese, all vehicles for brucellosis contagion (Evershed et al., 2008).

Presumptive human brucellosis cases in skeletal remains from the Bronze Age (4100–3550 ya) have been found in Palestine and
Moreno Zoonotic brucellosis

FIGURE 4 | Timeline of events associated with zoonotic brucellosis. The scale increases logarithmically from 5 million years in the past to 50 years estimated as the "present" (in 1950). Dates are designated as indicated in the main text.

Jordan (Capasso, 2002; D’Anastasio et al., 2011). It is not coincidental that these places are close to the Fertile Crescent and Taurus Mountains, sites where sheep, goats, cows, and pigs – all known to be preferred Brucella hosts – were domesticated between 12000 and 10000 ya (Nelson, 1998; Naderi et al., 2008; Pariset et al., 2011; Bonfiglio et al., 2012). Brucellosis has been also implicated in Bronze Age sites located in Bahrain, Persian Gulf (Rashidi et al., 2001; D’Anastasio et al., 2011). This archipelago belongs to a region where the dromedary camel – another common Brucella host – was domesticated about 6000 ya (Peters, 1997). In this area, human brucellosis acquired through the ingestion of camel dairy products is still endemic, mainly in semi-nomadic Bedouin populations (Rafai, 2002; Shimol et al., 2012). Analyses of human DNA remains from 5000 to 4500 ya have revealed that late Neolithic Europeans displayed lower frequency of lactase persistence than modern extant populations (Plantinga et al., 2012). It seems that water buffalo (Bubalus spp.) was also domesticated in China about 4000 ya (Teasdale and Bradley, 2012). However, milk and derived dairy products are not commonly found in East Asian cuisines, a culinary activity that is compatible by the lactose intolerance distribution in these populations (Itan et al., 2010). Two exceptions are human groups living in the Asian steppes and Mongolia who still consume milk and fermented dairy products; then keeping lactose tolerance and human brucellosis. It is likely that brucellosis was endemic in these areas before imperial times.

ZOONOTIC BRUCELLOSIS IN AFRICA AND INDIAN SUBCONTINENT

Human brucellosis is highly prevalent in India (Mantur and Amar Nath, 2008). Bovine Bos indicus zebu breeds were domesticated in Asia (Zhang et al., 2010; Denisov et al., 2013; Li et al., 2013). Paleopathological evidence indicates that Lapp people in the Artic area of Northern Eurasia domesticated reindeer (the preferred host for B. suis biovar 4) 3000–2000 ya or even earlier (Røed et al., 2011; van Kolfschoten et al., 2011) and that these inhabitants also suffered from brucellosis (Ortner, 2003; Røed et al., 2011). Bovine and swine were already present in China, Mongolia, and Korea, at least 5000 ya or even before, shortly after their domestication in the Fertile Crescent (Nelson, 1998; Giuffra et al., 2000; Zhang et al., 2013). Milk and derived dairy products are not commonly found in East Asian cuisines, a culinary activity that is compatible by the lactose intolerance distribution in these populations (Itan et al., 2010). Two exceptions are human groups living in the Asian steppes and Mongolia who still consume milk and fermented dairy products; then keeping lactose tolerance and human brucellosis. It is likely that brucellosis was endemic in these areas before imperial times.

Brucellosis is highly prevalent in Asia (Zhang et al., 2010; Denisov et al., 2013; Li et al., 2013). Paleopathological evidence indicates that Lapp people in the Artic area of Northern Eurasia domesticated reindeer (the preferred host for B. suis biovar 4) 3000–2000 ya or even earlier (Røed et al., 2011; van Kolfschoten et al., 2011) and that these inhabitants also suffered from brucellosis (Ortner, 2003; Røed et al., 2011). Bovine and swine were already present in China, Mongolia, and Korea, at least 5000 ya or even before, shortly after their domestication in the Fertile Crescent (Nelson, 1998; Giuffra et al., 2000; Zhang et al., 2013). It seems that water buffalo (Bubalus spp.) was also domesticated in China about 4000 ya (Teasdale and Bradley, 2012). However, milk and derived dairy products are not commonly found in East Asian cuisines, a culinary activity that is compatible by the lactose intolerance distribution in these populations (Itan et al., 2010). Two exceptions are human groups living in the Asian steppes and Mongolia who still consume milk and fermented dairy products; then keeping lactose tolerance and human brucellosis. It is likely that brucellosis was endemic in these areas before imperial times.

Brucellosis is highly prevalent in Asia (Zhang et al., 2010; Denisov et al., 2013; Li et al., 2013). Paleopathological evidence indicates that Lapp people in the Artic area of Northern Eurasia domesticated reindeer (the preferred host for B. suis biovar 4) 3000–2000 ya or even earlier (Røed et al., 2011; van Kolfschoten et al., 2011) and that these inhabitants also suffered from brucellosis (Ortner, 2003; Røed et al., 2011). Bovine and swine were already present in China, Mongolia, and Korea, at least 5000 ya or even before, shortly after their domestication in the Fertile Crescent (Nelson, 1998; Giuffra et al., 2000; Zhang et al., 2013). It seems that water buffalo (Bubalus spp.) was also domesticated in China about 4000 ya (Teasdale and Bradley, 2012). However, milk and derived dairy products are not commonly found in East Asian cuisines, a culinary activity that is compatible by the lactose intolerance distribution in these populations (Itan et al., 2010). Two exceptions are human groups living in the Asian steppes and Mongolia who still consume milk and fermented dairy products; then keeping lactose tolerance and human brucellosis. It is likely that brucellosis was endemic in these areas before imperial times.

ZOONOTIC BRUCELLOSIS IN AFRICA AND INDIAN SUBCONTINENT

Human brucellosis is highly prevalent in India (Mantur and Amar Nath, 2008). Bovine Bos indicus zebu breeds were domesticated in
the Indus Valley region (today Pakistan) about 7000 ya (Teasdale and Bradley, 2012). An independent domestication of water buffalo was achieved in India about 5000 ya (Kumar et al., 2007). Infected water buffalos shed *Brucella* in the milk; however, these animals are more resistant to *Brucella* induced abortion than Bos species (Borriello et al., 2006; Adams and Schutta, 2010). An independent domestication of goats also occurred in the Indus Basin in Pakistan already 9000 ya (Joshi et al., 2004). Considering these events, it is striking that up to 80% of the Indian population is lactose intolerant. It has been determined that the mutation for lactose tolerance was introduced later on to eastern India from the Middle East (Gallego Romero et al., 2012). This suggests that ingestion of dairy products started later in India than in other regions, and with it, zoonotic brucellosis. Another alternative comes from how Indians prepare their milk: they often ferment it in the form of lassi or paneers, processes that break down the lactose and also kills *Brucella* organisms.

Human brucellosis was described in Mediterranean African countries more than 100 ya (Rafai, 2002). It is likely that brucellosis was present in human settlements in Northern Africa already 3000 ya and highly prevalent in Egypt during biblical times (e.g., OT, Isaiah 37:8–9, and 2 Kings 19:8–9). Studies performed in Egyptian archeological sites dated 750 B.C. have revealed several human hip bones with signs of brucellosis in this region (Hodgkins, 2002). Brucellosis in southern Africa was detected in dairy herds as early 1913 and the first human cases in 1921 (Bevan, 1931). It seems that the introduction of Indian and Eurasian bovine, sheep, and goat breeds into Africa occurred rapidly after their domestication in the Fertile Crescent. Nevertheless, it has been established that different African ethnic groups have distinct lactase gene mutations that arose independently in different locations between 6800 and 2700 ya (Tishkoff et al., 2007). These data fits well with archeological evidence suggesting that pastoral peoples reached eastern Africa in different migration waves, about 4500–3500 ya.

It is feasible that brucellosis existed in indigenous African Artiodactyla species (which include a significant number of potential *Brucella* hosts) long before the introduction of domesticated herds. A paleopathological study has suggested the presence of *Brucella* infections in australopithecines, already 2.5–2.3-million ya (D’Anastasio et al., 2009, 2011). As expected, this proposal not only has implications on the origin of the disease in local African fauna but, remarkably, also on the feeding habits of these human ancestors. In spite of this, it seems that *Brucella* infections in indigenous African mammals remain low (Gomo et al., 2012) and only relevant when wildlife ungulates become in contact with infected domesticated cows, goats, or sheep (Madsen and Anderson, 1995).

