Brucellosis: 'One Health' challenges and opportunities

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Summary
Brucellosis is an ancient disease with host-specific evolutionary mechanisms that allow it to hide from or manipulate cellular immunity and achieve intracellular persistence. The disease yields low fatality rates but can cause substantial disabilities. Zoonotic brucellosis remains widespread and neglected in many areas despite notable advances in science, technology, and management in the 19th and 20th Centuries. The burden appears to remain greatest, and yet most under-prioritised globally, amongst pastoral peoples and small-scale livestock farmers. Capacity building for zoonotic brucellosis diagnosis, surveillance, management, and treatment in developing countries faces numerous challenges. Adaptive risk management can provide a framework to build stakeholder support for addressing the complexities and uncertainties, and learning from management actions. The challenges and opportunities for brucellosis management must be recognised as fundamentally multivariate, multifaceted, and integrative; it is thus crucial for veterinary, public health, and wildlife/conservation professions to collaboratively develop, adopt and promulgate a brucellosis One Health paradigm.

Keywords
Adaptive risk management – *Brucella* – Brucellosis – Collaboration – One Health.

Introduction

One Health is 'the collaborative efforts of multiple disciplines working locally, nationally, and globally, to attain optimal health for people, animals, and our environment' and 'truly one of the critical challenges facing humankind' (3). Karesh *et al.* (11) suggest that anthropogenic environmental changes have substantially altered the playing field for the survival and evolution of zoonotic pathogens. The primary drivers of such large-scale change include human population growth and accompanied land-use change, the introduction of invasive species, and climate change. These problems are aggravated by the increasing global demand for food and water, loss of biodiversity, elevated environmental toxicity, and emergence of drug-resistant pathogens (11, 12, 16, 18). With more people living in close contact with animals than at any time in history (20), the stage is set for inherent dilutive effects of intact ecosystems to decline, leading to exacerbated vector-borne and non-vector-borne zoonotic pathogen transmission within contact populations (11, 18).

Nearly 30 years ago, Schwabe (28) addressed the increasing interdependence of humans and animals (and their products) and reviewed brucellosis as an illustrative case study of an important zoonosis. Brucellosis knows no borders, moving liberally amongst humans, livestock, and terrestrial and aquatic wildlife (32). There is a need, therefore, for critical deliberation of its epidemiology, pathogenesis and diagnosis to improve prevention and management at local, regional, national and global levels (19). Mazet *et al.* (16) proposed that the core elements of a One Health approach to assessing and managing the impacts of zoonoses could be meaningfully grouped according to medical, ecological, socioeconomic and policy factors. This paper expands this list to include science, education and management factors,

and considers brucellosis through the One Health paradigm by examining issues raised in this issue of the OIE *Scientific and Technical Review* (34).

Key factors in the One Health approach

Medicine

Brucellosis is an ancient disease with evolutionary mechanisms that allow it to hide from or manipulate cellular immunity and achieve intracellular persistence; it yields low fatality rates but substantial residual disability. A recent historical medical analysis suggests that virulent *Brucella abortus* may have played a central role in the plague of Athens (430 BC to 420 BC) (13). Brucellosis remains the most common zoonotic disease in the world, with more than 500,000 new cases reported annually (1, 9, 29); the actual number of cases, including undetected and unreported cases, is believed to be considerably higher (2). Brucellosis is often a neglected disease despite being endemic with high zoonotic potential in many countries (21, 23, 29). Particularly in pastoral systems, human brucellosis is often confused with other febrile illnesses, especially malaria and typhoid fever (23).

The genus *Brucella* consists of ten species, with valid published names, that are highly related to each other, exhibiting sequence similarity values of 98% to 100% in aligned regions of the core genome (26). Although the majority of reported human brucellosis cases are caused by *B. melitensis*, *B. abortus*, and *B. suis*, in occurrence order, novel and atypical *Brucella* are also being investigated (2). Seven strains previously reported as *B. suis* biovar 3 were recently reinvestigated and molecular analysis indicated that all are distinct from known *Brucella* (26). Preliminary phenotypic and molecular analyses identified a novel lineage of *B. inopinata* from a human lung biopsy (26). A potential novel *Brucella* has been isolated from African bullfrogs (26); in contrast to other *Brucella*, the isolates are motile and equipped with a single laterally attached flagellum similar to that described for *Ochrobactrum anthropi*. It is apparent that we are only beginning to discover the full ecological spectrum of the genus *Brucella,* and the broad spectrum of animal species that may be carriers of novel *Brucella* species or *Brucella*-like organisms (26).

