Curr Clin Micro Rpt (2017) 4:1–10
DOI 10.1007/s40588-017-0052-z

BACTERIOLOGY (N BOREL, SECTION EDITOR)

# *Brucella abortus*: Current Research and Future Trends

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Published online: 27 January 2017


**Abstract**
*Purpose of review* *Brucella abortus* is a Gram-negative, facultative intracellular bacterium of the genus *Brucella* and is the main causative agent of bovine brucellosis. An update on the recent research on *B. abortus* and diseases caused by *B. abortus* in animals and humans is provided.
*Recent findings* In the last decade, intense efforts have focused on understanding the pathobiology, taxonomy, proteomics, and genomics of *B. abortus*. Proteomic analyses and complete genomic sequencing have provided information on the virulence of the brucellae; this information will help to identify novel antigens for better serodiagnosis and promising candidates for subunit vaccines.
*Summary* The bacteria affect a broad variety of animal host species as well as humans, causing seriously debilitating disease. Short-course treatment regimens or licensed vaccines in humans do not exist. Diagnosis remains a challenge in endemic and non-endemic countries, and the effectiveness of current surveillance and control programs in animals is still under discussion. Brucellosis in bovines is a re-emerging disease in developing countries but is neglected by public (veterinary) health and family doctors.

**Keywords** *Brucella abortus* · Taxonomy · Pathobiology · Diagnosis · Proteomics · Genomics · Review

## Introduction

Bovine brucellosis is an exhausting zoonosis caused by the genus *Brucella* (B.). *Brucella* affects a wide range of domesticated animals and wildlife. The genus *Brucella* represents Gram-negative, non-motile, non-spore forming, aerobic, facultative intracellular coccobacilli. Taxonomically, brucellae are placed in the α-2 subdivision class of the *Proteobacteria* [1]. To date, the genus includes 12 accepted nomo-species, of which *B. melitensis*, *B. abortus*, *B. suis*, and *B. canis* are well-

This article is part of the Topical Collection on *Bacteriology*

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known human pathogens. *B. abortus* was first described by Bernard Bang in 1895 and is the main etiologic agent of bovine brucellosis. *B. abortus* is endemic in most developing countries, but it also exists in the USA and countries of the Mediterranean basin. In livestock, the disease is known as "contagious abortion" and "Bangs disease" and provokes abortion and infertility. In humans, it often causes a chronic disease known as "undulant fever" or "Malta fever."

*B. abortus* taxonomy is perpetually being reshuffled. Based on differences in biochemical tests, $CO_2$ requirements, susceptibilities to dyes, and lysis by phages, *B. abortus* is divided into biovars. Nine *B. abortus* biovars (bv 1–9) were described initially, but biovars 7 and 8 were then removed from classification. Recently, four *B. abortus* strains isolated in Kenya, Turkey, and Mongolia showed agglutination with both anti-A and anti-M monospecific sera and concurred with the former phenotypic profile of *B. abortus* bv 7; because of this discovery, bv 7 was recognized again [2•]. To date, phenotypic classification of *B. abortus* is still used in bovine brucellosis epidemiology despite the availability of molecular tools. Thus, typing is not significantly important for diagnosis but is useful for the handling and control of the disease. *B. abortus* bv 1 is the most frequently isolated biovar from cattle in countries where biovar prevalence has been studied. *B. abortus* typically have a smooth phenotype, but strains of *B. abortus* bv 1 rough have been isolated from field samples [3••]. Conversion from the smooth to rough phenotype occurs spontaneously depending on the strain and growth conditions. In this review, we provide an update on *B. abortus* over the last decade. In the period between 2005 and 2015, 1155, 735, and 268 scientific papers were found by an online research in PubMed using the terms "*B. abortus*," "*B. melitensis*," and "*B. suis*," respectively (Fig. 1). Due to the public health impact and economic losses caused by *B. abortus* to the livestock industry, efforts have focused on vaccine research [4–7]. Due to a lack of vaccine targets and difficulties in treating *B. abortus*, omics (including genomics, transcriptomics, and proteomics) and bioinformatics technologies have been used increasingly.