### INTRODUCTION OF ZOONOTIC BRUCELLOSIS IN THE AMERICAN CONTINENT AND OCEANIA

The only indigenous *Brucella* specie in the American Continent seems to be *Brucella neotomae*, first isolated in United States from desert wood rats in 1957 (Stoenner and Lackman, 1957). *B. neotomae* is confined to these rodents with no other known hosts. The absence of domesticated ungulate reservoirs before European colonization very likely circumvented the presence of zoonotic brucellosis in the New World. This is revealed by the close to 100% lactose intolerance of adult Amerindians and in Inuit people (Alzate et al., 1969; Ellestad-Sayed et al., 1978; Sahi, 1994). Thus, it is unlikely that American inhabitants—who populated the continent between 12000 and 4000 ya—ingested milk from potential *Brucella* infected wild life ungulates such as bison, muskox, elk, or caribou. Therefore, the various zoonotic *Brucella* species were likely introduced in America during the last decade of the fifteenth century by the first Spaniards conquerors following the arrival of cattle in the colonies (Bowling, 1942). At that time brucellosis was probably highly endemic in the Iberian Peninsula. This is supported by the discovery of human remains from the late Middle Ages displaying pathological signs of brucellosis (Etxeberria, 1994) and by the description of the disease in Spain. For instance the clinical description of the “lousy fever” suffered by the mystic poet St. Teresa of Jesus—born 20 years after Christopher Columbus opened up the Western Hemisphere to European colonization—is compatible with brucellosis (Senra-Valera, 2006).

As for other infectious diseases, the spreading of brucellosis from the “Old World” to the “New World” very likely was a significant outcome of the conquests. It has been well documented that during his second voyage to the American Continent in 1493, Christopher Columbus introduced a significant number of cattle and pigs (de las Casas, 1951). Very probably by these means the introduction of brucellosis in the continent, including the contamination of indigenous fauna such as bison (Rhyen et al., 2013). Brucellosis was detected in a Yellowstone American buffalo herd already in 1917 (Mohler, 1917). Until the first half of the twentieth century, European cows shared with bison herds the same pastures lands (Bowling, 1942) making likely cross infection (Figure 1). Indeed, brucellosis in North American bison and elk has been related to cross contamination of bacterial strains (including vaccine strains) from infected European bovine breeds (Meagher and Meyer, 1994; Higgins et al., 2012). Furthermore, the same *B. abortus* biovars (1 and 2) are found in both classes of bovine herds. The disease in the American buffalo is similar to that of domesticated cattle (Rhyen et al., 2001b); though it is believed that bison, like water buffalo, may display some resistance to *Brucella* induced abortion (Herman, 2013).

The origin of *B. suis* biovar 4 infecting Canadian and Alaskan caribou and muskox has been traced to imported reindeer from Siberia, early in the twentieth century (Meyer, 1966; Forbes, 1991). Domesticated reindeer should be also considered a potential source of zoonotic disease since brucellosis—caused by *B. suis* biovar 4—has been found in Eskimos (Davies and Hanson, 1965; Meyer, 1966; Forbes, 1991). Alternatively, *B. suis* biovar 4 could have arrived with infected caribou and muskox through the Bering Land Bridge during the last glaciation (Campos et al., 2010; Roed et al., 2011).

Human brucellosis was prevalent in Mexico, USA, and Canada for centuries (Spink, 1956; Wise, 1980; Ruiz-Castañeda, 1986). The first human cases in North America were recognized between 1889 and 1894 (Craig, 1903; Gentry and Ferenbaugh, 1911). With the exception of Mexico, nowadays the presence of human brucellosis has become a rare event in northern hemisphere of the American continent. This was the result of the successful pasteurization of...
dairy products and the application of control programs based in extensive immunization of herds with smooth *Brucella* vaccines, diagnostic tests such as Rose Bengal and complement fixation and efficient culling and management of animal flocks during the second half of the twentieth century (Crawford and Hidalgo, 1977; Wise, 1980). In contrast, the absence of coordinated control programs, poor management of animal flocks, and the introduction of vaccines with low efficacy have kept brucellosis highly prevalent in Mexico, Central America, and most South American countries (Moreno, 2002; Vargas, 2002; Lucero et al., 2008; Herrera-López et al., 2010; Godfroid et al., 2011; Aznar et al., 2012; Román et al., 2013; Rubach et al., 2013).

*Brucella canis* – the last *Brucella* zoonotic specie described – was discovered in Southern United States in the late 1960s (Carmichael and Bruner, 1968). Dogs were the first animals to be domesticated in the world. The earliest archeological vestiges are from Siberia dated 35000 ya; while in the American continent the oldest known ancient remains date 11000 ya (Leonard et al., 2002; Ovodov et al., 2011). Then, it was expected to find *B. canis* in dog’s wild relatives. However, there are no reports of *B. canis* in wolf or coyote packs and these wild canines seem to display some resistance to smooth *Brucella* species (Davis et al., 1988; Tessaro and Forbes, 2004). Nevertheless, it seems feasible that *B. canis* evolved in dog’s ancestor after predation of *B. suis* biovar 4 infected hosts in Asia (e.g., caribou/reindeer), since these two brucellae species are closely related (Figure 3). Moreover, wolves and Arctic foxes can become naturally infected with *rangenierine brucellosis* (Neiland, 1975). As other zoonotic brucellae, *B. canis* might have penetrated to the American Continent during the European colonization. Alternatively, *B. canis* could have traveled in infected dogs through the Bering Strait already 12000 ya (Leonard et al., 2002). Presently, canine brucellosis has spread throughout the American Continent (Hollett, 2006; Tuemmers et al., 2013). In any case, the zoonotic potential of *B. canis* is low and just sporadic human cases have been reported in the world (Lucero et al., 2008).

Human and animal brucellosis were very important diseases in New Zealand and Australia as these countries keep large numbers of sheep and bovines. As expected, lactose intolerance occurrence with higher zoonotic spectrum are those from domesticated animals or humans (Moreno and Moriyón, 2006; Al Dahouk et al., 2012) and two unconventional *Brucella* strains (one in Australia and one in New Zealand) have been detected in humans (McDonald et al., 2006; Tiller et al., 2010b). In spite of this, no links with the transmission from animals to humans has been established in these cases. Canine brucellosis has just been recently found in domestic dogs in Australia (Gardner and Reichel, 1997; Hofer et al., 2012) but never reported in dingo or *kuri*’ dogs. Presently, human and animal brucellosis are just sporadic in Australia and New Zealand, remaining feral pigs as the only source of human infections (Eales et al., 2010).

**ARTIFICIAL SELECTION OF Brucella**

Pathogens and hosts evolve in response to each other and the genetic diversity of both parties represents a pool of possible variants to maintain adaptation via natural selection (Ewald, 2004). Thus, the “arm race” between *Brucella* and preferred hosts has been driven by genetic adaptation of the bacterium virulent systems confronted with the evolving immune defenses of the host. Domestication, anthropogenic modification of wild life and selection of animals by humans are not neutral phenomena. In each event a concomitant selection of the parasitic microbiota occurs (Pearce-Duvet, 2006). Consequently, it is expected that the prevalent extant *Brucella* strains have been selected through “narrow funnels” connected to these processes.

**Brucella SELECTION THROUGH DOMESTICATION OF ANIMALS**

It does not seem by chance that the most virulent *Brucella* species towards lower or higher virulence are those from wild life animals (Figure 5). Reports of human infections from wildlife reservoirs are scarce. Moreover, within the zoonotic brucellae there are some species that are more virulent than others (e.g., *B. melitensis* > *B. suis* biovars 1, 3, and 4 > *B. abortus* > *B. canis*; Spink, 1956; Bosseray et al., 1982; Ruiz-Castañeda, 1986; Caron et al., 1994). In contrast, *Brucella ceti* and *Brucella pinnipedialis* preferentially infecting free living cetaceans and pinnipeds, respectively, have seldom been found in other animal groups and their zoonotic potential and overall virulence for other animal species, including bovine and swine, seem low (Rhyán et al., 2001a; Perrett et al., 2004; Bingham et al., 2008; Guzmán-Verri et al., 2012). Likewise, *Brucella* species and strains (e.g., *B. neotomae*, *B. microti*, and *B. suis* biovar 5) having preference for wild land mammals are confined to their natural hosts and seldom found in domestic animals or humans (Moreno and Moriyón, 2006; Al Dahouk et al., 2012). Therefore, it is expected that the most prevalent virulent *Brucella* strains were selected during the domestication of animals.

