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BRUCELLOSIS AS A GLOBAL ZOONOTIC DISEASE: MODERN EPIDEMIOLOGY, PATHOGENESIS, CLINICAL MANIFESTATIONS, AND ADVANCES IN DIAGNOSIS AND TREATMENT (LITERATURE REVIEW)

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ABSTRACT

Background: Brucellosis is one of the most prevalent zoonotic diseases worldwide, with approximately 500,000 new human cases annually, though true incidence is substantially underreported. Caused by intracellular Gram-negative bacteria of the genus *Brucella*, the disease imposes considerable burden on public health and agricultural economies in endemic regions.

Objective: To provide a critically synthesized, up-to-date narrative review of brucellosis encompassing global epidemiology, molecular pathogenesis, clinical spectrum, diagnostic advances, and treatment strategies.

Methods: A structured search of PubMed/MEDLINE, Scopus, and Web of Science was conducted using MeSH terms and free-text keywords. Articles published between 2006 and 2025 were prioritized for quality, relevance, and citation impact.

Key Findings: Brucellosis is concentrated in the Mediterranean basin, Arabian Peninsula, Central Asia, and sub-Saharan Africa. Molecular studies have clarified intracellular survival mechanisms, particularly the roles of atypical LPS and the Type IV secretion system. PCR platforms have improved diagnostic sensitivity. Doxycycline-based combination regimens remain first-line therapy, though relapse and chronic disease remain challenges.

Conclusion: Integrated One Health approaches, improved diagnostic access, and sustained vaccine research are essential to reduce the global brucellosis burden.

Keywords

brucellosis; zoonotic diseases; *Brucella* spp.; epidemiology; molecular diagnostics; antibiotic treatment; One Health; neglected tropical diseases

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1. INTRODUCTION

Zoonotic diseases account for approximately 60% of all known human infectious diseases. Among these, brucellosis stands out as one of the most widespread yet neglected bacterial zoonoses globally. First described by David Bruce in 1887 during outbreaks among British soldiers in Malta, the disease has since been recognized across all inhabited continents. The WHO estimates 500,000 new human cases annually, but multiple analyses suggest the true figure is five- to twenty-five-fold higher owing to diagnostic limitations and passive surveillance systems in endemic regions.

The causative agents — facultative intracellular bacteria of the genus *Brucella* — survive within host macrophages by evading classical immune clearance pathways, rendering brucellosis clinically challenging to manage. Its manifestations range from self-limiting febrile illness to chronic debilitating disease with serious complications including spondylitis, endocarditis, and neurobrucellosis. Economic losses from livestock productivity decline, trade restrictions, and human morbidity are estimated in the billions of dollars annually, particularly in Central Asia, the Middle East, and sub-Saharan Africa.

This review synthesizes current knowledge across the key dimensions of brucellosis: epidemiological distribution, pathogenic mechanisms, clinical manifestations, diagnostic methods, treatment protocols, and prevention strategies, with emphasis on developments from the past decade and persistent scientific gaps.

2. GLOBAL EPIDEMIOLOGY OF BRUCELLOSIS

2.1 Geographic Distribution and Endemic Regions

Brucellosis distribution is shaped by agricultural practices, animal husbandry traditions, and veterinary control program effectiveness. The highest incidence rates are consistently reported from the Mediterranean basin (Greece, Turkey, Spain), the Arabian Peninsula (Iran, Saudi Arabia, Iraq), Central and South Asia (Kazakhstan, Kyrgyzstan, India), and parts of sub-Saharan Africa. In these regions, *Brucella melitensis* — the most virulent species for humans — circulates primarily in sheep and goats, while *B. abortus* persists in cattle populations. Iran reports incidence exceeding 50 cases per 100,000 in some provinces; Turkey and Saudi Arabia similarly document substantial annual burdens.

Sub-Saharan Africa presents a different epidemiological profile: brucellosis in livestock is widespread, but human case identification is sporadic, reflecting near-absent systematic surveillance rather than genuine disease absence. Seroprevalence studies in pastoral communities in Ethiopia, Tanzania, and Nigeria document rates

of 5–15% among high-exposure groups. The overlap with malaria, typhoid, and leptospirosis further complicates clinical recognition.

2.2 Incidence Trends

Western Europe and North America have driven human case rates below 0.5 per 100,000 through robust veterinary eradication programs and pasteurization mandates. Central Asian republics, by contrast, experienced resurgent brucellosis after Soviet-era collapse disrupted veterinary services and mass vaccination campaigns. Kazakhstan, Kyrgyzstan, and Tajikistan report incidence exceeding 20–30 per 100,000 in rural provinces. China presents a particularly alarming contemporary trend: incidence increased more than tenfold since the early 2000s, with over 70,000 cases officially reported in 2021, driven by livestock industry expansion and population mobility.