## Pathobiology of *B. abortus*

The pathogenesis of *B. abortus* in its hosts is based on a few critical sequential events during infection. The capacity of *B. abortus* to cause disease is related to its ability to invade epithelial cells, survive intracellularly, and prevent activation of the host innate immune system [8]. The known classical virulence factors are absent in *Brucella*; however, it possesses several mechanisms associated with pathogenicity, e.g., lipopolysaccharides (LPSs). In smooth *B. abortus*, the LPS O-chain is essential for bacterial entry and intracellular survival. It can inhibit cellular apoptosis and has low immunogenicity [9]. *B. abortus* may express some immunodominant proteins promoting survival in the host system during the early stage of infection [10•]. *Brucella* efficiently acquires resources, e.g., nitrogen, from the host to avoid cell death [11].

The pathogenesis of *B. abortus* is largely influenced by host factors. It has been demonstrated that the infection of host macrophages by *B. abortus* results in the secretion of platelet-activating factor (PAF), a platelet-activating factor receptor (PAFR) agonist. PAFR accelerates the uptake of *B. abortus* by phagocytic cells and markedly increases *B. abortus* uptake into macrophages, leading to metastasis of bacteria to different sites in the body. This receptor-related phagocytic mechanism affects the host cell response towards *B. abortus* infection and correlates with the receptor-mediated cellular signaling and pathogenic strategy of *B. abortus* [12•]. Digestive, genitourinary, and respiratory epithelia are the most important portals of entry for *B. abortus*. When *B. abortus* adheres to and invades the epithelial cells, the intra-epithelial phagocytes tend to transport the bacteria deeply into the lamina properia and submucosa. Growth and intracellular survival of *B. abortus* is dependent on its ability to resist the acidified intraphagosomal

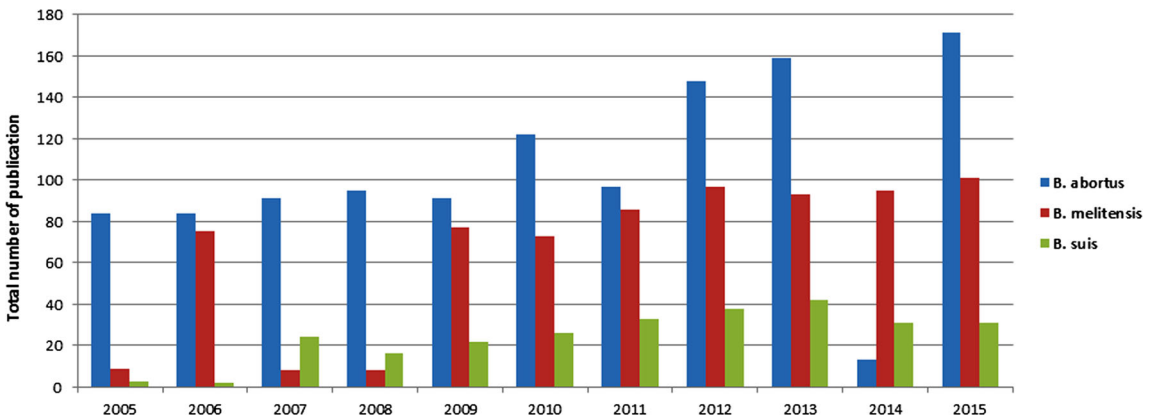


**Fig. 1** Diagram showing a comparative analysis of the number of studies published on NCBI for *B. abortus*, *B. melitensis*, and *B. suis* in the period 2005–2015

environment. It is worth mentioning that not all cell types are permissive for intracellular growth and survival of *B. abortus*. For example, the bacteria survive and multiply well in macrophages but not in neutrophils because the intracellular trafficking of pathogens in macrophages is similar to non-phagocytic cells [9, 13]. Then, the brucellae drain into the regional lymph nodes. Originating from these foci, bacteremia develops and the bacteria settle down in other lymphoid tissues, such as the spleen and peripheral lymph nodes. The bacteria also tend to localize in certain predilection sites within female and male reproductive tracts, including the uterus, testes, and udder, leading to the most common clinical signs of brucellosis, e.g., abortion and infertility. Late-term abortion, retained placenta, birth of weak calves, and neonatal mortality are the main clinical manifestations of *B. abortus* infections in cattle [8]. Infected fetuses often develop acute diffuse severe fibrinous pleuritis, pneumonia, bronchopneumonia, and fibrinous pericarditis [8].