The selection of *Brucella* towards lower or higher virulence has been demonstrated experimentally. Through mutagenesis of genes coding for the so called virulent determinants or regulatory molecules *Brucella* may become attenuated (González et al., 2008;
Barrio et al., 2009; Wang et al., 2012). Likewise, by means of genetic manipulation or selection through serial passages into animals, *Brucella* strains can become robust pathogens (Gibby and Gibby, 1965; Jiménez de Bagüés et al., 2010; Grilló et al., 2012; Terwagne et al., 2013).

In addition of displaying host preferences, the various *Brucella* species and strains also form genetic groups that relate with distinctive geographic origins (Le Flèche et al., 2006; Foster et al., 2012; Garofolo et al., 2013; Jiang et al., 2013; Di et al., 2014). This means that *Brucella* clones rapidly expand and transmit within domesticated groups of animals. In spite of their high DNA similarity, the various bacterial species and strains are selected and form discrete family clusters. These observations parallel those showing that some *Brucella* strains may have been removed or minimized from the bacterial pool as consequence of the control programs. Indeed, several *B. abortus* biotypes described decades ago (Crawford et al., 1990; Meyer, 1990) have not been isolated for more than 40 years; instead, predominant variants have been isolated for more than 40 years; instead, predominant variants may have been also subjected to selection processes during the domestication of sheep, it remains non-pathogenic for humans or for other animals (Blasco, 1990). In general, rough *brucella* such as *B. ovis* are less virulent than their smooth counterparts and have narrower ability to infect other hosts (Moreno and Moriyón, 2006; González et al., 2008). It may be that *B. ovis* was already selected towards a higher affinity for venereal transmission in sheep before domestication of ovine, as suggested before (Moreno, 1992). Moreover, the basal “deep” phylogenetic location of *B. ovis* in relation to *B. abortus, B. melitensis, B. suis*, and *B. canis* clusters (Foster et al., 2012), also suggests earlier adaptation of *B. ovis* to its host.

HERD SIZE AND POPULATION DENSITY IN THE SELECTION OF *Brucella*

Other trend that has favored the prevalence and dissemination of *brucellosis* corresponds to the intensive exploitation of productive animals (Crawford et al., 1990). Humans have taken advantage of the innate social behavior of ungulates and canines and clustered them in small areas. In addition, following anthropocentric purposes, the genetic background of these domestic animals has been narrowed. As in other infectious disease, lower genetic diversity and crowded effect may favor transmission and select for faster replicating organisms with major zoonotic potential (McDaniel et al., 2013). Examples of these were observed in the early days of *brucellosis* in Malta (Wyatt, 2005, 2009a), and more recently in foodborne outbreaks in Peru (Román et al., 2013) and massive outbreaks in Inner Mongolia, threatening hundreds of thousands of people.

Inner Mongolia, which keeps the largest sheep population (18.2% of the flock), also ranks first in animal and human *brucellosis* in China (Pu et al., 2009; Mi et al., 2010; Zhang et al., 2010). In 2007, new *brucellosis* cases were reported in 85 out of 102 districts in Inner Mongolia, with positive prevalence remaining in the other 47 districts. From 1996 to 2010, 78246 human cases were detected with 90% of the new cases reported between 2005 and 2010. This accounts for 40% of the near 200000 cases detected in China for this period. In 2010, this figure reached 47.2%. According to various models, this may be just the “tip of the iceberg” and it is expected that the number of human cases will increase dramatically in the following years (Hou et al., 2013). Moreover, it has been demonstrated that in endemic areas about 20% of the infected individuals remain undiagnosed. Indeed, family members of the patients with *brucellosis* are under increased risk of acquiring the disease (Tabak et al., 2008). Thus, family screening in endemic areas is recommended.

Novel circumstances for fast transmission of zoonotic *brucellosis* have also been observed in confined semi-nomadic Bedouins infected from camel’s milk (Shimol et al., 2012; Shemesh and Yagupsy, 2013) and commercial dog kennels. Camels cohabiting with goats and sheep in small areas are becoming a common practice in Middle East and Arab countries. Dog packs seldom exceed more than a dozen individuals. Consequently, in crowded kennels *B. canis* spreads rapidly inducing massive abortions in bitches, testicular degeneration in males, and becomes a zoonotic
risk (Lucero et al., 2008; Gyuranecz et al., 2011; Reynes et al., 2012; Marzetti et al., 2013). Therefore, intensive exploitation and clustering of animals in poor epidemiological control conditions may favor selection for faster Brucella transmission and zoonotic disease.

**SELECTION OF Brucella IN WILDLIFE ANIMALS**

Distinct Brucella clusters have also been identified in wild life animal populations located in areas separated by natural barriers (Forbes, 1991; Maquart et al., 2009; Guzmán-Verri et al., 2012). As with domesticated species, anthropogenic modification of wild life may also have narrowed the genetic diversity, impact host susceptibility and pathogen transmission. A noteworthy event has been the threatening of the American buffalo which was close to extinction (Hornaday, 1889). Thus, the prevailing bison herds have been founded by a small group of few surviving individuals (Gross and Wang, 2005). This is relevant since North American bison herds remain infected with B. abortus (Rhyán et al., 2001b). The European counterpart of this incident corresponds to the Alpine ibex (Capra ibex). Historically these wild goats were endemic throughout the European Alps. Due to excessive hunting and constrains of their natural habitat, the ibex herds in Central Europe declined to low dangerous numbers. As consequence, the founding of new ibex herds in the Alps come from a pool of few animals, narrowing their genetic diversity (Biebach and Keller, 2009). In certain areas ibex herds are infected with B. melitensis strains displaying also high seroprevalence (Ferroglio et al., 1998; Mick et al., 2014). Therefore, these wild goats may become a source for the reintroduction of B. melitensis in domestic ruminants and humans in Central Europe (Mailles et al., 2012; Hars et al., 2013; Rautureau et al., 2013).

Another example relates to the hunting of marine mammals, linked to the overexploitation of their natural food resources and contamination of the seas. These negative activities have promoted clustering of different Brucella infected marine mammals in reduced areas where food is available, causing excessive competition, undernutrition, stress, and immunosuppression (Ohishi et al., 2008; Van Bressem et al., 2009). As revealed by the increasing brucellosis case reports in some species of cetaceans over others (Maquart et al., 2009; Guzmán-Verri et al., 2012), these unnaturally conditions may favor the selection of Brucella organisms with higher transmission rate.

Brucella divergence seems linked to selective forces within the host environment, and consequently, to the evolution of the host (Moreno, 1998). However, this constrain is not absolute and Brucella species living in wild life or in semi-domesticated hosts may still qualify as potentially pathogens for humans and domestic animals (Godfroid et al., 2011). The phenotypes of B. ceti, B. pinnipedialis, B. microti, and B. neotomae correspond to smooth types equipped with all known “virulent” factors (Audié et al., 2009; Guzmán-Verri et al., 2012). Up to now “mysterious” subtle differences with the classical zoonotic Brucella have kept these other wildlife species out from causing disease in humans. But the correlation of the various species in relation to host preference is not perfect and phylogenetic patterns suggest that Brucella organisms are capable to breakdown the species barrier and “jump” from one mammal order to a very differ one (Figure 3). Eventually, this might favor the persistence of a distinct Brucella clone in a different “preferred” host.

**COPING WITH BRUCELLOSIS**

In the presence of brucellosis, management becomes highly demanding (Spink, 1956; Ruiz-Castañeda, 1986; Moreno and Moriýón, 2006). Domesticated animals and humans have coexisted for millennia without significant intervention measures to control the disease. It is likely that a large part of the prevalent Brucella zoonotic species was selected in flocks during this long-lasting initial period. In some regions of the world, mainly in low income countries, these weak control actions are still common (Rubach et al., 2013). It is likely that a fraction of the genetic background of both humans and animals has been also shaped during the coexistence with Brucella organisms; mainly nearby to the regions where domestication took place (Pashaei et al., 2009; Asaei et al., 2013; Rasouli et al., 2013).

