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A Comprehensive Review Examination Study of Zoonotic Bacterial Infections: Anthrax and Brucellosis, Epidemiology, Surveillance, Clinical Manifestations, Prevention and Control Strategies

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Abstract

The two significant zoonotic bacterial infections that have remained a concern due to the complex dynamics involved in transmission and global prevalence are anthrax and brucellosis. The present paper attempts to address some of the most important zoonotic pathogens, highlighting their epidemiology, clinical manifestations, diagnosis, treatment, and prevention strategies. Anthrax is largely transmitted through direct contact with the infected animals or their products resulting in cutaneous, inhalational, and gastrointestinal forms, all with specific clinical outcomes and approaches for treatment. Similarly, the genus Brucella primarily transmits brucellosis to humans by occupational exposure and consumption of contaminated animal products. Its presentation may be acute, chronic, or in relapse. Diagnosis is made by a combination of serological, molecular, and culture-based techniques, while the treatment focuses on antimicrobial regimens specific to the pathogen. However, this increases the problem of antimicrobial resistance, which makes their effective management challenging, necessitating an integrated approach. Mitigating risks through biosecurity measures, vaccination, public health education, and a One Health approach that includes human, animal, and environmental health, all facilitate prevention

and control of an outbreak. Advanced surveillance and diagnostic technologies further support prompt interventions to contain outbreaks. It then goes on to highlight the importance of interdisciplinarity for decreasing the global burden of zoonotic bacterial diseases.

Keywords: Zoonotic Bacterial Infections; Anthrax; Brucellosis; Public health; Antimicrobial resistance; Biosecurity measures; Diagnosis; Surveillance systems; Epidemiology; Foodborne pathogens; Pathogen transmission.

1. Introduction

Direct contact with infected animals represents one of the principal modes of transmission. Brucellosis is a significant example of a zoonotic disease that has been caused by the species of Brucella and was transmitted either directly by direct contact with infected stock or by consuming unpasteurized dairy products (Algahtani et al., 2017; AlNahhas et al., 2020). In regions where livestock is common, such as parts of Saudi Arabia and Bangladesh, the risk of transmission is increased due to occupational exposure during animal handling and slaughtering practices (Islam et al., 2013; Aloufi et al., 2015). In addition, the contaminated environments like soil and water sources contribute to the spreading of zoonotic bacteria like Escherichia coli that has been reported in various agricultural settings ("Animal Ecology Enhances Farmers' Zoonotic Bacterial Occupational Diseases at High Altitude Area", 2021). Indirect transmission is also a major facilitator of zoonotic infections. For example, pet animals, including dogs and cats, can be vectors because they acquire disease-causing pathogens from wildlife or rodents and then transmit them to their human owners (Sari et al., 2022). Ecologic interplay between humans and animals, especially with rapid urbanization and habitat encroachment, has heightened the propensity for interspecies transmission of pathogens, including E. coli strains identified in both human and animal reservoirs (Amoah, 2023).

Another significant mode through which zoonotic bacterial infections become prevalent is vector-borne. This provides vectors, that is through ticks and mosquitoes while transferring the animal's pathogen to human beings through disease like Lyme disease and others relating to bacterial infections (Messenger et al., 2014). Such zoonotic diseases also often emerge and spread due to favorable conditions created by interactions between environmental factors and human activities; therefore, there is a need for a One Health approach that integrates the strategies of human, animal, and environmental health towards mitigating risks (Cross et al., 2019; "Potential Role of Zoonoses in Bioterrorism", 2023).

Zoonotic bacterial infections are of extreme importance to global public health, with a high prevalence, a potential for serious health effects, and a complex relationship among human, animal, and environmental health. Most human diseases are caused by zoonotic pathogens; therefore, understanding and managing such infections are crucial (McDaniel et al., 2014). The World Health Organization puts forward an estimate that zoonotic diseases account for nearly 25% of the infectious disease burden in low-income countries where close contact with livestock and wildlife is common (Asante et al., 2019). Such a heavy burden is compounded by various

factors, including poverty, that makes people more vulnerable to such infections, and globalization of trade and travel which enhances the rapid spread of the pathogens (Bernstein & Dutkiewicz, 2021). This suggests a close link between anthropogenic changes and the remergence and emergence of zoonotic diseases. One of these changes includes agricultural intensification, which in addition to causing urbanization is bringing about various wildlife-livestock-human interfaces and making the chances of zoonotic transmission rise (White & Razgour, 2020).