3. ETIOLOGY AND PATHOGENESIS

3.1 Brucella Species and Taxonomy

The genus *Brucella* (class Alphaproteobacteria) comprises at least twelve recognized species. Classical pathogenic species of greatest medical relevance are *B. melitensis* (goats/sheep; most virulent), *B. abortus* (cattle), *B. suis* (swine), and *B. canis* (dogs). Despite phenotypic differences, all species share >90% nucleotide identity. Whole-genome sequencing and MLVA typing now enable refined phylogeographic analysis and outbreak source-tracing.

3.2 Intracellular Survival and Immune Evasion

Following phagocytosis, *Brucella* resides within a specialized *Brucella*-containing vacuole (BCV) and actively prevents phagolysosome fusion. This depends on its atypical lipopolysaccharide (LPS), which differs from classic enterobacterial LPS in possessing long-chain fatty acids and a non-canonical lipid A structure that poorly activates TLR4/MD-2, dramatically limiting pro-inflammatory cytokine induction at the point of initial infection. Subsequently, the BCV is redirected toward the endoplasmic reticulum, where bacterial replication occurs — a process orchestrated by the VirB Type IV secretion system (T4SS). VirB translocates over thirty effector proteins into the host cytoplasm, modulating ER stress, autophagy, and apoptosis to sustain an intracellular permissive niche.

3.3 Host Immune Response and Chronicity

Innate immune activation via TLR2, TLR9, and NOD1/NOD2 triggers IL-12 production, driving a Th1 adaptive response dominated by IFN-γ-producing CD4+ and CD8+ T cells. Macrophage activation via IFN-γ upregulates microbicidal mechanisms, yet rarely achieves sterile clearance without antibiotic support. Chronic brucellosis (>12 months) is associated with bacterial persistence in macrophages, granuloma formation, elevated regulatory T-cell activity, and a low-

replication persister state analogous to *M. tuberculosis* dormancy. Host polymorphisms in TLR4, TLR2, TNF-α, and Vitamin D receptor genes modulate chronicity risk.

4. CLINICAL MANIFESTATIONS

4.1 Acute Brucellosis

Incubation typically spans two to four weeks. Acute brucellosis presents as a non-specific febrile syndrome with undulant fever, profuse sweating, malaise, myalgia, arthralgia, and headache. Hepatosplenomegaly is present in 20–30% of cases. Laboratory findings — leukopenia, elevated inflammatory markers, mild transaminasemia — are non-specific. The absence of pathognomonic features makes clinical diagnosis alone unreliable, contributing to well-documented diagnostic delays averaging several weeks in endemic settings.

4.2 Complications and Chronic Disease

Focal complications arise in approximately 30% of patients, affecting virtually any organ system. Musculoskeletal involvement — spondylitis (predominantly lumbar L4-L5), sacroiliitis, peripheral arthritis, and osteomyelitis — is most common. Neurobrucellosis occurs in 1–5% of cases, presenting as meningitis, encephalitis, cranial nerve palsies, myelitis, or cerebrovascular events; CSF shows lymphocytic pleocytosis, elevated protein, and normal or mildly reduced glucose, mimicking tuberculous meningitis. Brucella endocarditis, though occurring in <2% of patients, accounts for the majority of brucellosis-related deaths and frequently requires surgical valve replacement. Orchitis/epididymo-orchitis affects up to 20% of adult males. Brucellosis in pregnancy carries risks of spontaneous abortion, fetal demise, and premature delivery.

5. MODERN DIAGNOSTIC METHODS

5.1 Serological Tests

The serum agglutination test (SAT/Wright test) remains the most widely used diagnostic tool, achieving sensitivity of 70–85% in acute disease at a titer ≥1:160. Its limitations include false positives from cross-reacting organisms (*Yersinia enterocolitica* O:9, *F. tularensis*), failure to detect *B. canis*, and residual titers from prior infection in endemic populations. ELISA platforms offer superior sensitivity in chronic brucellosis where SAT titers fall below diagnostic thresholds, and competitive ELISA formats using monoclonal anti-O-polysaccharide antibodies improve specificity. The Rose Bengal plate test serves as a rapid screening tool in resource-limited settings.

5.2 Molecular Diagnostics

Real-time PCR — particularly targeting the *IS711* insertion sequence — provides high sensitivity (71–96%) and specificity (>95%) across blood, bone

marrow, CSF, and joint fluid specimens, and is especially valuable in the early febrile phase before antibody responses develop. Multiplex PCR platforms capable of simultaneously detecting multiple febrile illness pathogens hold promise for endemic settings with broad differential diagnoses. Automated closed-tube systems (e.g., Cepheid GeneXpert) are under evaluation and could substantially improve diagnostic access if cost barriers are addressed.

5.3 Culture and Emerging Approaches

Blood culture using automated continuous-monitoring systems achieves positivity rates of 40–80% in acute disease; bone marrow culture offers ~90% sensitivity but requires invasive sampling and BSL-3 facilities, limiting its use to referral centers. MALDI-TOF MS with updated Brucella reference libraries now enables species identification in minutes following positive culture. Lateral flow immunoassays using recombinant antigens, cytokine biomarker panels (TNF-α, IFN-γ, IP-10), and host transcriptomic signatures represent emerging research tools with potential for clinical translation.