**ERADICATING BRUCELLOSIS**

After the discovery of Brucella organisms and their mode of transmission, direct measures toward the control and eradication of the disease were taken in several countries. As stated, killing of the bacterium by milk heating was one of the first procedures that prevented the transmission of brucellosis. A second relevant action was the discovery of diagnostic techniques capable to distinguish infected animals (Alton et al., 1988). Third, was the development of efficient vaccines for protecting bovine, caprine, and ovine herds (Cotton et al., 1933; Elberg and Meyer, 1958). In addition, in some areas systematic slaughter of the infected animals reduced the density of the bacterium (Ebel et al., 2008). Though, the control of brucellosis by the sole action of culling the infected animals is extremely expensive and not practical under high disease prevalence conditions (Moreno, 2002; Office International des Épizooties, 2013). Following this, massive vaccination in combination with serological diagnoses and culling of the infected animals has become the chief strategy for the control of brucellosis (Office International des Épizooties, 2013). Countries where brucellosis has effectively been controlled have used the following procedures: reliable live vaccines (e.g., S19 and Rev1), adequate immunization protocols (e.g., single dose vaccination, reduced dose), extensive protection coverage (e.g., 100% of the herds at risk), suitable diagnostic tests (e.g., Rose Bengal, RID, Complement fixation, ELISA), sustained removal of the infected animals and restriction in the traffic of animals from infected herds to free herds (e.g., control transhumance herds; Davidson, 1970; Whittet, 1978; Wise, 1980; Moreno and Moriýón, 2006; Ebel et al., 2008). Accordingly, these countries have also narrowed the genetic pool of virulent brucellae and succeeded in eradicating human brucellosis.

**THE BASIC REPRODUCTIVE NUMBER AND SELECTION OF VIRULENCE THROUGH VACCINATION**

The basic reproductive number, also known as $R_0$, is the average number of secondary infections arising from one infected individual in a completely susceptible animal population (Gandon
et al., 2001). That is, for the disease to spread and for an effective animal to animal *Brucella* transmission it is required that the pathogen’s *R₀* exceeds 1 (Figure 6). In contrast if *R₀* < 1, then the disease has the tendency to fade away. Higher the *R₀* value, higher will be the number of subsequently infected individuals. Concomitantly, larger and denser the population of susceptible individuals higher would be the chances for the pathogen to achieve a steady and successful adaptation in the host. As consequence of a collection of unsuccessful events in many middle and low income countries (Moreno, 2002; Blasco and Moriyón, 2005), the *R₀* value exceeds 1; thus keeping the disease and the zoonotic potential high (Vargas, 2002; Godfroid et al., 2011; Aznar et al., 2012; Chand and Chhabra, 2013; Denisov et al., 2013; Jiang et al., 2013; Li et al., 2013; Rubach et al., 2013).

Yet, brucellosis is a complex disease and significant political and economic interests are often in play (Moreno, 2002; Pappas and Memish, 2007; Lundquist, 2012). Of all the problems in control programs, the introduction of low protection rate vaccines stands as a major drawback (Blasco et al., 1993; Verger et al., 1995; Moriyón et al., 2004; Godfroid et al., 2011). Apart from their failure in controlling brucellosis, there are long-term consequences in the use vaccines with low efficacy. In this direction a variety of evolutionary scenarios are possible (Gandon et al., 2001; Gandon and Day, 2007), including the selection of more virulent *Brucella* strains.

Effective vaccination limits *Brucella* infection, restricts shedding, hampers transmission from animal to animal and diminishes the risk of zoonosis (Nicoletti, 1990). In addition, when combined with removal of positive infected animals, efficient vaccination may select for breeds with higher resistance against the disease (Adams and Schutta, 2010). Immunization with efficient vaccines may replace natural infections by inducing competent immunity (Plommet et al., 1987); likewise, culling of the infected animals replaces the natural selection of hosts displaying reproduction impairments, such abortion, placenta retention, and infertility (Fogel and Fogel, 2011). Eventually, these sustained combined strategies establish a *R₀* < 1 with the concomitant peter out of the disease. Moreover, when *R₀* < 1 the pathogen evolution rate towards higher virulence may be overcome and virulent field *Brucella* strains eradicated from domestic flocks (Davidson, 1970; Whittem, 1978; Wise, 1980; Moreno and Moriyón, 2006; Office International des Épizooties, 2013).

In contrast, inefficient vaccines currently used in many countries for the control of bovine, sheep, or caprine brucellosis might work in the opposite direction. Indeed, the protection afforded...
to non-immune animals by the presence of sufficient numbers of immune individuals, known as “herd immunity” (Figure 6) is threatened if the immune status of the herd is low. That is, inefficient vaccines may promote a fertile niche in weakly immune hosts allowing virulent Brucella to be transmitted through vaccinated animals (Herrera-López et al., 2010, 2011; Arellano-Reynoso et al., 2013). In curse this will increase the number of secondary infections. For example, if the anti-Brucella vaccine fails to generate immunity in a fraction \( p \) of those animals vaccinated, then to achieve herd immunity we need to vaccinate a proportion of individuals equivalent to \( R_0 - 1/R_0(1 - p) \) (Figure 7). Hence, if \( p \) is too big it may be impossible to eradicate brucellosis as it has been the case in many countries where vaccines of low-efficacy have extensively been used (Blasco et al., 1993; Moreno, 2002; Vargas, 2002; Blasco and Moriyón, 2005; Arellano-Reynoso et al., 2013; Chand and Chhabra, 2013; Denisov et al., 2013; Hou et al., 2013; Jiang et al., 2013; Li et al., 2013; Oseguera-Montiel et al., 2013; Rubach et al., 2013).

In cases in which the relative fitness of competing pathogens depends on the immune status of their host, low-efficacy vaccines inducing responses below the protective threshold may also prompt pathogen evolution towards higher virulence (Figure 8; Read and Mackinnon, 2008). Selection pressures may work in the same direction observed for non-sterilizing antibiotic treatments, in which the surviving microbes may display a higher resistance edge (Davies and Davies, 2010). Furthermore, anti-Brucella vaccines lacking some fundamental virulent molecular determinants or displaying a large collection of mutations (Wang et al., 2012), give a competitive advantage to virulent strains possessing full set of these factors, as it has been already shown for rough Brucella strains devoid of O-polysaccharide antigen (González et al., 2008; Barrio et al., 2009; Herrera-López et al., 2010).

ANTI-Brucella VACCINES AND A FALSE SENSE OF SECURITY

In certain contexts vaccination induces a “sense of security” in non-specialized general public. This sense of security is sustained in the trust and faith that people have developed on vaccines that successfully prevented and eradicated diseases. If the vaccine is highly efficient, then the faith and trust is justified and not harm is done. However, this complacency is particularly dangerous when vaccines with low efficacy and short-term protective duration are introduced; then, a “false sense of security” may be generated, mainly when the information is not given properly (Henderson et al., 2011). Generally speaking, the false sense of security lays between the optimal expected efficacy for a given vaccine and the real performance of that vaccine (Figure 8) and it has a direct impact in the assessment of herd immunity. The use of anti-Brucella vaccines displaying low efficacy could generate a false sense of security in the minds of livestock farmers and Veterinary Health authorities, who may believe that herds are fully protected.

Under low threshold immunity conditions the host becomes a favorable environment for the replication and spread of field bacterial strains (Moreno, 2002; Herrera-López et al., 2010, 2011; Arellano-Reynoso et al., 2013; Denisov et al., 2013; Jiang et al., 2013) and a potential niche for Brucella selection. This is particularly relevant when prevalence is high and surveillance is low to begin with and when the favored virulent microbe emerges within a restricted population. These arguments are supported by several mathematical and epidemiological models (Gandon et al., 2001; Scherer and McLean, 2002; Day and Gandon, 2007; Gandon and Day, 2007).
One exception is canine antibiotic resistant \textit{Brucella}. In the light of unrestricted use of antibiotics the emergence of \textit{Brucella} has been explained elsewhere (Moreno, 1998). In this sense, the short-term emergence of antibiotic resistant \textit{Brucella} does seem plausible.

**CONCLUDING REMARKS**

The capabilities of \textit{Brucella} to infect and propagate in the preferred hosts follow at least five stages: (i) ability to invade; (ii) power to circumvent the initial defenses; (iii) competence to replicate; (iv) capacity to be transmitted; and (v) endurance to be maintained within the host population (Moreno and Moriyón, 2006; Martirosyan et al., 2011). How, when, and where pathogens cross the boundaries that separate their natural hosts from human populations and provoke an epidemic disease, is not entirely known. Human-to-human \textit{Brucella} transmission would require that the pathogen’s \( R_0 \) exceeds 1 (Gandon et al., 2001). Although \textit{Brucella} animal pathogens have already achieved the first three stages in humans and in occasions the fourth stage (Meltzer et al., 2010), still the disease in humans is terminal and human mediated transmission is not of epidemiological importance (Figure 1). Thus, \textit{Brucella} has not yet reached the \( R_0 \) threshold to emerge as permanent pathogen within human populations and contadaion remains dependent on animal reservoirs. However, under these circumstances human brucellosis may display a \( R_0 \) above the threshold that depends on the zoonotic infection rate. For instance, as consequence of high prevalence in domestic animal reservoirs (sheep) in Inner Mongolia, the \( R_0 \) for human infection corresponds to 1.8 (Hou et al., 2013). Under the prevailing control measures and use of low protective vaccines (Blasco et al., 1993; Verger et al., 1995) it was predicted that human brucellosis will continue to increase for the next decade in China.