The pathogenesis of *B. abortus* in wildlife and in domestic animals is similar, i.e., tropism for reproductive and mammary tissues and the genital tract. However, differences in the course of disease are obvious and are believed to be caused by differences in immune systems and species behavior [14]. The virulence factors in *B. abortus* may not directly cause clinical manifestations of the disease. The presence of *B. abortus* in the trophoblast of the uterus induces steroid synthesis and modulates the metabolism of prostaglandin precursors, resulting in a condition that mimics what occurs during parturition, i.e., an increase of prostaglandin F2$\alpha$, estrogen, and cortisol level accompanied by a decrease of the levels of progesterone, leading to expulsion of the fetus in a process similar to parturition in the third trimester [13]. However, we cannot ignore the fact that acute reproductive tract lesions and abortion may occur as a result of extensive replication of the bacteria in placental trophoblasts. Infection with high amounts of bacteria may lead to abortion even in the early stage of gestation, which is caused by the onset of fever and placentitis.

## *B. Abortus* in Animal Populations

*Brucella abortus* mainly infects bovines. Infection in sheep, goats, pigs, camels, and humans is less common [15]. Infection with *B. abortus* has been reported in the cattle population worldwide except in some countries of North and Central Europe, Canada, Japan, Australia, and New Zealand [16]. It infects a wide variety of domestic and wild animal species [8, 17]. This pathogen seems to have no specific host preference and can cross species barriers.

Infection is transmitted via direct contact with contaminated excreta and aborted material or indirectly through ingestion of contaminated feed or water [18]. Infected bovines act as potential sources in mixed and open herds when animals are in close contact [19, 20]. *B. abortus* can persist for longer periods in environments of high humidity, low temperature, in soil, moisture, or organic matter [21, 22]. Grazing and watering places act as common contact points and important risk factors for the horizontal transmission of infection [23, 24]. Venereal transmission is not predominant under natural conditions, but artificial insemination may play an important role if semen is contaminated [25]. The infection is usually asymptomatic in young and non-pregnant females. However, in adult and pregnant animals, it causes fever, retained placenta, orchitis, seminal vasculitis, epididymitis, arthritis, and abortion in the last trimester due to placentitis [23]. The severity of signs depends upon the species, sex, and immune system of the host animal. After the primary onset of infection, *B. abortus* can remain in a latent state for several years. Acquired immunodeficiency prompts reactivation of infection [26]. Abortion in cows mainly occurs once. Thereafter, cows can give normal birth without complications, resulting in latent carrier phenomena.

Small ruminants (sheep and goat) are not considered hosts for *B. abortus*; however, *B. abortus* bv 6 has been isolated from both species, especially in mixed herds with cattle and buffalo [27, 28]. In one study, sheep and goats were identified as more likely sources of both *B. abortus* and *B. melitensis* transmission to humans and animals other than cattle [29]. Infection in equines is seldom and has been reported in Brazil, Egypt, Iran, India, Africa, and the Middle East but rarely in Europe [30, 31]. *B. abortus* has also been isolated from asymptomatic equine vaginal swabs [19, 20]. Equines are infected via close contact with infected cattle; however, they are not considered as a primary source of infection for other animals [18]. Fistulous withers, poll evil, knee hygroma, and various joint illnesses are the most common non-specific symptoms of *B. abortus* infection in equines [31, 32].