6. CURRENT TREATMENT STRATEGIES

6.1 Standard Regimens

Treatment requires prolonged combination antibiotic therapy due to the intracellular pathogen niche. WHO-endorsed first-line therapy for uncomplicated adult brucellosis is doxycycline (100 mg twice daily) plus rifampicin (600–900 mg daily) for six weeks. The alternative regimen of doxycycline for six weeks combined with streptomycin (1 g IM daily) for the first two to three weeks has demonstrated comparable or superior efficacy in randomized trials, with lower relapse rates in several meta-analyses. Fluoroquinolones (ciprofloxacin, levofloxacin) offer good intracellular and CNS penetration and are valuable in complicated cases, particularly neurobrucellosis, but must never be used as monotherapy due to high relapse risk.

6.2 Focal, Chronic, and Challenging Cases

Spinal brucellosis warrants a minimum of three months of combination therapy, often including trimethoprim-sulfamethoxazole for its favorable spinal penetration. Brucella endocarditis typically requires doxycycline-rifampicin-cotrimoxazole for at least six to nine months alongside surgical valve replacement in most cases. Relapse occurs in 5–15% of patients after standard therapy and is attributed to intracellular bacterial persistence. Chronic brucellosis — characterized by fatigue, musculoskeletal pain, and cognitive symptoms persisting after apparent bacteriological cure — remains poorly understood and inadequately validated therapeutically; its overlap with post-infectious syndromes warrants controlled clinical investigation. Isolated rifampicin-resistance reports from Iran and China

(rpoB mutations) underscore the importance of combination therapy and resistance surveillance.

7. PREVENTION AND CONTROL STRATEGIES

7.1 Veterinary and Food Safety Measures

The most effective long-term strategy for reducing human brucellosis is animal reservoir control. Western European and North American countries have achieved near-elimination through test-and-slaughter programs, livestock movement controls, and mass vaccination using *B. abortus* S19 (cattle) and *B. melitensis* Rev.1 (small ruminants) vaccines. Both are live attenuated strains with high protective efficacy but induce serological responses interfering with SAT-based surveillance. DIVA (Differentiating Infected from Vaccinated Animals) diagnostics based on protein antigens absent from vaccine strains are actively being developed to address this. Milk pasteurization (71.7°C for 15 seconds) reliably eliminates *Brucella*; however, informal raw dairy markets persist in endemic countries, sustained by cultural preferences, economic incentives, and weak regulatory enforcement. Community-based behavior change programs and affordable small-scale pasteurization technologies are priority interventions.

7.2 One Health Approach

Brucellosis provides one of the clearest operational cases for the One Health paradigm. Programs addressing only the human health dimension without engaging veterinary services and food regulatory agencies consistently underperform. Effective integration requires shared surveillance data systems, joint outbreak investigation protocols, and coordinated laboratory capacity for both human and animal specimens. Regional WHO/FAO/WOAH initiatives in the Eastern Mediterranean and Central Asia have provided structural frameworks, though sustained political commitment and resource allocation remain inconsistent.

8. FUTURE RESEARCH DIRECTIONS

The absence of a licensed human brucellosis vaccine is the most significant gap in global control. Subunit vaccine candidates — including outer membrane proteins Omp16, Omp19, and BLS (Brucella Lumazine Synthase) — have demonstrated protective efficacy in murine models; nanoparticle delivery systems and reverse vaccinology approaches are expanding the pipeline. Commercial incentives for vaccine development against a predominantly low-income-country disease remain limited, requiring sustained public sector investment. Whole-genome sequencing has enabled unprecedented resolution for outbreak investigation and phylogeographic analysis; metagenomic approaches applied directly to clinical specimens offer diagnostic utility in culture-negative cases. Validated host

biomarker panels — cytokine signatures, metabolomic profiles, blood transcriptomics — could improve prediction of relapse risk and chronic disease, though prospective multicohort validation is required. Critically, reversing the neglect of brucellosis demands deliberate research investment in endemic countries, capacity building for clinical trial infrastructure, and global partnerships positioning endemic-country researchers as principal contributors rather than peripheral participants.

9. CONCLUSION

Brucellosis remains a major, underappreciated global health problem disproportionately affecting resource-limited populations. This review has documented a disease whose molecular biology is increasingly well characterized, whose clinical manifestations span a wide spectrum, and whose control tools — including effective antibiotics, veterinary vaccines, and pasteurization — already exist yet remain insufficiently deployed. The most urgent priorities are: accessible point-of-care diagnostics for endemic settings; rigorous evaluation of chronic and relapsing disease management; accelerated human vaccine development; and sustained One Health surveillance and control programs. Brucellosis is preventable, treatable, and reducible — but only through persistent, coordinated, and adequately resourced efforts that address the disease across the human-animal-environment interface.

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ЦЕНТР АКУШЕРСТВА И ГИНЕКОЛОГИИ АССОЦИАЦИЯ ВРАЧЕЙ ЧАСТНОЙ ПРАКТИКИ УЗБЕКИСТАНА КЛИНИКА «MAHLIYO-SHIFO» & V, 23.

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