For example, evidence exists that the introduction of invasive alien species contributes to the spreading of serious human pathogens. Here, studies have shown the human-mediated introduction of rats to novel environments has facilitated the transmission of bacteria like Leptospira and Yersinia (Roy et al., 2022). This underlines the significance of understanding ecological dynamics in the context of the emergence of zoonotic diseases. Moreover, zoonotic infections impose heavy costs to human health as well as to the agricultural and veterinary sectors in terms of their productivity. The economic toll that zoonotic diseases exact is enormous, with millions of new cases reported annually with severe mortality and chronic health effects (Christou, 2011). For example, diseases such as brucellosis and salmonellosis that are zoonotic in nature threaten the production and trade of livestock in addition to the risk to human health, thus increasing complexity to the challenges in food security (Baghi et al., 2021). This human, animal, and environmental health interrelation calls for a "One Health" approach emphasizing discipline integration working together to neutralize the dangers of zoonoses (Cantas & Süer, 2014).

2. Overview of Zoonotic Bacterial Infections

Zoonotic bacterial diseases are among the critical health concerns globally and with multiple routes of transmission from animals to human beings. The most transmitted zoonotic bacterial diseases include Salmonella, Escherichia coli, Campylobacter, Listeria monocytogenes, and Brucella, among others. These are foodborne pathogens mainly related to contaminated animal products and have severe risks on their persons, involving gastrointestinal infections and systemic diseases. Salmonella species constitute one of the most frequently isolated zoonotic bacteria globally. Its incidence is highly associated with foodborne outbreaks, notably poultry, eggs, and dairy products. Statistics show laboratory-confirmed cases of almost 6,000 to 7,000 incidents in Canada per year associated with non-typhoidal salmonellosis while the actual incidence is higher because many are left unnoticed and undiagnosed due to lack of symptoms or proper check-ups (Plotogea et al., 2022). The World Health Organization has also listed Salmonella as one of the most common causes of foodborne illnesses. It is hence mandatory that proper surveillance and control are performed (Abebe et al., 2020).

Other zoonotic pathogens are Escherichia coli and some variants including Enterohemorrhagic E. coli, or EHEC. The route is commonly the food and water chain with the reservoir in farm animals. Studies have shown that farmers and those who interact closely with livestock are prone to infections mainly due to contact with infected animals or polluted environments ("Animal Ecology Enhances Farmers' Zoonotic Bacterial Occupational Diseases at High Altitude Area",

Eman Fahad Alsehli, Yousra Khudran Alzahrani, Manal Ali Alsharif, Fares Hussain Fares Alsharif, Bandar Saleem Saeed Alsaedi, Majed Mohammed Alharbi, Ibrahim Ghalib Mohammed Alharbi, Mamdouh Mathhan Alrashidi, Eman Mohsen Nahhas, Nemat Nourullah Enaam Aldeen, Majed Badr Al-Mutairi, Omar Hamed Alsalemi, Najla Qabl Ayed Almutairi, Abdulnasser Ayed Alrashedi, Abdulla Matar Alsehli 2021). The existence of pathogenic strains within the major metropolitan rodent populations has also put their potential as reservoirs for zoonotic E. coli into high-risk alarm (Guenther et al., 2012). Campylobacter species, particularly Campylobacter jejune, are important bacterial pathogens of gastroenteritis. Campylobacter species inhabit poultry and may be transmitted to humans through undercooked contaminated poultry meat or by other mechanisms of crosscontamination during the processing of food (Abebe et al., 2020). The presence of Campylobacter in animals and its association with foodborne disease necessitates constant observation and monitoring in public health intervention (Ali & Alsayeqh, 2022).

More risk is presented by Listeria monocytogenes because of its characteristic feature of having the ability to grow at temperatures that commonly occur in refrigeration. This bacterium presents quite major infections, especially to pregnant women, neonates, and immunocompetent hosts (Abebe et al., 2020). Its zoonotic potential is enhanced because, besides its existence in a range of processed meats, it is established to occur in the presence of dairy products. Brucella species, which cause brucellosis, are transmitted to humans from infected animals, mainly through unpasteurized dairy products or direct contact with infected animals. The disease still constitutes an important public health problem in many areas, especially in developing countries where livestock farming is common (Abebe et al., 2020). The zoonotic bacteria also associated with a global burden of diseases such as Mycobacterium bovis and Staphylococcus aureus are added factors that make infections tough to deal with since the fact remains that antimicrobial resistance in these bacteria is alarming, necessitating a One Health approach considering human health, animal health, and the environment (Ghareeb, 2023).