Ecological factors and human activities may influence and induce changes in the microbial virulence patterns. But to distinguish \textit{Brucella} clones displaying higher virulence is not an easy task (Moreno and Moriyón, 2002). \textit{Brucella} organisms lack classical molecular markers commonly used to trace virulence such as toxins, fimbria, plasmids, capsules, antigenic variation or resistant forms. The so called “virulent factors” are intertwined with the overall \textit{Brucella} structure and physiology (Moreno and Moriyón, 2002; Barbier et al., 2011) and are found in practically all \textit{Brucella} species examined, independently of their pathogenicity for...
humans (Audic et al., 2009, 2011). Moreover, many of the molecular determinants such as cell envelope components, secretion systems, regulatory systems, transporters, and effectors assigned as virulent factors are also found in soil bacteria related to brucelae (Barquero-Calvo et al., 2009). As stated before, Brucella species form a compact genetic cluster and display host preference for their valuable discussions. This work was partially funded by www.frontiersin.org May 2014 | Volume 5 | Article 213 | 13

ACKNOWLEDGMENTS
Edgardo Moreno wrote and revised the manuscript and made the figures.

AUTHOR CONTRIBUTIONS
Edgardo Moreno wrote and revised the manuscript and made the figures.

REFERENCES
Abdel-Maksoud, M., House, B., Wasfy, M., Abdel-Rahman, B., Pimentel, G., Roushdy, G., et al. (2012). In vitro antibiotic susceptibility testing of Brucella isolates from Egypt between 1999 and 2007 and evidence of probable rifampin resistance. Ann. Clin. Microbiol. Antimicrob. 11, 24. doi: 10.1186/1476-0711-11-24
Adams, G., and Schutta, C. J. (2010). Natural resistance against brucellosis: a review. Open Vet. Sci. J. 4, 61–71. Roushdy, G., et al. (2012). In vitro antibiotic susceptibility testing of Brucella isolates from Egypt between 1999 and 2007 and evidence of probable rifampin resistance. Ann. Clin. Microbiol. Antimicrob. 11, 24. doi: 10.1186/1476-0711-11-24
Adams, G., and Schutta, C. J. (2010). Natural resistance against brucellosis: a review. Open Vet. Sci. J. 4, 61–71.
Blasco, J. M. (1990). "Brucella ovis," in Animal Brucellosis, eds K. Nielsen and J. R. Duncan (Boca Raton, FL: CRC Press), 351–382.

Blasco, J. M., Marin, C., Jiménez-de Bagüés, M. P., and Barberán, M. (1993). Efficacy and safety of Brucella abortus strain 2 vaccine against Brucella ovis in rams. Vaccine 11, 1291–1294. doi: 10.1016/0264-410X(93)90097-H

Blasco, J. M., and Moriyón, I. (2005). Protection of Brucella abortus RB51 revaccinated cows. Comp. Immunol. Microbiol. Infect. Dis. 28, 371–373. doi: 10.1016/j.cimid.2005.05.002

Bonfiglio, S., Ginja, C., De Gaetano, A., Achilli, A., Olivieri, A., Colli, L., et al. (2012). Origin and spread of Bos taurus: new clues from mitochondrial genomes belonging to haplogroup T1. PLoS ONE 7:e38601. doi: 10.1371/journal.pone.0038601

Borriello, G., Capparelli, R., Bianco, M., Fenizia, D., Alfonso, F., Capuano, E., et al. (2006). Genetic resistance to Brucella abortus in the water buffalo (Bubalus bubalis). Infect. Immun. 74, 2115–2120. doi: 10.1128/IAI.74.4.2115-2120.2006

Bosilkovski, M., Krteva, L., Dimzova, M., Vidinov, I., Sopova, Z., and Spasovska, K. (2010). Human brucellosis in Macedonia – 10 years of clinical experience in endemic region. Croat. Med. J. 51, 327–336. doi: 10.3325/cmj.2010.51.327

Bosseray, N., Plommet, M., and De Rycke, J. (1982). Evolution de l’infection de la Bovinae de la région de la France. J. Hyg. (Lond.) 51, 327–336. doi: 10.1017/S0022172400044612

Crawford, R. P. and Hidalgo, R. M. (1977).

Cotton, W. E., Buck, J. M., and Smith, H. E. (1933). Efficacy and safety of abortion vaccines prepared from Brucella abortus strains of different degrees of virulence. J. Agric. Res. 46, 291–314.

Day, T., and Gandon, S. (2007). Applying population-genetic models in theoretical evolutionary epidemiology. Evol. Lett. 10, 876–888. doi: 10.1111/j.1461-2028.2007.01091.x

De, B. K., Stauffer, L., Koylass, M. S., Sharp, S. E., Gee, J. E., Helsel, L. O., et al. (2008). Novel Brucella strain (BO1) associated with a prostatic breast implant infection. J. Clin. Microbiol. 46, 43–49. doi: 10.1128/JCM.01494-07 de las Casas, B. (1951). Historia de las Indias. Buenos Aires: Fondo de Cultura Economica.

Denisov, A. A., Sclyarov, O. D., Salmakov, K. M., and Shumilov, K. V. (2013). The Russian experience in brucellosis veterinary public health. Rev. Sci. Tech. 32, 229–237.

Díaz, R., Casanova, A., Ariza, J., and Moriyón, I. (2011). The Rose Bengal test in endemic region. J. Wildl. Dis. 47, 237–246. doi: 10.7589/0090-3558-44.2.237

Dutot, M. B. (1956). Studies on Brucella ovis (msp.), a cause of genital disease of sheep in New Zealand and Australia. J. Hyg. (Lond.) 54, 351–364. doi: 10.1017/S0022172400044612

Cotton, W. E., Buck, J. M., and Smith, H. E. (1933). Efficacy and safety of abortion vaccines prepared from Brucella abortus strains of different degrees of virulence. J. Agric. Res. 46, 291–314.

Day, T., and Gandon, S. (2007). Applying population-genetic models in theoretical evolutionary epidemiology. Evol. Lett. 10, 876–888. doi: 10.1111/j.1461-2028.2007.01091.x

De, B. K., Stauffer, L., Koylass, M. S., Sharp, S. E., Gee, J. E., Helsel, L. O., et al. (2008). Novel Brucella strain (BO1) associated with a prostatic breast implant infection. J. Clin. Microbiol. 46, 43–49. doi: 10.1128/JCM.01494-07 de las Casas, B. (1951). Historia de las Indias. Buenos Aires: Fondo de Cultura Economica.

Denisov, A. A., Sclyarov, O. D., Salmakov, K. M., and Shumilov, K. V. (2013). The Russian experience in brucellosis veterinary public health. Rev. Sci. Tech. 32, 229–237.

Di, D., Cui, B., Wang, H., Zhao, H., Piao, D., Tian, L., et al. (2014). Genetic polymorphism characteristics of Brucella canis isolated in China. PLoS ONE 9:e84682. doi: 10.1371/journal.pone.0084862

Diaz, R., Casanova, A., Ariza, J., and Moriyón, I. (2011). The Rose Bengal test in human brucellosis: a neglected test for the diagnosis of a neglected disease. PLoS Negl. Trop. Dis. 5:e950. doi: 10.1371/journal.pntd.0000950

Eales, K. M., Norton, R. E., and Keheesan, N. (2010). Brucellosis in northern Australia. Am. J. Trop. Med. Hyg. 83, 876–878. doi: 10.4269/ajtmh.2010.10-0027

Ebel, E. D., Williams, M. S., and Tomlinson, S. M. (2008). Estimating herd prevalence of bovine brucellosis in 46 USA states using slaughter surveillance. Prev. Vet. Med. 85, 295–316. doi: 10.1016/j.prevetmed.2008.02.005

Elberg, S. S., and Meyer, K. F. (1958). Carpine immunization against brucellosis. A summary of experiments on the isolation, properties and behavior of a vaccine strain. Bull. World Health Organ. 19, 711–724.

Elstad-Sayed, J. H., Haworth, J. C., and Hildes, J. A. (1978). Disaccharide malabsorption and dietary patterns in two Canadian Eskimo communities. Am. J. Clin. Nutr. 31, 1473–1478.