A large number of reports have described *B. abortus* infection in both dromedaries and bactrian camels throughout the world [33, 34]. In addition to abortion and orchitis in pregnant females and males, respectively, lameness, lacrimation, arthritis, hygroma of joints, and diarrhea are common clinical manifestations [34, 35]. Dogs are susceptible to *B. abortus* infection and become infected after ingestion of fetal material, placenta, raw meat, or milk from infected animals in livestock farms or abattoirs. Infected dogs then transmit the infection to other dogs possibly via venereal contact [23, 36]. Recently, *B. abortus* bv 1 was isolated from a female cat and a bitch (in close contact with infected cattle), suggesting the susceptibility and potential role of dogs and cats in the transfer of the infection to other animals [3••]. Infection in wild animals has been reported, including water deer, goral, elk, bison, and African buffalo [17, 37]. Free-range elk in Yellowstone National Park, USA, are now considered a potential reservoir for livestock brucellosis [18].

Several treatment protocols have been evaluated in productive animals, but none of them have proven to be 100% safe.

Different combinations of long-acting oxytetracycline, streptomycin, isoniazid, and rifampicin have been found to be somewhat successful, keeping in view the economic feasibility of the animals [38–40]. Thus, testing and slaughtering of reactor animals is still considered the most cost-effective control measure when its prevalence in the herd is lower than 2% [41].

Surveillance and control programs in endemic countries are often assisted by vaccine campaigns [42]. Two vaccines against *B. abortus* infection are widely used: *B. abortus* S19 (which interferes with serodiagnosis) and *B. abortus* RB51 [43]. Both are live vaccines, and safety concerns exist for both [44]. Vaccination of animals with the *B. melitensis* vaccine does not provide protection against *B. abortus* infection. Heat-killed *B. abortus* bv 1 strain 45/20 has been evaluated with an oil adjuvant in pregnant animals but has been stopped due to variable protective responses and reports of adverse reactions at the site of injection [43, 45••]. It is worth mentioning that engineered vaccines, e.g., DNA, subunit, vectored, and recombinant mutant vaccines, have not been proven to be sufficiently protective [5, 7]. These vaccines have several drawbacks; they are multi-booster dose dependent, have high economic costs, and to date have never been practically tested in their natural hosts. Moreover, such vaccines need a large amount of antigen to mimic the protective response of natural infection [43, 45••]. Further studies are thus recommended to develop and evaluate safer and more effective vaccines.

## *B. abortus* in Humans

At present, the true burden of human brucellosis due to *B. abortus* remains unknown due to the limitation of species-specific population-based studies. The majority of human cases are mainly diagnosed using serological investigations, but serology tools are unable to discriminate between disease-causing *Brucella* species [46]. Available molecular- and bacteriological-based studies show that the majority of human brucellosis cases are attributed to *B. melitensis* [47, 48]. Most recently, *B. abortus* strains detected in humans are mainly associated with case reports or limited outbreaks. Much of these publications are from the Middle East and Asia. In the Middle East, a recent study reported *B. abortus* infection in 63.8% of patients suspected for brucellosis in Iran [49]. In Turkey, *B. abortus* bv 3 was detected in two samples out of 75 clinical specimens obtained between 2009 and 2011 [50]. A mixed *B. abortus*/*B. melitensis*-associated outbreak had been reported in Qatar [51], while *B. abortus* was found in 10% of patients with acute febrile illness in Saudi Arabia [52]. One *B. abortus* isolate was successfully isolated from a cohort of ten patients presenting with fevers of unknown origin in India [53]. A *B. abortus* associated outbreak was reported on an island of Korea and isolated from a case of septic knee arthritis [54, 55]. *B. abortus* bv 1 is the most prevalent biovar isolated from humans in Korea [56]. Two studies describe *B. abortus* as the only causative agent among high-risk occupational groups in Pakistan and Bangladesh [57, 58]. Recent data reporting on *B. abortus* infection in humans in other regions is limited. In Sudan, *B. abortus* S19 vaccine was detected in a milker, demonstrating the potential for this vaccine strain to be transmitted to humans [59]. Within Latin America, *B. abortus* accounted for 20.4% ($n = 75$) of all *Brucella* isolates obtained between 1994 and 2006 from human cases in Argentina. The majority of strains were identified as *B. abortus* bv 1, although *B. abortus* bv 2 and the S19 vaccine were identified in five cases [60]. Evidence of *B. abortus* infection in humans is rare in Europe and the USA, except in returning travelers from endemic regions and recently arriving immigrants [61].

