

Brucellosis: Current Advances in Epidemiology, Molecular Pathogenesis, Diagnosis, and Vaccine Development

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Abstract

Review Article

As one of the most prevalent bacterial zoonotic diseases, brucellosis has caused public health and veterinary challenges, especially in developing countries. Such challenges arise in regions with active livestock farming and the consumption of unpasteurized dairy products. Diagnosing brucellosis is complicated because the causative bacteria of the disease are Gram-negative, facultative intracellular bacteria of the genus *Brucella*. Among the species, *Brucella melitensis*, *Brucella abortus*, *Brucella suis*, and *Brucella canis* are the most common in human infections. There are many innovations in the control of brucellosis and its surveillance systems; however, it still has a chronic socio-economic impact. This review gives a comprehensive account of brucellosis to date, encompassing its epidemiology, taxonomy, modes of transmission, molecular pathogenesis and virulence, host immune response, clinical features, diagnosis, and advances in genomics and vaccine development. Because *Brucella* is adept at surviving and thriving within host cells, this review focuses on its immune evasion tactics and its ability to alter host signaling pathways. It also incorporates recent advances in diagnostics and brucellosis vaccines, especially for human and veterinary use. Currently, live-attenuated vaccines remain the primary method for controlling livestock brucellosis; however, safety and diagnostic concerns are leading researchers to seek new platforms. Combined with improved diagnostics and vaccination programs, incorporating a One Health approach is vital for controlling brucellosis, and continued multidisciplinary studies are necessary for innovative methods of controlling this endemic zoonosis.

Keywords: Brucellosis, Zoonotic disease, Diagnosis, *Brucella* spp., *Brucella melitensis*, Pathogenesis, Virulence factors, Intracellular pathogens, Immune response.

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INTRODUCTION

One of the largest bacterial zoonotic diseases, brucellosis, is a leading global public health concern and an endemic disease in livestock that especially affects the economies of developing countries that rely on livestock. The disease originates from the Gram-negative, facultative intracellular bacteria of the genus *Brucella*. These bacteria infect both domestic and wild animals and can infect humans through direct contact with infected animals. *Brucella* also contaminates animal products, especially milk and dairy products which are not pasteurized [1,2]. After zealous attempts to reduce brucellosis in some industrialized countries, the disease still remains endemic in the Middle East, the Mediterranean basin, and parts of Africa, Asia, South and Central America due to poor biosecurity practices, unguided disease monitoring, and lack of public awareness [2–4]. Of all *Brucella* species, *Brucella melitensis* is the most pathogenic and the species most commonly isolated from humans. The other commonly

isolated species are *Brucella abortus*, *Brucella suis*, and, rarely, *Brucella canis* [1,5]. These bacteria are extremely flexible and resilient to the host immune response, thus facilitating the establishment of chronic infections [6,7]. The intracellular nature also facilitates the persistence and relapsing nature of brucellosis, even when antimicrobial intervention is instituted.

Human brucellosis spans relatively mild presentations to chronic multi-system disease, potentially involving the central nervous system [CNS], the musculoskeletal system, the hepatobiliary system, the genitourinary system, and the cardiovascular system, among others. Because the symptoms of brucellosis overlap with inflammatory and infectious conditions, clinical diagnosis is particularly difficult [3,8]. The lack of distinctive symptoms during the disease also lengthens the time to diagnosis and increases the risk of developing chronic and irreversible disability.

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Brucella presents a challenge to host immune systems through its intracellular survivability and immune-evading mechanisms. This genus of bacteria is unique in that it lacks many of the 'typical' virulence factors, including exotoxins, capsules, and fimbriae. Instead, *Brucella* relies on smooth lipopolysaccharides, outer membrane proteins, cyclic β -glucans, the BvrR/BvrS two-component regulatory system, and the VirB Type IV secretion system [T4SS]. These components work together to facilitate cellular invasion, replication and persistence, immune evasion, and inhibition of phagosome-lysosome fusion. Advances in molecular biology have broadened the understanding of the disease-causing and persistence mechanisms of *Brucella*, which perturbs the host immune system to escape immune clearance. The immune clearance mechanism involves cell-mediated immunity of the Th1-type response, which activates macrophages via IFN- γ and TNF- α . Even with an active immune response, *Brucella* persists by evading clearance mechanisms and reducing inflammation, thereby establishing chronic infections.