Despite recent advancements, molecular determinants and mechanisms of *Brucella* virulence are only just beginning to be understood (21). *Brucella* spp. lack classical bacterial virulence factors and possess mechanisms that prevent activation of the host innate immune system. The bacteria are capable of invading many different organ systems and the resulting infection has a range of clinical manifestations (21). Once the disease has been acquired by humans, only early diagnosis and adequate antibiotic therapy can prevent serious sequelae in patients (2). The most common form in humans is osteoarthritis, occurring in 20% to 60% of cases. Central nervous system invasion by *Brucella* results in an inflammatory syndrome known as neurobrucellosis, which may be the most severe form of the disease (4). Mortality is rare but most often occurs as a result of myocarditis associated with *Brucella* localisation in cardiac muscle. In livestock, the mechanisms of *Brucella*-induced abortions are poorly understood, but placentitis has been hypothesised (21). Thus, identification and characterisation of mechanisms that control expression of cellular invasion genes inside the host will be critical for understanding intracellular behaviour and designing improved attenuated live vaccines and new therapeutic tools (21). It has been observed that killed bacteria or subunit vaccines do not appear to mimic *Brucella* trafficking through phagosomes, which may explain why non-living vaccines are unable to induce immunity that equals the protection provided by live attenuated vaccines (17).

Serological tests cannot differentiate between *Brucella* species and cannot therefore identify which species has induced host antibodies; only isolation of the *Brucella* sp., or specific DNA detection by polymerase chain reaction (PCR), allows identification of the infecting strain (9). Diagnosis of human brucellosis is thus based on combining bacteria isolation from clinical samples with standard microbiological identification, detection of anti-*Brucella* antibodies using serological tests, and/or molecular methods for the detection of *Brucella* DNA (2). In developed non-endemic countries diagnosis should be based on clinical presentation, patient history (including details of any travel to an endemic region or consumption of animal products from an endemic region) and corresponding laboratory findings. In endemic countries with limited financial resources, diagnosis of brucellosis should rely on clinical presentation and laboratory diagnosis (2). Meta-analyses comparing various diagnostic tests in terms of their analytical and diagnostic specificity and sensitivity are crucial yet generally lacking (2).

Brucella melitensis, B. abortus and *B. suis* are transmitted between animals both vertically and horizontally, and can cause abortion and infertility in their primary natural hosts (8). Typical transmission to humans occurs via direct handling or consumption of infected animal products, primarily non-pasteurised milk products. It remains unclear whether wildlife is a crucial zoonotic concern globally. Direct interaction between infected wildlife and livestock at a local interface may be the most important driver for periodic spillback transmission (9). Direct transmission of *Brucella* spp. from wildlife to humans seems to be primarily associated with the handling and consumption of bushmeat

(9). Transmission via marine mammals is also possible, as people from at least 114 countries have frequent contact with, and consume, products from one or more potential marine mammal host species (10).

Ecology

For wildlife and livestock hosts, seasonal food restriction during pregnancy has the potential to limit resources available for immune defence and may be an important factor sustaining brucellosis at the population level (31). Higher prevalence of infection in reproductively immature bison suggests that this age and sex class may be a primary long-term reservoir for sustaining brucellosis in wild ungulates (31). Vertebrate scavengers may serve as an important mechanism in limiting *Brucella* survival in environments outside the host (6). Indeed, environmental contamination with *Brucella* is not thought to play a significant role in persistence, rather it seems that ecological drivers of wildlife host density, group size and behaviour may be important to understanding transmission dynamics in wildlife (27). Amongst wildlife, coexistence of multiple host species seems to be the general condition rather than the exception (9, 10, 25). Currently, 53 species of marine mammals have been shown to be serologically positive for *Brucella,* with *B. ceti* or *B. pinnipedialis* isolated or identified by PCR in 18 marine mammal species, as well as from fish, amphibians, and pinniped and cetacean lung worm parasites (10). Spillover of *Brucella* from free-ranging wild ungulate populations to livestock remains a concern. Risks of transmission can be highly complex as they are based on a number of factors, including wildlife and livestock population sizes, location, seasonal frequency of spatiotemporal interactions, disease prevalence in wildlife, and the susceptibility of livestock (27). Adaptive risk management that takes ecological drivers into account can be successful in constraining large-scale spillback to livestock (6, 27, 31, 33). Where threatened and endangered wildlife serve as *Brucella* hosts, conservation policies should consider the extent to which brucellosis may impact populations (10).