The disease can be transmitted to humans either by direct contact with infected animals and animal excreta or through the ingestion of unpasteurized milk and milk products, contaminated food, and water containing large quantities of brucellae [62]. Direct person-to-person transmission is still considered to be rare. However, sexual and breast milk transmission has been reported for *B. melitensis* [63–65]. Although these routes of transmission have not been documented for *B. abortus*, such circumstantial transmission cannot be ruled out. No distinct clinical differences exist between brucellosis caused by different *Brucella* species. However, some studies have reported that *B. abortus* is often associated with less severe presentation compared with infections caused by *B. melitensis* and *B. suis* bv 1, 3, and 4. Limited evidence suggests that infection with *B. abortus* is frequently subacute and prolonged [66, 67]. More recent publications have reported unusual clinical presentations and complications due to *B. abortus*. For instance, *B. abortus* bv 1 was associated with prepatellar bursitis and septic knee arthritis [54, 68]. There is a need for multi-center case control studies to investigate the potential for emerging unusual clinical complications due to *B. abortus*.

The WHO-recommended regimen for the treatment of acute brucellosis in adults is a combination of rifampin 600 to 900 mg and doxycycline 100 mg twice daily for a minimum of 6 weeks. Rifampin could also be replaced with streptomycin, administered intramuscularly for 14 days [69]. However, disease relapse still represents one of the most important therapeutic problems. Some authors have proposed a triple treatment regimen (doxycycline-aminoglycoside-rifampicin), with aminoglycoside administered for the first 7–14 days and doxycycline-rifampicin continued for 6 to 8 weeks. Although the few triple combination therapy trials conducted so far were found to be significantly more effective than most of the effective dual regimens [69, 70], further clinical trials are still needed to establish the superiority and safety of the

triple drug regimens. Currently, there is no licensed vaccine for *B. abortus* in humans, and available animal vaccines are considered unsuitable for use in humans due to concerns about their safety [47]. Using modern recombinant DNA and protein techniques, a series of new candidate vaccine variants has been engineered and evaluated. However, the majority have failed to clearly demonstrate adequate protective efficacy in animal models and clinical trials [47, 71]. Nevertheless, these approaches have been successful for other antigens and may prove successful in future studies. Therefore, prevention and control will continue to rely on early and accurate diagnosis, best therapeutic regimens, and effective control of the disease in farm animals.

## Updated Knowledge for *B. abortus* Diagnosis

Diagnosis of *B. abortus* remains challenging and is still based mainly on serology and isolation [1]. Serological tests basically rely on the detection of anti-*Brucella* lipopolysaccharide (LPS) antibodies. It is worth mentioning that the antigen used in most of the available serological tests is *B. abortus* S-LPS, which has limited specificity due to cross-reactions resulting from similarity between immunodominant epitopes of *Brucella* O-polysaccharide and those of other Gram-negative bacteria, e.g., *Yersinia enterocolitica*, *Salmonella* spp., and *Escherichia coli* O:157 [72]. Moreover, all available serological assays are not able to discriminate between different *Brucella* spp. or biovars, nor are they able to differentiate infected and vaccinated animals. Recent use of test regimen combining c-enzyme linked immunosorbent assay (ELISA) and rose bengal plate test (RBPT) for the diagnosis of brucellosis showed relatively high sensitivity and specificity and was able to reduce the number of false positives [73–75]. An ELISA based on recombinant *B. abortus* outer membrane proteins (r*Omps*) and individual r*Omps* had high sensitivity and specificity and differentiated infection from vaccination [76•]. A perfect antigen having 100% sensitivity and specificity has not been discovered, and a vaccine that does not interfere with serodiagnosis has not been developed [77, 78]. Purified *B. abortus*-specific proteins, e.g., malate dehydrogenase protein (rMDH) [79], bacterioferritin (rBfr) [80••] metal-dependent hydrolase (r0628), and thiamine transporter substrate-binding protein (rTbpA) [81] have been discussed as potential candidates but lack validation.