Even though bacterial isolation is still considered the gold standard for diagnosis, it is an inadequate method because of time constraints, biosafety restrictions for BSL-3 laboratories, and reduced sensitivity in chronic conditions [5]. Consequently, serological methods such as the Rose Bengal Test [RBT], serum agglutination tests [SAT], enzyme-linked immunosorbent assay [ELISA], and molecular methods such as polymerase chain reaction [PCR] have been relied upon for expedient diagnosis and epidemiological studies [5,14]. In addition, whole genome sequencing and flexible methods of multilocus sequence typing and comparative genomics have aided the study of *Brucella*, contributing to a better understanding of its evolution, host adaptation, transmission, and diversity, with applications in outbreak studies and molecular surveillance [15,16]. Containment of brucellosis remains a significant challenge because no licensed human vaccine is available, and the currently used live-attenuated animal vaccines offer restricted safety, leave residual virulence, and interfere with serological diagnosis [17]. Safer and more effective candidates have been proposed using reverse vaccinology, bacterial-ghost vaccinology, and vector-based and DNA vaccines that can elicit humoral and cell-mediated immune responses [17,18]. This review aims to summarize the advancements made in these areas and to provide an integrated One Health perspective on brucellosis and its current state of control and prevention, with emphasis on new research areas for more effective diagnosis and control of the disease.

TAXONOMY AND MICROBIOLOGY OF BRUCELLA

The genus *Brucella* consists of the causative agents of brucellosis, which are Gram-negative, coccobacilli, and facultative intracellular bacteria

affecting humans and many animals. *Brucella* is classified under the family Brucellaceae, the order Hyphomicrobiales [formerly Rhizobiales], the class Alphaproteobacteria, and the phylum Pseudomonadota [formerly Proteobacteria] [19,20]. *Brucella* is closely related to environmental bacteria including *Ochrobactrum* and *Mycoplana*. Comparative genomic and taxonomic studies on *Brucella* have identified high conservation across genomes, although there is greater ecological and host diversity than previously known [19,21]. Traditionally, classification of *Brucella* species was based on host preference, pathogenicity, biochemistry, and phenotypic traits, with six classical species: *B. melitensis*, *B. abortus*, *B. suis*, *B. canis*, *B. ovis*, and *B. neotomae*. The development of whole genome sequencing, multi-locus sequencing, and average nucleotide identity [ANI] analysis has since revealed additional *Brucella* species from marine mammals, amphibians, rodents, non-human primates, and environmental sources [20–22]. Nevertheless, for veterinary and clinical purposes, separate species designations remain justified for concerns of host specificity and virulence, despite considerable genetic similarity among species [20,23]. Among identified *Brucella* species, *B. melitensis* is the most pathogenic and causes the majority of human infections where sheep and goats are the main host.

Brucella abortus infects mainly cattle and causes a milder disease in humans, while *B. suis* mainly infects pigs and is known to cause severe systemic infections in humans. *Brucella canis* infects dogs and is a potential emerging zoonosis, while *B. ovis* is mainly a parasite of sheep and is infrequently pathogenic to humans. More recently described species, including *B. ceti*, *B. pinnipedialis*, *B. microti*, *B. inopinata*, and other atypical *Brucella* species, have further expanded the ecological diversity of this genus [20–22]. *Brucella* are small [0.5–0.7 $\mu\text{m} \times 0.6$ –1.5 μm], non-motile, non-spore-forming, non-encapsulated coccobacilli. They are strictly aerobic, and catalase-, oxidase-, and urease-positive, with a slow growth rate. On enriched media, colonies [after 48–72 hours] are smooth, translucent, and convex, though some species [e.g., *B. ovis*, *B. canis*] may yield rough colonies [19,24]. The unique facultative intracellular lifestyle of *Brucella* contributes to its resistance to conventional therapy. In the infected host, *Brucella* primarily targets macrophages, dendritic cells, and other phagocytic cells, where it persists within specialized intracellular compartments termed Brucella-containing vacuoles.