2.1. Direct Contact Transmission:

This is the transmission of diseases that take place by means of physical direct contact from infected animals to humans. It happens by handling them or getting infected through secretions and bites. Direct contact transmits the highest proportion of most zoonoses, especially in cases such as rabies and brucellosis through contacting infected animals and their excretions (Christou, 2011). In pet shops, zoonotic transmission poses a significant risk because animals are capable of carrying pathogens in an asymptomatic manner, enhancing the possibility of human infections during handling (Halsby et al., 2014). Agricultural workers often come under the risk of acquiring zoonotic infections when in direct contact with livestock and hygiene practices play a prominent role in reducing such risks (Kulkarni & Reddi, 2018).

2.2. Vector-Borne Transmission:

Vectors like insects or ticks also play a significant role in transmitting zoonotic infections from animals to humans by carrying the pathogens. The pathway is of especial importance for diseases such as Lyme disease and West Nile virus, in which the vector is important for the epidemiology of the disease (Christou, 2011). Documentations about emerging zoonoses have proven to relate to changes in the environment and changes in agricultural practices; land use change can enable vector-borne transmission due to changing habitats and exposing humans more to vectors (Loh et al., 2015; Jones et al., 2013). For example, the Ebola virus disease has been associated with bat reservoirs, but it is primarily transmitted to humans through direct contact with infected bodily fluids rather than through mosquito vectors (Pigott et al., 2014).

2.3. Ingestion Transmission:

Ingestion is another critical route through which zoonotic pathogens can infect humans, typically through contaminated food or water. Foodborne zoonoses are commonly caused by the intake of insufficiently cooked or contaminated animal products, especially in cases of Yersinia enterocolitica and Hepatitis E virus (Choi et al., 2013). Consumption of raw or poorly cooked meat from infected deer and pigs has been implicated in outbreaks of zoonotic disease; therefore, correct handling and cooking of food reduces the spread of disease. In addition, dairy products play an important role in zoonotic transmission. Poor storage and handling can easily facilitate the transmission of Brucella and Cryptosporidium, among others (Mosalagae et al., 2010; Ng et al., 2012).

Table 1: Modes of Transmission of Zoonotic Bacterial Infections.

Mode of	Pathogens/Diseases	/Diseases Examples of Exposure	
Transmission	ē	1	
Direct contact	Brucella spp., Bacillus anthracis	Handling infected animals, skinning, or contact with animal products (e.g., unpasteurized dairy, raw meat); common in occupational exposure like farming or veterinary practices	Christou, 2011; Kulkarni & Reddi, 2018
Vector-borne	Borrelia burgdorferi (Lyme disease), Francisella tularensis (Tularemia)	Bites from infected ticks, fleas, or mosquitoes; exposure in areas with high wildlife activity or agricultural expansion	Loh et al., 2015; Nakamura et al., 2018
Ingestion	Salmonella spp., Escherichia coli, Listeria monocytogenes	Consuming undercooked or contaminated food, unpasteurized milk, or water contaminated by livestock or wildlife excreta	Mosalagae et al., 2010; Abebe et al., 2020
Inhalation	Bacillus anthracis, Coxiella burnetii (Q fever)	Inhaling aerosolized spores from infected animals, contaminated soil, or animal products; occupational exposure in slaughterhouses or during animal carcass disposal	Greene et al., 2002; Rahravani et al., 2022

3. Anthrax

Bacillus anthracis is gram-positive, spore forming bacterium; the illness it causes is one of the most infectious diseases at times referred to as anthrax. The B. cereus group consists of several closely related species, for example, Bacillus cereus and Bacillus thuringiensis. It is astonishing that the genetic constancy of B. anthracis is described without much genetic diversity over long periods which suggests a relatively stable evolution history (Khan, 2023; Kim, 2002). Virulence factors make up the primary contributors to pathogenicity and are located on two plasmids, namely pXO1 and pXO2. These plasmids are fundamental in allowing the bacterium to be pathogenic for disease in its host (Hurtle et al., 2004; Jeong et al., 2013).

3.1. Skin Anthrax:

This is the most common type of human anthrax. It normally occurs following direct contact with contaminated animal products or infected people. It is manifested by the appearance of an initially painless sore that eventually evolves into a typical black necrotic ulcer. Cutaneous anthrax was reported to have a mortality rate between 10% and 40% based on history, but this has significantly decreased to less than 1% with the use of modern medical interventions (Pertea, 2024). The disease may result in complications like compartment syndrome, especially if it is a severe case (Pertea, 2024).