Isolation and identification of a causative agent is still considered the gold standard but has many drawbacks. Some *B. abortus* strains grow slowly and require enriched media. Additionally, *Brucella* culturing is hazardous and requires specially trained personnel. In field samples, the results are also ambiguous and the isolation rate is reported to be between only 20 and 25%, even in experienced laboratories, due to massive contamination and a low number of bacteria in samples [77]. Recently, a new medium has been developed based on the modified Thayer-Martin medium in which different concentrations of antimicrobials and amphotericin B were added. This modified medium inhibited contaminants without inhibiting the growth of *Brucella* spp. but lacks validation [82]. Classical and routine identification of *Brucella* that is mainly based on phenotyping characteristics, i.e., $CO_2$ requirement, $H_2S$ production, urea hydrolysis, dye sensitivity, agglutination with monospecific antisera, and phage lysis [1], is unable to be traced back to the origin of *Brucella* [83]. Precise strain identification of bacteria at the subspecies level has become a necessity to design effective control programs for bacterial pathogens [84]. Recently, the multiple locus variable-number tandem repeat analysis (MLVA) typing assay has been discussed as a good tool for *Brucella* species identification and has a higher discriminatory power between the *Brucella* isolates originating from restricted geographic areas, confirming its potential as an epidemiological tool [85]. Matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) has been used as a method for the direct identification of *B. abortus* isolates and is based on peptide spectra obtained by mass spectrometry. This technique is able to differentiate *Brucella* spp. but not biovars. A combination of MALDI-TOF diagnosis and genomic typing may replace classical techniques in the future.

Different PCR protocols, either conventional or real-time PCR, have been developed for the detection and accurate differentiation of certain biovars of *B. abortus* field and vaccine strains [86–88]. A multiplex *Bruce*-ladder PCR assay has been developed to differentiate *B. abortus* bv 1, 2, 4 from bv 3, 5, 6, 9, and vaccine strains [86, 89]. However, the DNA extraction protocol, type of clinical sample, and detection limits of each protocol are factors that can influence the efficiency of this technique [90, 91]. Real-time PCR using hybridization probes (hybprobe) designed from a specific single-nucleotide polymorphism (SNP) of the *fba*A has been recommended for diagnosis of *B. abortus* [92•] but lacks validation. A loop-mediated isothermal amplification (LAMP) assay used for rapid, sensitive, and specific identification of *B. abortus* has also been described [93] but lacks validation. Different molecular biological techniques can be used for typing of *B. abortus* isolates and serve as tools for diagnostic, epidemiological, taxonomic, and evolutionary diagnostic studies, such as PCR-restriction fragment length polymorphism (RFLP) assays of specific gene loci of various outer membrane proteins (*Omp*) [94], SNPs [95], tandem repeat-based typing (VNTR), and MLVA [96, 97]. A new qPCR assay for the *Omp* was used to differentiate virulent *B. abortus* strains and *B. abortus* S19 vaccine strains in bovine raw milk [98].

New diagnostic approaches have been discussed for an accurate and rapid detection of bovine brucellosis. The Nano sensing technique allows for the precise detection of anti-*B. abortus* antibodies (IgG) in 50-μl milk samples via capture by fluorescent silica nanosensors [99]. The Luminex xMAP

technology allows simultaneous, rapid, and specific detection of anti-*Brucella* spp., anti-*Bacillus anthracis*, anti-*Francisella tularensis*, and anti-*Yersinia pestis* antibodies within a single sample [100]. Investigation of the immune response at the peptide level rather than the protein level may be the way forward. ELISAs containing non-LPS antigen may be more effective diagnostic tools and may also be used as tools for differentiating vaccinated and naturally infected animals [101]. Synthetic oligosaccharide antigens were used to develop individual indirect enzyme-linked immunosorbent assays (iELISAs) that had excellent diagnostic capabilities [102]. Lateral flow assay (LFA) as field tests accurately detected antibodies against *B. abortus* in buffalo serum [103]. Nanoparticle time resolve fluorescence (NTRF) and use of up-converting phosphor technology can also be used for lateral flow (LF) immunoassay formats to increase analytical sensitivity [104, 105]. None of those tools are validated yet.