This ability to adapt to the intracellular environment underlies the chronic nature of brucellosis and complicates therapeutic resolution, often leading to relapses [19,25]. *Brucella* species have a relatively small genome of approximately 3.2–3.4 Mb, comprising two circular chromosomes with about 57% GC content, and classical pathogenic *Brucella* species share over 95% nucleotide identity. Variations in insertion sequence

elements, genomic islands, and pseudogenes have been reported to influence pathogenicity, host-range specificity, and environmental adaptation [21,26]. Recent studies differentiating highly specialized intracellular classical species from environmental atypical species have broadened our understanding of the genus [21,22]. *Brucella* species lack many conventional virulence factors, such as exotoxins, capsules, and classical fimbriae, possessed by many other facultative and obligate intracellular pathogens; instead, they rely on notable factors such as low-endotoxicity smooth lipopolysaccharides, outer membrane proteins, and the VirB T4SS [25]. Continued development of comparative genomics, molecular phylogenetics, and microbial taxonomy is expected to further elucidate genus taxonomy, host adaptation, transmission, and pathogenicity, ultimately improving brucellosis surveillance, diagnostics, vaccine development, and global control strategies [21–26].

EPIDEMIOLOGY AND GLOBAL DISTRIBUTION

Brucellosis is the most prevalent zoonotic bacterial infection and constitutes a serious public health and economic challenge in low- and middle-income countries with rural communities dependent on livestock. Considerable efforts to mitigate the disease in industrialized countries through vaccination, surveillance, and pasteurization have succeeded in many regions, but brucellosis remains endemic in the Mediterranean Basin, the Middle East, Central and South Asia, Africa, and Latin America [27–29]. Underestimation due to poorly developed surveillance and reporting means the true global burden is uncertain; estimates of human brucellosis incidence range from 1.6 to 2.1 million infections per year, substantially higher than earlier estimates of around 500,000 cases [28,30]. The vast majority of infected persons are farmers, veterinarians, slaughterhouse and laboratory personnel, and others with direct contact with infected livestock or who consume unpasteurized milk and dairy products [27,31]. The distribution and severity of brucellosis are shaped by livestock population and movement, veterinary and socioeconomic infrastructure, and food-safety and public-health policy.

In many regions, the convergence of political instability, mass population movement, and poor veterinary infrastructure correlates with higher disease prevalence and recurring outbreaks of animal and zoonotic diseases [29,31]. Brucellosis remains endemic in the Middle East, including Iraq, reflecting variable livestock vaccination, diagnostic capacity, and management practices. Rural populations are affected more than urban populations because of greater contact with livestock and consumption of raw milk [29,32]. Recent epidemiological studies show that re-emergence of the disease in previously controlled areas is largely driven by globalization, international travel, changing livestock trade patterns, and climate-related ecological changes [30,31]. Given the widespread morbidity and

mortality caused by this neglected zoonotic disease, there is an urgent need for integrated, system-wide surveillance and collaborative One Health strategies that address animal, human, and ecosystem health simultaneously [30,32].

TRANSMISSION AND RISK FACTORS

Brucellosis is transmitted to humans from infected animals through multiple routes of exposure. The most frequent route is consumption of raw or unpasteurized dairy products, with *Brucella melitensis* most commonly associated with human infection worldwide [33,34]. Infection can also result from direct handling of infected animals or their blood, tissue, placenta, fetuses, and reproductive secretions — a route of particular risk to veterinarians, farmers, livestock workers, and slaughterhouse and laboratory personnel [35,36]. Inhalation of aerosolized *Brucella* is a significant transmission route and the most frequent cause of laboratory-acquired brucellosis, underscoring the need for strict biosafety procedures when handling specimens [34,37]. Human-to-human transmission is uncommon but has been documented via vertical transmission, breastfeeding, sexual contact, blood transfusion, and organ transplantation [33,35]. High incidence is particularly associated with occupational exposure to livestock, low vaccination coverage, and consumption of unpasteurized dairy, and the disease is especially endemic in rural regions of low socioeconomic status and areas with unregulated cross-border livestock trade. A comprehensive One Health approach — incorporating livestock vaccination, food safety, protective measures, public education, and workplace and surveillance procedures — remains the most effective strategy for reducing the global burden of brucellosis [36,37].

PATHOGENESIS AND HOST–PATHOGEN INTERACTION

Various *Brucella* spp. share a similar pathogenesis, involving evasion of innate and adaptive immunity through persistence and replication within host cells. Infection usually begins at mucosal surfaces, and *Brucella* can also enter via the respiratory, gastrointestinal, conjunctival, or damaged skin routes. Once inside the host, *Brucella* is readily engulfed by phagocytes [38,39] but is able to survive and multiply within macrophages, a property that distinguishes it from most bacterial pathogens. It survives within phagocytes by evading phagosome–lysosome fusion and by directing formation of a *Brucella*-containing vacuole [39,40], which it then associates with the endoplasmic reticulum, the organelle in which it replicates most efficiently. *Brucella* also controls the inflammatory response to aid immune evasion; its smooth lipopolysaccharide surface, together with the VirB T4SS, cyclic β -1,2-glucans, and the BvrR/BvrS system, assists in establishing persistent infection [40–42]. Within reticuloendothelial organs [38,41], *Brucella* establishes chronic infection and disseminates through the body by limiting bactericidal mechanisms and inflammatory

responses. This complex host–pathogen interaction underlies the persistence of brucellosis and informs the development of new therapeutic, vaccine, and immunomodulatory strategies [39–42].