Socioeconomics

Most data and evidence on the economic burden of brucellosis and the benefits of disease control are from developed countries, however, social and economic burdens of brucellosis are thought to be greatest in developing countries where prospects for feasible and economically viable national brucellosis control programmes are limited (14). In such circumstances, it can be challenging to assess the economic feasibility and value of targeted control efforts (14). Treatment of human cases can increase local visibility and community understanding of the disease and thus may increase appreciation of the benefits of control programmes in livestock reservoirs (30). Assessing and understanding the costs associated with brucellosis prevalence requires a multifaceted approach that includes:

a) reliable information on burdens, epidemiology and transmission dynamics in different systems

b) an understanding of how disease prevalence might change under different control options

c) economic assessment of specific impacts of brucellosis on livestock and public health

d) integrated impact analysis to identify tactics and strategies that may increase the economic benefits of brucellosis control for animal and human populations

e) engagement of policy-makers and investors from households through market chains, and up to national and regional economies (14).

Policy

International standards to harmonise testing, reporting, vaccines, and prevention and control processes for protecting human and animal health are a critical element in transparent and acceptable brucellosis prevention and management measures (24). The development of international standards is a complex undertaking that involves many challenges across the full spectrum of political, economic, social, technical, and legal considerations (24). Politically, stakeholders can view standards as an intrusion into sovereign authority or see trade barriers as favouring those who possess sufficient economic and technical abilities (24). Economically, implementation of international standards can initially involve market restrictions and start-up costs, but may ultimately provide a high return on investment. However, initial costs can limit the ability of some countries to participate (24). Despite international standards that combine incentives for compliance and penalties for non-compliance, social normative behaviours often remain resistant to change (24). Policies and standards must strive to recognise and align with sovereignty, import/export requirements, and national health and fiscal laws (24). In the United States, *Brucella* is regulated as a 'Select Agent and Toxin', with the intention of reducing the potential for it to be used for harm (5), although similar regulations have not been widely implemented in other countries.

Science

Given the impact of brucellosis on public health, agricultural productivity, and wildlife conservation, it is vitally important to maintain research capacity and capability for brucellosis science worldwide. Experiences gained through brucellosis research over the past 90 years suggest that advances in knowledge to improve diagnostics and vaccines will be technologically challenging. Still, there remains a worldwide need for brucellosis science in order

to develop more effective diagnostics and vaccines and to improve knowledge of its pathogenesis. Current knowledge demonstrates that laboratory animal models of brucellosis do not accurately predict *in vivo* clearance, immunogenicity, or efficacy of vaccines in domestic livestock or wildlife hosts; and although similarities in immune responses to vaccines across natural host species can exist, appropriate safety and efficacy data for vaccine candidates will need to be acquired for each targeted host before the vaccine can be recommended for use (17). Studies have demonstrated that the financial cost of brucellosis vaccination and control programmes can be offset by the reduction in human treatment costs alone (17). Modern molecular diagnostic methods facilitate potential novel *Brucella* species recognition (26), and technologies such as DNA vaccines and nanoparticles may be capable of delivering *Brucella* antigens in a manner that induces protective immunity in both livestock and wildlife (17). Thus, for greatest value, tests need to be conducted in the host species of interest using a relevant, virulent strain of *Brucella* (17). There is also the need to ensure that public health, livestock producers, and laboratory workers remain safe from the consequences of intentional or unintentional release/transmission of brucellosis. Currently, most countries require or recommend Biosafety Level 3 containment for laboratories or animal facilities conducting research with *Brucella*. Progress in research is restricted because laboratories with this level of biosafety are expensive to build and operate; consequently, there are not many of them, they have limited availability and some of them have limited animal-holding capacity. Striking the appropriate balance between national security/safety and facilitation of *Brucella* science remains challenging.