## Recent Advances in Genomics and Proteomics of *B. abortus*

Whole genomic sequencing (WGS) and complete proteomic analysis are the major current tools applied for understanding microbial physiology, gene expression, and interactions between microbes and host cells [106, 107]. A comprehensive understanding of the intricate relationship between *B. abortus* and the host cell will improve the development of new treatments, diagnostic tools, and vaccines. Recently, *B. abortus* genomics and proteomics were extensively investigated. The genomics data for all *Brucella* spp. are highly similar [108]. However, they evoke different immune responses in natural hosts and display different protein expression profiles [10•, 109, 110••].

Rapid and large-scale identification of proteins by utilizing current proteomic techniques, such as two-dimensional electrophoresis (2DE) and MALDI-TOF, will help us understand many interesting aspects of *Brucella* biology. Beyond these techniques, proteomic studies may be helpful in the development of potent *Brucella* vaccines. The identification of specific immunogenic proteins from *B. abortus* has been the focus of scientists in the last decade. These proteins will replace LPS antigens used in serology to increase specificity. Most studies of the *B. abortus* proteome mainly focused on the use of reference strains, e.g., *B. abortus* 1119-3 [72] and *B. abortus* 2308 [111–113], and on experimentally produced hyperimmune serum. Use of fully virulent *B. abortus* field strains in proteomic studies is rare [10•, 110••]. Protein expression profiles can differentiate stages of infection, hosts, and *Brucella* species. Consequently, proteomic analysis of *B. abortus* biovars is needed to match the real picture of infection. Proteomic analysis of the culture supernatant of *B. abortus* 544 revealed 27 proteins that may help to understand the mechanism of *B. abortus* infection [114]. The classical serological diagnosis of brucellosis is unable to detect the stage of infection, i.e., acute vs. chronic. By contrast, proteomic analysis can monitor the time course of the immune responses [115]. This information will aid the appropriate management of this disease. Even though several *B. abortus* immunoreactive proteins were previously reported, to date, a perfect antigen having 100% sensitivity and specificity has not been discovered, and an effective and safe subunit recombinant vaccine that does not interfere with serodiagnosis has not been developed [77, 78]. Thus, the study of immunoreactive soluble proteins of *B. abortus* to develop a species-specific protein antigen devoid of non-specific moieties is currently the focus of much effort.

Meanwhile, the WGS technology for *B. abortus* became available in the last decade [116, 117•]. It can provide deep insights into the process of attenuation and tracing genomic differences among the field of *Brucella* isolates [118]. The WGS of *B. abortus* isolates from livestock was used to identify the current genetic diversity between isolates in a certain geographical area [119]. Comparative genomic analysis of *B. abortus* vaccine isolates was also used to identify a set of candidate genes associated with virulence [117•]. Recently, WGS was used to investigate evolution and cross-species transmission that occurred in *B. abortus* at the wildlife/livestock interface within the same endemic area in the USA. Moreover, it provides beneficial information about spatial diffusion and host movement [18].

## Concluding Remarks

*B. abortus* is of public health and veterinary public health significance because infection is not restricted to specific hosts, and the bacteria can circulate in various wild and domesticated host species cycles. Short-term treatment regimens considered to be patient-friendly do not exist. Furthermore, safe and effective human vaccine candidates are not available and animal vaccines are infectious to humans. The intracellular lifestyle of the bacteria and their strong tissue tropism for the lymphoreticular system reduces the effectiveness of antibiotics and facilitates escape from the host's innate and adaptive immunity. Testing and slaughtering of seropositive animals are still the best choices for its effective control in farm animals. Differential diagnostic tools for biovars, vaccines and field strains, and for rough and smooth *B. abortus* are nonexistent. NGS will replace classical typing methods in developed countries. Complete genomic sequencing and comparative proteomic analysis will help us understand the nature of the bacterium and could be helpful in developing suitable antigens for serodiagnosis and vaccines against *B. abortus* in the future.

**Compliance with Ethical Standards**

**Conflicts of Interest** The authors declare that they have no conflicts of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance


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