VIRULENCE FACTORS

Brucella species rely on specialized virulence factors to establish intracellular persistence and immune evasion rather than conventional bacterial toxins. Compared with other Gram-negative pathogens, *Brucella* lacks exotoxins, capsules, pili, and strong endotoxins, and instead uses uniquely evolved molecular mechanisms for colonization and replication within the host [43,44]. Its smooth lipopolysaccharide [LPS] has a lipid A component that lacks strong endotoxicity; this unusual LPS diminishes Toll-like receptor 4 activation, reduces pro-inflammatory cytokine production, and increases resistance to complement-mediated killing and antimicrobial peptides [44,45]. Another key virulence factor is the VirB Type IV secretion system [T4SS], encoded by the virB operon, which allows *Brucella* to translocate effector proteins into host cells, alter intracellular trafficking, delay phagosome–lysosome fusion, and generate the endoplasmic-reticulum-derived Brucella-containing vacuole required for replication [43,46]. Outer membrane proteins Omp25 and Omp31 facilitate bacterial adhesion, regulate membrane integrity, and modulate the host immune response, aiding intracellular persistence. The BvrR/BvrS two-component regulatory system controls gene expression related to the cell envelope, virulence, and metabolism [45–47]. Additional factors — cyclic β -1,2-glucans, urease, superoxide dismutase, catalase, and iron-uptake-related proteins — further support bacterial virulence and intracellular survival [46,47]. Together, these factors enable *Brucella* to cause chronic infection, evade antimicrobial therapy, and disseminate to multiple organs, making them attractive targets for next-generation vaccines [43–47].

HOST IMMUNE RESPONSE

The host immune response to *Brucella* combines innate and adaptive immunity, determining whether the pathogen is eliminated or establishes chronic, persistent infection. Following infection, *Brucella* is recognized by pattern recognition receptors [PRRs], including Toll-like receptors TLR2, TLR4, and TLR9 on macrophages, dendritic cells, and neutrophils, triggering pro-inflammatory cytokine and chemokine production that recruits immune cells to the infection site [48,49]. However, *Brucella*'s atypical, low-endotoxicity LPS enables it to evade efficient innate recognition and attenuate inflammatory responses during early infection [49,50]. Natural killer [NK] cells and activated macrophages contribute to initial containment through production of interferon-gamma [IFN- γ], tumor necrosis factor-alpha [TNF- α], reactive oxygen species [ROS], and nitric oxide [NO], which enhance intracellular bactericidal activity [48,51].

Adaptive immunity, particularly cell-mediated immunity, is essential for long-term protection. Protective immunity is predominantly driven by T helper 1 [Th1] lymphocytes secreting IFN- γ and interleukin-2 [IL-2], which promote macrophage activation and intracellular killing of *Brucella*, while cytotoxic CD8+ T cells eliminate infected cells and dendritic cells facilitate antigen presentation [50–52]. B cells produce antibodies against *Brucella* antigens, but humoral immunity alone is insufficient to eliminate intracellular bacteria; it nonetheless helps limit pathogen spread and supports serological diagnosis [49,52]. Chronic disease and persistence can result from excessive production of the anti-inflammatory cytokine IL-10, which suppresses the Th1 response and reduces macrophage activation [51,52]. *Brucella* exploits cytokine manipulation, control of apoptosis, inhibition of antigen presentation, and regulation of dendritic cell maturation to maintain long-term intracellular survival despite an active immune response. Understanding these interactions is central to developing effective vaccines and immunotherapeutic strategies that stimulate protective cellular immunity [48–52].

CLINICAL MANIFESTATIONS

Brucellosis presents with considerable variability across affected systems, which poses diagnostic challenges, especially in endemic areas. The incubation period is notoriously inconsistent, ranging from one to four weeks in most cases to several months in others, particularly with prolonged or direct exposure or in immunocompromised patients [53,54]. The acute form most commonly presents with intermittent or continuous fever and profuse nocturnal diaphoresis, typically accompanied by fatigue, anorexia, significant weight loss, headache, and generalized myalgia and arthralgia.