Management

In many endemic areas, uncontrolled animal movement and lack of veterinary infrastructure are major obstacles to disease control (15). Brucellosis is persisting in pastoral areas of the world, despite various control efforts (23). While diagnostics, surveillance, and management may be generally well understood in many countries, brucellosis remains largely under-diagnosed and uncontrolled amongst many pastoral peoples and small-scale livestock holders. Lack of resources combined with difficulty in local diagnosis, limited knowledge of regional epidemiology, and little understanding of the social factors contributing to disease may underpin persistence of brucellosis in pastoral ecosystems (23). Surveillance information assists in epidemiological characterisation of brucellosis in a targeted area but, more importantly, provides precise aetiological knowledge for guiding vaccine choice (1, 7). Yet, while serodiagnostic assays have been shown to be an important part of sustained brucellosis control or eradication, the costs of sustaining the necessary management and infrastructure support can be economically and socially prohibitive. Thus, few countries have totally eradicated the disease; indeed, in many countries disease prevalence is increasing (15). Given this situation, there is a need to improve serodiagnosis by reducing costs, increasing specificity, improving mobility, and developing reliable assays for differentiating infected and vaccinated animals (15).

Despite the arsenal of available tools and regulations, eradication of brucellosis from wildlife is not likely. Where traditional lifestyle and belief systems contribute to the creation of favourable conditions for the spread and transmission of brucellosis, integrated adaptive risk management may be an appropriate alternative (30). Adaptive management is an iterative decision-making process whereby:

a) the problem and uncertainties are described

b) factors contributing to the problem are assessed

c) understanding of the system is modelled

d) measurable desired outcomes (objectives) are described and responses to management actions are predicted

e) management actions to reach these desired outcomes are designed and implemented

f) the effects and effectiveness of actions are monitored to evaluate if progress is being made towards the desired outcomes

g) actions and models are adjusted as necessary to enhance progress towards the desired outcomes (33).

Given that substantial uncertainties will always exist in resolving brucellosis management issues, adaptive learning is crucial to progress (33).

Education

Educated and willing stakeholders were a critical component of early brucellosis investigation and control, and remain so (35). Because many people lack basic understanding of infectious diseases, education is crucial to explain/demonstrate transmission risks and encourage acceptance of specific measures to minimise the further spread or re-emergence of the disease; particularly where traditional practices and beliefs conflict with disease intervention strategies (30). There is a demonstrated need for integrated brucellosis education across social strata; education programmes should aim to increase awareness not only among animal owners, but also among citizen advocates, local officials and other respected individuals, veterinarians and public health workers (30). Through effective dissemination of public health information, medical services could improve the efficacy of veterinary public health programmes by enhancing understanding, cooperation and adherence (30). In such situations,

well-designed and simple-to-understand brucellosis education is crucial in helping citizens understand, accept, and follow preventive measures (30). Brucellosis education should utilise the full spectrum of modern communication tools that reach across social strata.

Conclusion

In summary, given its evolutionary position as a persistent pathogen in multiple host species, zoonotic brucellosis remains widespread and neglected or under-prioritised in many areas despite notable advances in science, technology, and management in the 19th and 20th centuries. The burden appears to remain greatest globally amongst pastoral and small-scale livestock farmers. Capacity building for brucellosis diagnosis, surveillance, management, and treatment in developing countries faces numerous challenges. International standards and policies can provide a common framework for discussion and planning, yet widespread and consistent adoption and implementation can face seemingly intractable challenges. In countries where progress has been made in disease control, there remains potential for re-emergence and spillback from wild host reservoirs. At the same time, the full extent of marine brucellosis is just now being appreciated, and indications are that across ecosystems and hosts, novel *Brucella* species and strains may yet be discovered and found to be zoonotic pathogens.