Ennah, N. S., Jensen, T. G., Nielsen, M., Lewinski, R., Kuokkanen, M., Rasina, H., et al. (2008). Independent introduction of two lactase-persistence alleles into human populations reflects different history of adaptation to milk culture. Am. J. Hum. Genet. 82, 57–72. doi: 10.1016/j.ajhg.2007.09.012

Etcheverbia, F. (1994). Vertebral epiphysitis: early signs of brucellar disease. J. Paleopathol. 6, 41–49.

Evans, A. C. (1918). Further studies on bacterium abortus and related bacteria: a comparison of bacterium abortus with bacterium bronchisepticus and with the organism that causes Malta fever. J. Infect. Dis. 22, 580–593. doi: 10.1093/infdis/i401093

Evershed, R. P., Payne, S., Sherratt, A. G., Copley, M. S., Coolidge, J., Urem-Kotsu, D., et al. (2008). Earliest date for milk use in the Near East and southeastern Europe linked to cattle herding. Nature 455, 538–531. doi: 10.1038/nature07180

Ewald, P. W. (2004). Evolution of virulence. Infect. Dis. Clin. North Am. 18, 1–15. doi: 10.1016/S0891-5520(03)00099-0

Ferroglio, E., Tolari, F., Bollo, E., and Bassano, B. (1998). Isolation of Brucella melitensis from alpine ibex. J. Wildl. Dis. 34, 400–402. doi: 10.7589/0090-3558-34.2.400

Fogel, G. B., and Fogel, D. B. (2011). Simulating natural selection as a culling mechanism on finite populations with the hawk-dove game. Biosystems 104, 57–62. doi: 10.1016/j.biosystems.2011.01.002

Forbes, L. B. (1991). Isolates of Brucella suis biovar 4 from animals and humans in Canada, 1982–1990. Can. Vet. J. 32, 686–688.
Foster, J. T., Price, L. B., Beckstrom-Sternberg, S. M., Pearson, T., Brown, W. D., Kiesling, D. M., et al. (2012). Genotyping of Brucella species using clade specific SNPs. BMC Microbiol. 12:110. doi: 10.1186/1471-2180-12-110

Gallego Romero, I., Basu Mallick, C., Liebert, A., Crivellaro, F., Chauvey, G., Itan, Y., et al. (2012). Herders of Indian and European cattle share their predominant allele for lactase persistence. Mol. Biol. Evol. 29, 249–260. doi: 10.1093/molbev/msr190

Gandon, S., and Day, T. (2007). The evolutionary epidemiology of vaccination. J. R. Soc. Interface 4, 803–817. doi: 10.1098/rsif.2006.0207

Gandolfi, J., and Rasa, M. (1997). No evidence of Brucella canis infections in New Zealand dogs. Surveillance 24, 17–18.

Gardinier, E., and Reichel, M. P. (1997). No evidence of Brucella canis infections in New Zealand dogs. Surveillance 24, 17–18.

Gibby, I., and Gibby, A. M. (1965). Host–parasite relationships with Brucella neotomae. J. Bacteriol. 89, 9–16.

Gillen, M., Flynn, M., and Brownning, Y. (1989). The Founders of Australia: A Biographical Dictionary of the First Fleet. Sydney: Library of Australian History.

Giuffra, E., Kijas, J. M., Amarger, C., Vair, C., Lejon, J. T., and Andersson, L. (2000). The origin of the domestic pig: independent domestication and subsequent introgression. Genetics 154, 1785–1791.

Godfroid, J., Scholz, H. C., Barbier, T., Nicolas, C., Wattiaux, P., Fretin, D., et al. (2012). A survey of Brucella canis in the chihuahua rough mutants defective in core and O-polysaccharide synthesis and export. PLoS ONE 7:e32670. doi: 10.1371/journal.pone.0032670

Gomo, C., de Garine-Wichatitsky, M., Caron, A., and Pfukenyi, D. M. (2012). Survey of the etiological agents associated with abortion and reproductive failure in African elephants. J. Zoo Wildl. Med. 43, 511–517. doi: 10.1177/0364810612455223

Harré-Laëpée, L., Rivera, A., Palomares, E. G., Hernández-Castro, R., and Díaz-Aparicio, E. (2011). Isolation of Brucella melitensis from a RB51-vaccinated seronegative goat. Trop. Anim. Health Prod. 43, 1069–1070. doi: 10.1007/s11250-011-9822-4

Harré-Laëpée, L., Suárez-Guèmes, F., Hernández-Andrade, L., Córdova-López, D., and Diaz-Aparicio, E. (2010). Epidemiological study of brucellosis in cattle, immunized with Brucella abortus RB51 vaccine in endemic zones. Vaccine 28 (Suppl.) 5,F59–F63. doi: 10.1016/j.vaccine.2010.03.057

Higgins, J., Stuber, T., Quance, C., Edwards, W. H., Tiller, R. V., Linfield, T., et al. (2012). Molecular epidemiology of Brucella abortus isolates from cattle, elk, and bison in the United States, 1998 to 2011. Appl. Environ. Microbiol. 78, 3674–3684. doi: 10.1128/AEM.00045-12

Hodgkins, J. M. (2002). The role that tail bones tell about the antiquity of the human disease brucellosis. Am. J. Phys. Anthropol. 53, 115–115.

Hofer, E., Bag, Z. N., Revilla-Fernández, S., Melzer, F., Tomasino, H., Piz-Go, I. I., et al. (2012). First detection of Brucella canis infections in a breeding kennel in Austria. New Microbiol. 35, 507–510.

Hollett, R. B. (2006). Canine brucellosis: outbreaks and compliance. Theriogenology 66, 575–587. doi: 10.1016/j.theriogenology.2006.04.011

Hornaday, W. T. (1889). The Extermination of the American Bison. From the Report of the Department of Agriculture. Washington: United States Department of Agriculture.

Hornaday, W. T. (1980). The Extermination of the American Bison. From the Report of the Department of Agriculture. Washington: United States Department of Agriculture.

Horrillo, J., Hollet, R. B. (2006). Canine brucellosis: outbreaks and compliance. Theriogenology 66, 575–587. doi: 10.1016/j.theriogenology.2006.04.011

Hou, Q., Sun, X., Zhang, J., Liu, Y., Wang, Y., and Jin, Z. (2013). Modeling the transmission dynamics of sheep brucellosis in Inner Mongolia Autonomous Region, China. Math. Biosci. 242, 51–58. doi: 10.1016/j.mbs.2012.11.012

Itan, Y., Jones, B. L., Ingram, C. J., Swallow, D. M., and Thomas, M. G. (2010). A worldwide correlation of lactase persistence phenotype and genotypes. BMC Evol. Biol. 10:36. doi: 10.1186/1471-2148-10-36

Jiang, H., Wang, H., Xu, L., Hu, G., Ma, J., Xiao, P., et al. (2013). MLVA genotyping of Brucella melitensis and Brucella abortus isolates from different animal species and humans and identification of Brucella suis vaccine strain 2r from cattle in China. PLoS ONE 8:e76332. doi: 10.1371/journal.pone.0076332

Jiménez de Bagüés, M. P., Ouahrani-Bettache, S., Quintana, J. F., Mitjana, O., and Tsiodras, S. (2012). The plague of Thebes, a historical epidemic in Sophocles’ Antigone. J. Infect. Dis. 203, 2–10. doi: 10.1086/653084

Joshi, M. B., Rout, P. K., Mandal, A. K., Smith, K., Singh, L., and Thangaraj, K. (2004). Phylogeography and origin of Indian domestic goats. Mol. Biol. Evol. 21, 454–462. doi: 10.1093/molbev/msi38

Keeling, M. J., Tildesley, M., House T., and Danon, L. (2013). The mathematics of vaccination. Math. Today 49, 40–43.