Constitutional symptoms are often accompanied by hepatomegaly, splenomegaly, and lymphadenopathy, reflecting the organism's preference for the reticuloendothelial system [54,55]. Chronic, unremitting fatigue, recurrent fever, musculoskeletal symptoms, and other organ involvement may develop after prolonged, untreated infection, affecting quality of life [53,56]. Osteoarticular complications are the most common focal manifestation, affecting up to 40% of patients, including sacroiliitis, spondylitis, peripheral arthritis, osteomyelitis, and bursitis [54,57]. Genitourinary manifestations include epididymo-orchitis, prostatitis, and pyelonephritis, while neurobrucellosis encompasses meningitis, meningoencephalitis, radiculopathy, and peripheral neuropathy [55,56]. Cardiovascular involvement, although rare, remains the leading cause of brucellosis-related mortality, chiefly through infective endocarditis [53,57]. The pathogen can also disseminate to the respiratory, gastrointestinal, hepatobiliary, and dermatological systems [54–57], and bone marrow and hypersplenism contribute to hematological abnormalities

including anemia, leukopenia, thrombocytopenia, and pancytopenia [55]. Because the clinical presentation resembles many other infectious and inflammatory disorders, early detection supported by laboratory confirmation is essential to initiate antimicrobial treatment and prevent complications [53–57].

LABORATORY DIAGNOSIS

Brucellosis is notoriously difficult to diagnose clinically because of its nonspecific symptoms, making laboratory diagnosis critical to disease management and control. Diagnosis of human brucellosis involves clinical history, epidemiological data, microbiological culture, serological tests, and molecular techniques [58,59]. Isolation of *Brucella* spp. from blood, bone marrow, cerebrospinal fluid, or other clinical specimens remains the gold standard for definitive diagnosis, as it identifies the specific infecting organism. However, culture is hampered by the slow growth of *Brucella* spp., low detection rates in chronic cases, and a high risk of laboratory-acquired infection, requiring Biosafety Level 3 [BSL-3] facilities [58,60]. For these reasons, serological tests are the most widely used diagnostic approach in brucellosis-endemic areas.

The Rose Bengal Test [RBT] is a rapid, sensitive screening assay in routine use, while the Standard Agglutination Test [SAT], Coombs anti-*Brucella* test, Complement Fixation Test [CFT], and enzyme-linked immunosorbent assay [ELISA] are used for confirmation and to differentiate acute from chronic disease via IgM/IgG detection [59–61]. Molecular techniques, particularly PCR and its variants, have surpassed earlier methods by enabling rapid, sensitive, and specific detection of *Brucella* DNA from clinical samples, including in relapse cases and before seroconversion [60,62]. Further advances such as Multilocus Sequence Typing [MLST], whole genome sequencing [WGS], and MALDI-TOF MS provide improved species characterization along with richer molecular epidemiology, outbreak tracking, and antimicrobial-resistance surveillance [61,62]. The combination of traditional microbiology with modern molecular techniques represents the most reliable approach for detecting and controlling brucellosis.

MOLECULAR BIOLOGY AND GENOMICS

The genus *Brucella* has a small genome of about 3.2–3.4 Mb comprising two circular, GC-rich [~57%] chromosomes, with approximately 95% genome identity among classical species that differ by geography and host [63,64]. Whole genome sequencing has revealed that virulence is governed less by large genomic rearrangements than by small SNPs, non-expressed genes, insertion sequences, and horizontally transferred elements [64,65]. Genes implicated in intracellular survival and replication, immune-response regulation, and chronic infection include the *virB* operon [encoding the T4SS], lipopolysaccharide biosynthetic genes, and genes such as *omp25*, *omp31*, *btPA*, *btPB*, and *vceC* [65–

67]. High-throughput sequencing, MLST, MLVA [Multi-Locus Variable-number Tandem Repeat Analysis], and phylogenomic analysis have enhanced understanding of the phylogenetic relationships between classical and newly defined *Brucella* species and improved outbreak investigation and species delineation [63,66]. The integration of these '-omics' technologies with molecular epidemiology is expected to deepen insight into host–pathogen interactions and support tailored approaches to diagnosis, monitoring, and management of *Brucella* infections.