Brucellosis operates within a complex web of interactions between humans, animals, and the environment, and thus demands a 21st Century One Health approach (22). The challenges and opportunities for both human and animal brucellosis management must be recognised as fundamentally multivariate, multifaceted, and integrative. It is crucial for veterinary, public health, and wildlife/conservation professions to jointly develop and adopt an integrative brucellosis One Health training curriculum. This curriculum would provide a common framework for collaboration that translates into interactive education and outreach materials for governance, clinicians and technicians, and the general public. Development of integrative brucellosis One Health assessments and impact analyses is crucial to prioritising and demonstrating socioeconomic benefits from major investments in brucellosis research, diagnosis, surveillance and management in human and animal health sectors. Adaptive risk management will increasingly provide the framework to address dynamic and complex brucellosis system components, deliberately process substantial uncertainties, and learn from system response to management actions. Localised case examples should be identified and documented to support the case for adopting a widespread One Health approach. Now is the moment to transform brucellosis from an underestimated and often neglected disease into a well-understood and well-managed disease that benefits from a flourishing integrative global One Health approach to its control.

Brucellose : défis et opportunités dans une perspective « Une seule santé »

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Résumé

La brucellose est une maladie ancienne dotée de mécanismes évolutifs à spécificité d'hôte, grâce auxquels la bactérie peut se soustraire à l'immunité cellulaire ou la manipuler, assurant ainsi sa persistance intracellulaire. Les taux de mortalité associés à l'infection brucellique sont faibles mais la maladie occasionne des troubles invalidants chez l'hôte. Dans bien des régions, la brucellose zoonotique reste très répandue et négligée, en dépit des avancées remarquables accomplies par la science, la technologie et la gestion sanitaire au cours des XIXe et XXe siècles. Ce sont les populations pastorales et les petits élevages familiaux qui payent le plus lourd tribut à la brucellose au niveau mondial, alors même qu'elle y est le plus négligée. Dans les pays en développement, de nombreuses difficultés font obstacle au renforcement des capacités en matière

de diagnostic de la brucellose zoonotique, de sa gestion et de son traitement. La gestion du risque adaptatif fournit un cadre permettant de fédérer le soutien des parties prenantes au moment d'affronter la complexité et les incertitudes et de tirer les enseignements des opérations de gestion. Il importe de prendre conscience du fait que les défis et les opportunités en matière de gestion de la brucellose présentent de nombreuses variables et facettes, qui requièrent une démarche d'ensemble ; les professionnels de la santé animale, de la santé publique, de la protection et de la santé de la faune sauvage ont donc tout intérêt à travailler de concert à l'élaboration et à la mise en œuvre d'une stratégie « Une seule santé » en matière de lutte contre la brucellose.

Mots-clés
Brucella – Brucellose – Collaboration – Gestion adaptative du risque – Une seule santé.

Problemas y posibilidades de "Una sola salud" en relación con la brucelosis

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Resumen
La brucelosis es una enfermedad antigua que ha adquirido evolutivamente, adaptándose a cada anfitrión, una serie de mecanismos específicos para escapar a la inmunidad celular o interferir en ella y persistir de este modo en el medio intracelular. La enfermedad provoca a un tiempo bajos índices de letalidad e importantes discapacidades. Pese a los notables adelantos científicos, tecnológicos y de gestión que han tenido lugar en los siglos XIX y XX, la brucelosis zoonótica sigue muy extendida y desatendida en numerosas zonas. La carga de la enfermedad parece alcanzar sus niveles máximos en sociedades de pastores y pequeños ganaderos, pese a lo cual no se le concede en absoluto prioridad a escala mundial. Hay muchas dificultades para reforzar la capacidad de los países en desarrollo en materia de diagnóstico, vigilancia, gestión y tratamiento de la brucelosis zoonótica. Instaurando una gestión adaptable del riesgo se puede sentar un marco de trabajo que aglutine el apoyo de las partes interesadas para afrontar la complejidad y la incertidumbre y aprender de las medidas de gestión instituidas. Es preciso entender que las dificultades y oportunidades de la lucha contra la brucelosis son básicamente multifactoriales, poliédricas e integrales, y que por ello es indispensable que los profesionales de la veterinaria, la salud pública y la protección de la fauna salvaje trabajen de consuno para definir, adoptar y promulgar un paradigma de "Una sola salud" en relación con la brucelosis.

Palabras clave
Brucella – Brucelosis – Colaboración – Gestión adaptable del riesgo – Una sola salud.

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