Koussoulis, A. A., Economopoulou, K. P., Poulakou-Rebelakou, E., Androutsos, G., and Tsiodras, S. (2012). The plague of Thebes, a historical epidemic in Sophocles’ Oedipus Rex. Emerg. Infect. Dis. 18, 153–157. doi: 10.3201/eid1801.A1801

Kumar, M., Nagarajan, M., Sandhu, J. S., Kumar, N., and Behl, V. (2007). Phylogeography and domestication of Indian river buffalo. BMC Evol. Biol. 7:186. doi: 10.1186/1471-2148-7-1

Ledbetter, E. C., Landry, M. P., Stokol, T., Kern, T. J., and Messick, J. B. (2009). Brucella canis endophthalmitis in 3 dogs: clinical features, diagnosis, and treatment. Vet. Ophthalmol. 12, 183–191. doi: 10.1111/j.1463-5224.2009.00690.x

Le Fleèche, P., Jacobs, H., Grayon, M., Dal Dahouk, S., Bouchon, P., Denoeud, F., et al. (2006). Evaluation and selection of tandem repeat loci for a Brucella MLVA typing assay. BMC Microbiol. 6:9. doi: 10.1186/1471-2180-9-6

Leonard, A. J., Wayne, R. K., and upstairs, J. (2012). Ancient DNA evidence for Old World origin of New World dogs. Science 298, 1613–1616. doi: 10.1126/science.1207980

Li, Y. J., Li, X. L., Liang, S., Fang, L. Q., and Cao, W. C. (2013). Epidemiological features and risk factors associated with the spatial and temporal distribution of human brucellosis in China. BMC Infect. Dis. 13:547. doi: 10.1186/1471-2334-13-547

Lucero, N. E., Ayala, S. M., Escobar, G. I., and Jacob, N. R. (2008). Brucella isolated in humans and animals in Latin America from 1968 to 2006. Epidemiol. Infect. 136, 496–503. doi: 10.1017/s0950268807008795

Lundquist, L. (2012). State Agencies and B Politicians Push for New Brucellosis Listing: Bozeman Daily Chronicle. Available at: http://www.Bozemandailychronicle.com/news/wildlife (accessed April 29, 2014).

Madsen, M., and Anderson, E. C. (1993). Serologic survey of Zimbabwean wildlife for brucellosis. J. Zoo Wildl. Med. 26, 240–245.
Moreno, E. (1998). Genome evolution within the alpha Proteobacteria: why do some bacteria not possess plasmids and others exhibit more than one different chromosome? FEMS Microb. Lett. 22, 255–257. doi: 10.1111/j.1574-6968.1998.tb00370.x

Moreno, E. (2002). Brucella in Central America. Vet. Microbiol. 90, 31–38. doi: 10.1016/S0378-1135(02)00242-0

Moreno, E., and Moriyón, I. (2002). Brucella melitensis: a nasty bug with hidden credentials for virulence. Proc. Natl. Acad. Sci. U.S.A. 99, 1–3. doi: 10.1073/pnas.022626699

Moreno, E., and Moriyón, I. (2006). "The genus Brucella," in The Prokaryotes, Vol. 5, Part 1, Section 31, eds M. Dworkin, S. Falkow, E. Rosenberg, K.-H. Schleifer, and E. Stackebrandt (New York: Springer-Verlag), 315–456.

Moriyón, I., Grillo, M. J., Monreal, D., González, D., Marín, C., López-Gómez, L., et al. (2004). Rough vaccines in animal brucellosis: structural and genetic basis and present status. Vet. Res. 35, 1–38. doi: 10.1051/vetres:2003007

Mutolo, M. J., Jenny, L. L., Buszek, A. R., Fenton, T. W., and Foran, D. R. (2012). Osteological and molecular identification of brucellosis in ancient Butrint, Albania. Am. J. Phys. Anthropol. 147, 253–263. doi: 10.1002/ajpa.21643

Naderi, S., Rezaei, H. R., Pomponon, F., Blum, G. M., Negrini, R., Naghash, H. R., et al. (2008). The goat domestication process inferred from large-scale mitochondrial DNA analysis of wild and domestic individuals. Proc. Natl. Acad. Sci. U.S.A. 105, 17659–17664. doi: 10.1073/pnas.0804782105

Neglia, G., Veneziano, V., De Carlo, G., Galiero, G., Borriello, G., Franchello, M., et al. (2013). Detection of Brucella abortus DNA and RNA in different stages of the development of the suckling mouse Haemophilus somnus. BMC Vet. Res. 9:236. doi: 10.1186/1746-6148-9-236

Nieland, K. A. (1975). Rangiferine brucellosis in Alaskan canids. J. Wildl. Dis. 3, 136–139. doi: 10.7589/0090-3558-6.3.136

Nelson, S. M. (1998). Ancestors for the Pigs. Pigs in Prehistory. Philadelphia, PA: University of Pennsylvania Museum of Archeology; University of Pennsylvania Press.

Nicolletti, P. (1989). "Relationship between animal and human disease," in Brucellosis Clinical and Laboratory Aspects, eds E. Young and M. J. Corbel (Boca Raton, FL: CRC Press), 42–51.

Nicolletti, P. (1990). Vaccinations against Brucella. Adv. Biotecnol. Processes 13, 147–168.

Office International des Epizooties (eds.). (2013). Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, 7th Edn, Vol 1 and 2, Chap. 2.4.3., 2.7.2., and 2.7.9. Paris: OIE. Available at: http://www.oie.int/en/international-standard-setting/terrestrial-manual/access-online/ (accessed April 29, 2014).

Ohishi, K., Fujise, Y., and Maruyama, T. (2008). Brucella spp. in the western North Pacific and Antarctic cetaceans: a review. J. Cetacean Res. Manag. 10, 67–72.

Ortner, J. D. (2003). "Infectious diseases: introduction, biology, osteomyelitis, periostitis, brucellosis, glanders, and septic arthritis," in Identification of Pathological Conditions in Human Skeletal Remains, ed. J. E. Ortner (San Diego: Academic Press), 179–226.

Oseguera-Montiel, D., Frankena, K., Udo, H., Keiblach Baer, N. M., and van der Zipp, A. (2013). Prevalence and risk factors for brucellosis in goats in areas of Mexico with and without brucellosis control campaign. Trop. Anim. Health Prod. 45, 1383–1389. doi: 10.1007/s11250-013-0375-6

Ovodov, N. D., Crockford, S. J., Kuzmin, Y. V., Higham, T. F. G., Hodgins, G. W. L., and van der Plicht, J. (2011). A 33,000-year-old incipient dog from the Altai Mountains of Siberia: evidence of the earliest domestication disrupted by the last glacial maximum. PLoS ONE 6:e22821. doi: 10.1371/journal.pone.0022821

Pappas, G., and Memish, Z. A. (2007). Brucellosis in the middle East: a persistent medical, socioeconomic and political issue. J. Chemother. 19, 243–248. doi: 10.1111/j.1747-659 X.2007.00003.x

Pariset, L., Mariotti, M., Gargani, M., Joost, S., Negrini, R., Perez, T., et al. (2011). Genetic diversity of sheep breeds from Albania, Greece, and Italy assessed by mitochondrial DNA and nuclear polymorphisms (SNPs). BMC Vet. Res. 9:236. doi: 10.1186/1746-6148-9-236

Ponnusamy, A., Farreras, P., Foo, A., Surós, J., Surinyach, R., and Frouchtman, R. (1986). Enfermedades Infecciosas. IIA. Enfermedades Producidas por Bacterias. Brucelosis. Patología y Clínica Médicas, Vol. VI. Madrid: Salvat Ediciones S.A.
Perrett, L. L., Brew, S. D., Stack, J. A., MacMillan, A. P., and Bashiruddin, J. B. (2004). Experimental assessment of the pathogenicity of Brucella strains from marine mammals for pregnant sheep. Small Rumin. Res. 51, 221–228. doi: 10.1016/S0921-4488(03)00233-5

Peters, J. (1997). The dromedary: ancestry, history of domestication and medical treatment in early historic times. Tierarztl. Prax. Ausg. G Großtiere Nutztiere 25, 559–565.

Plantinga, T. S., Alonso, S., Izagirre, N., Hervella, M., Fregel, R., van der Meer, J. W., et al. (2012). Low prevalence of lactase persistence in Neolithic South-West Europe. Eur. J. Hum. Genet. 20, 778–782. doi: 10.1038/ejhg.2011.254

Plommet, M. (1992). Prevention of Brucellosis in Mediterranean Countries. Wageningen: Pudoc Scientific Publishers.

Plommet, M., Serre, A., and Fensterbank, R. (1987). Vaccines, vaccination in

Puto, K., Papa, S., and Hila, N. (2010). Dynamic spread of brucellosis in

Plommet, M. (1992).