VACCINES AND RECENT ADVANCES

Vaccination remains the most effective strategy for controlling brucellosis in livestock and reducing zoonotic transmission to humans. Despite decades of research, no licensed vaccine is currently available for human use, primarily because of concerns about safety, residual virulence, and insufficient long-term protective immunity [68,69]. In animals, the live-attenuated vaccines *Brucella melitensis* Rev.1, *Brucella abortus* S19, and RB51 have been widely used in national eradication programs and have significantly reduced disease prevalence in many countries. Nevertheless, these vaccines have important limitations, including the potential to induce abortion in pregnant animals, interference with serological diagnostic tests, incomplete protection, and the risk of accidental infection during handling [69,70].

Considerable research has therefore focused on safer, more effective next-generation vaccines. Advances in molecular biology, genomics, and immunology have accelerated development of recombinant subunit vaccines, DNA vaccines, vector-based vaccines, outer membrane protein [OMP]-based formulations, bacterial ghost vaccines, and nanoparticle delivery systems [70–72]. Candidate antigens such as *Omp25*, *Omp31*, *BP26*, the *L7/L12* ribosomal protein, *Cu/Zn* superoxide dismutase [SOD], and *VirB T4SS* components have shown promising immunogenicity in experimental animal models, inducing strong Th1-mediated cellular responses characterized by increased IFN- γ production and cytotoxic T-lymphocyte activation [71,72]. Reverse vaccinology, comparative genomics, immunoinformatics, and AI-assisted antigen prediction have further facilitated identification of novel candidates capable of providing broader, more durable protection against multiple *Brucella* species [72,73]. Nanotechnology-based delivery systems and new adjuvants have improved vaccine platforms by enhancing targeted delivery, controlled immune activation, and antigen stability while reducing side effects. Although many candidates show promise in preclinical studies, further safety, long-term-effect, and cross-immunity investigations are required before human testing. Continued integration of genomic technologies, structural vaccinology, and One Health strategies is expected to accelerate development of safe,

effective vaccines that contribute to the global control and eventual elimination of brucellosis [68–73].

FUTURE PERSPECTIVES

The World Health Organization has designated *Brucella* a top-priority pathogen given its ongoing impact on public health and the economy. Future work should focus on rapid, field-deployable diagnostics sensitive enough to differentiate past exposure from current infection while also identifying *Brucella* species and antimicrobial resistance [74,75]. Integration of artificial intelligence, machine learning, and new sequencing technologies is expected to advance diagnostics and epidemiology through real-time monitoring and investigation, while progress in transcriptomics, proteomics, and metabolomics will support immune-response research and inform new therapies and vaccines [75,76]. With no licensed human vaccine currently available, development of recombinant-protein and mRNA vaccines capable of eliciting long-lasting immune responses remains a priority [76,77]. Rising antimicrobial resistance will also require new therapeutic approaches, including host-directed strategies, antimicrobial peptides, advanced bacteriophage therapies, and novel immune-modulation methods [74,77]. Continued multidisciplinary research integrating genomics, systems biology, immunology, and precision medicine will be essential for enhancing the prevention, diagnosis, treatment, and global control of brucellosis in both humans and animals [74–77].

CONCLUSION

Brucellosis is an important global zoonotic disease that threatens both public health and the livestock industry in endemic areas. This review has provided an overview of *Brucella* infections, including their epidemiology, microbiology, transmission, pathology, and virulence, along with host immune response, clinical presentation, and advances in diagnostics, genomics, and vaccinology. The ability of *Brucella* species to evade the host immune response and survive within host cells remains the main impediment to diagnosis, treatment, and control. Advances in molecular biology have illuminated the evolution and virulence of these bacteria and the precise mechanisms underlying chronic infection and disease progression, paralleling improvements in molecular epidemiology from PCR to whole genome sequencing, multilocus sequence typing, and other genomic technologies. Although effective livestock vaccines have had a significant impact on brucellosis control, the absence of a licensed human vaccine and the need for progressive veterinary vaccine policy remain important gaps. A combination of advanced laboratory diagnostics, innovative molecular epidemiology, active vaccination campaigns, and improved One Health policy spanning human and veterinary medicine is essential to control brucellosis. Further elucidating the molecular biology, immunology, and genomics of *Brucella* will deepen understanding of the pathogen and facilitate the

development of more effective and safer next-generation vaccines, diagnostic tools, and therapeutics to address the global problem of brucellosis.

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