Ryder, M. L. (1981). A survey of European primitive breeds of sheep. Genet Sel. Evol. 13, 381–418. doi: 10.1186/1297-9686-13-4-381

Sahi, T. (1994). Genetcs and epidemiology of adult-type hypolactasia. Scand. J. Gastroenterol. Suppl. 202, 7–20. doi: 10.3109/0365559490917470

Scherer, A., and McLean, A. (2002). Mathematical models of vaccination. Br. Med. Bull. 62, 187–199. doi: 10.1093/bmb/d62.1.187

Scholz, H. C., Nöckler, K., Golliner, C., Bahn, P., Vergnaud, G., Tomaso, H., et al. (2010). Brucella inopinata sp. nov., isolated from a breast implant infection. Int. J. Syst. Evol. Microbiol. 60, 801–808. doi: 10.1099/ijs.0.011148-0

Schurig, G. G., Roop, R. M. II, Bagchi, T., Boyle, S., Buhrman, D., and Srian- ganathan, N. (1991). Biological properties of RBS1: a stable rough strain of Brucella abortus. Vet. Microbiol. 28, 171–188. doi: 10.1016/0378-1135(91)90091-S

Senra-Valera, A. (2006). Las enfermedades de Santa Teresa. Religión Cult. (Spain) 52, 605–814.

Shenesh, A. A., and Yagupsky, P. (2013). Increasing incidence of human brucellosis in southern Israel after the cessation of a veterinarian control campaign. Air Water Borne Dis. 2, 2. doi: 10.4172/2167-7719.1000122013

Shimol, S. B., Dukhan, L., Belmaker, I., Bardenstein, S., Sibirskey, D., Barrett, C., et al. (2012). Human brucellosis outbreak acquired through camel milk ingestion in southern Israel. Isr. Med. Assoc. J. 14, 475–478.

Spink, W. W. (1956). The Nature of Brucellosis. Minneapolis: The University of Minnesota Press.

Stoennner, H. G., and Lackman, D. B. (1957). A new species of Brucella isolated from the desert wood rat, Neotoma lepida Thomas. Am. J. Vet. Res. 18, 947–951.

Tabak, T., Hakko, E., Mete, B., Ozaras, R., Mert, A., and Ozurt, R. (2008). Is family screening necessary in brucellosis? Infection 36, 357–357. doi: 10.1007/s15010-008-0022-6

Teasdale, M. D., and Bradley, D. G. (2012). The Origins of Cattle. Bovine Genomics. Oxford: Wiley-Blackwell. doi: 10.9788/11830.1739.ch1

Terwagane, M., Ferozj, J., Rolán, H. G., Sun, Y. H., Atluri, V., Xavier, M. N., et al. (2013). Innate immune recognition of flagellin limits systemic persistence of Brucella. Cell. Microbiol. 15, 942–960. doi: 10.1111/cmi.12088

Tessaro, S. V., and Forbes, L. B. (2004). Experimental Brucella abortus infection in wolves. J. Wildl. Dis. 40, 60–65. doi: 10.7589/0090-3558-40.1.60

Tiller, R. V., Gee, J. E., Frace, M. A., Taylor, T. K., Setubal, J. C., Hoffmaster, A. R., et al. (2010a). Characterization of novel Brucella strains originating from wild native rodent species in North Queensland, Australia. Appl. Environ. Microbiol. 76, 5837–5845. doi: 10.1128/AEM.00620-10

Tiller, R. V., Gee, J. E., Lonsway, D. R., Grickle, S., Bell, S. C., Jennison, A., et al. (2010b). Identification of an unusual Brucella strain (BO2) from a lung biopsy in a 52-year-old patient with chronic destructive pneumonia. BMC Microbiol. 10.23. doi: 10.1186/1471-2180-10-23

Tishkoff, S. A., Reed, F. A., Ranciaro, A., Voight, B. F., Babbitt, C. C., Silverman, J. S., et al. (2007). Convergent adaptation of human lactase persistence in Africa and Europe. Nat. Genet. 39, 31–40. doi: 10.1038/ng1946

Traun, J. (1914). Report of the Chief of the Bureau of Animal Industry. Washington: United States Department of Agriculture (USDA).

Tuermers, C., Lüders, C., Rojas, C., Serri, M., Castillo, C., and Espinoza, R. (2013). Detección de Brucella canis por método de inmunocromatografía en perros vagos capturados en la ciudad de Temuco, Chile, 2011. Rev. Chilena Infectol. 30, 395–401. doi: 10.4067/S0710-01932013000400007

Van Bressem, M. E., Raga, J. A., Di Guardo, G., Jepson, P. D., Duignan, P. J., Siebert, U., et al. (2009). Emerging infectious diseases in cetaceans worldwide and the possible role of environmental stressors. Dis. Aquat. Organ. 86, 143–157. doi: 10.3354/dao02011

van Kolfschoten, T., van der Jagt, L., Beeren, Z., Argití, V., van der Leije, J., van Essen, H., et al. (2011). A remarkable collection of Late Pleistocene reindeer (Rangifer tarandus) remains from Woerden (The Netherlands). Quat. Int. 238, 4–11. doi: 10.1016/j.quaint.2010.12.033

Vargas, F. I. (2002). Brucellosis in Venezuela. Vet. Microbiol. 90, 39–44. doi: 10.1016/S0378-1135(02)00243-2

Verger, J. M., Grimon, F., Zundel, U., Lechopier, P., and Olivier-Bernardin, V. (1995). Comparison of the efficacy of Brucella suis strain 2 and Brucella melitensis Rev. 1 live vaccines against a Brucella melitensis experimental infection in pregnant ewes. Vaccine 13, 191–196. doi: 10.1016/0264-410X(95)31315-V

Verger, J. M., Grimon, F., Grimon, P. A., and Grignon, M. (1985). Brucella, a monospecific genus as shown by deoxyribonucleic acid hybridization. Int. J. Syst. Evol. Microbiol. 35, 292–295.

Wang, Y., Ke, Y., Wang, Z., Yuan, X., Qiu, Y., Zhen, Q., et al. (2012). Genome sequences of three live attenuated vaccine strains of Brucella species.
and implications for pathogenesis and differential diagnosis. *J. Bacteriol.* 194, 6012–6013. doi: 10.1128/JB.01483-12

Whittern, J. H. (1978). Bovine brucellosis eradication Australia. *Proc. Annu. Meet. U. S. Anim. Health Assoc.* 82, 139–141.

Wise, R. I. (1980). Brucellosis in the United States. Past, present, and future. *JAMA* 244, 2318–2322. doi: 10.1001/jama.1980.03310200058031

Wyatt, H. V. (2000). Dr. G. Caruana Scicluna, the first Maltese microbiologist. *J. Med. Biogr.* 8, 191–193.

Wyatt, H. V. (2005). How Temistocles Zammit found Malta fever (brucellosis) to be transmitted by the milk of goats. *J. R. Soc. Med.* 98, 451–454. doi: 10.1258/jrsm.98.10.451

Wyatt, H. V. (2009a). Brucellosis and Maltese goats in the Mediterranean. *J. Maltese Hist.* 1, 4–18.

Wyatt, H. V. (2009b). James Crawford Kennedy and the sexual transmission of brucellosis. *J. R. Army. Med. Corps* 155, 239–240. doi: 10.1136/jramc-155-03-17

Wyatt, H. V. (2010). Surgeon Captain Sheldon F. Dudley and the person to person spread of brucellosis by inhalation. *J. R. Nav. Med. Serv.* 96, 185–187.

Wyatt, H. V. (2011). The curious affair of the identity of Fioravanti Sammut (b.1863) and Temistocle Zammit (d.1935). *J. Med. Biogr.* 19, 128–131. doi: 10.1258/jmb.2010.010058

Yagupsky, P., and Baron, E. J. (2005). Laboratory exposures to brucelae and implications for bioterrorism. *Emerg. Infect. Dis.* 11, 1180–1185. doi: 10.3201/eid1108.041197

Zhang, H., Paijmans, J. L., Chang, F., Wu, X., Chen, G., Lei, C., et al. (2013). Morphological and genetic evidence for early Holocene cattle management in northeastern China. *Nat. Commun.* 4, 2755. doi: 10.1038/ncomms3755

Zhang, W. Y., Guo, W. D., Sun, S. H., Jiang, J. F., Sun, H. L., Li, S. L., et al. (2010). Human brucellosis, Inner Mongolia, China. *Emerg. Infect. Dis.* 16, 2001–2003. doi: 10.3201/eid1612.091081

Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 25 January 2014; accepted: 23 April 2014; published online: 13 May 2014.

Citation: Moreno E (2014) Retrospective and prospective perspectives on zoonotic brucellosis. *Front. Microbiol.* 5:213. doi: 10.3389/fmicb.2014.00213

This article was submitted to Infectious Diseases, a section of the journal Frontiers in Microbiology.

Copyright © 2014 Moreno. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.