3.2. Inhalational Anthrax:

This form arises from the inhalation of spores. The disease will then develop into severe respiratory illness. Initial symptoms may seem like a common cold, but the disease will progress to be serious, respiratory distress, and even septic shock. Inhalation anthrax is particularly fatal if it is untreated and diagnosed late. The onset of systemic infection develops very quickly (Greene et al., 2002). Advanced molecular techniques such as PCR are usually relied on in diagnosing disease based on specific virulence genes (Berg et al., 2006; Khariri et al., 2019).

3.3. Gastrointestinal Anthrax:

This variety occurs following exposure to infected meat. The typical symptoms include vomiting, abdominal pain, and severe gastrointestinal disturbance with nausea. Gastrointestinal anthrax is rare and invariably fatal unless the correct measures are undertaken for treatment (Greene et al., 2002). Laboratory diagnoses involve isolation of B. anthracis in stool specimens or using serological tests (Khariri et al., 2019; Felder et al., 2009). An anthrax infection is predominantly a zoonotic infection, which means it passes from animals to humans through some pathways primarily by direct contact with infected animals or contaminated products from those animals. Such transmission dynamics are especially vivid in areas where livestock farming is common, and all the risk factors related to human infection are directly associated with agricultural practices and socio-economic conditions. Direct contact with infected animals, especially during slaughtering or handling of animal products, is one of the leading modes of transmission.

Several research studies have shown that cutaneous infections in humans are typically observed after an outbreak among the animals, thus there is a well-defined time gap between the animal and the human infections. In Bangladesh, significant risk factors for transmission of the disease to humans were observed by handling raw meat and contacting the skin of infected animals at the time of slaughtering (Islam et al., 2016; Islam et al., 2018). Besides that, the burial of carcasses in grazing pastures of other animals will lead to the consumption of anthrax spores and thus continue the cycle of infection (Chakraborty et al., 2012; Islam et al., 2013). Environmental factors also play a significant role in the spread of anthrax, besides direct contact. B. anthracis spores can survive in the environment for a long time, contaminating pastures and water sources.

Animals grazed on these areas, ingesting the spores leading to outbreaks in livestock which, hence increases the risk of transmission from animals to humans (Rahman et al. 2020). Insect vectors are also believed in the mechanical transmission of the spores through anthrax because their ability to carry the bacillus from infected animals to the human host (Fasanella et al. 2010). Socio-economic conditions also pose a huge influence on the risk of anthropogenic anthrax

transmission. The other factors that expose them to risk include low levels of education and knowledge regarding anthrax among rural communities, especially in developing countries, coupled with the culture of scavenging for meat from carcasses (Sardar, 2023; Malakar, 2023). Besides, there is a lack of vaccination and veterinary services, which leaves the disease to survive among animals and expose humans to increased risk (Islam et al., 2013; Maukayeva, 2019).

4. Symptoms of Anthrax Infections

4.1. Cutaneous Anthrax:

It is the most common with an incidence of about 95%. It usually starts out as a small, raised papule that resembles an insect bite evolving into a vesicular lesion and then to a painless ulcer with a classic black necrotic eschar. Systemic symptomatology may include fever, general malaise, and generalized lymphadenopathy, usually if the infection has spread in the body (Pillai et al., 2015; Demirdag et al., 2003; Doğanay et al., 2010). The systemic symptoms may even develop, giving manifestations of sepsis. These include high fever and shock in severe cases (Elbahr et al., 2022).

4.2. Gastrointestinal Anthrax:

It usually presents with symptoms such as nausea, vomiting that is mostly bloody, abdominal pain, and bloody stools, from eating contaminated meat. Gastrointestinal symptoms may frequently lead to significant fluid loss and electrolyte imbalances that can subsequently progress into shock (Kau et al., 2005; Kanafani et al., 2003). Hemorrhagic signs, such as stooling with blood, often add to the complexity of symptoms (Kau et al., 2005).

4.3. Inhalational Anthrax:

This is the most critical form and tends to carry a high mortality rate. Initially, symptoms are the same as for a common cold: fever, cough, and general malaise that can readily deteriorate into severe respiratory distress, mediastinal hemorrhage, and shock. The rapid decline in respiratory function can result in death in days if left untreated (Pillai et al., 2015; Demirdag et al., 2003; Doğanay et al., 2010). This form is characterised by the presence of hemorrhagic lesions in the lungs and mediastinum (Kau et al., 2005).

5. Outcomes of Anthrax Infections

The outcomes of anthrax infections are mostly determined by the form of the disease and the promptness of treatment. Cutaneous anthrax is relatively favorable to prognosis with less than a 1% mortality rate when appropriately treated (Pillai et al., 2015; Doğanay et al., 2010). But it causes systemic infection if left untreated, and it may be fatal in some cases (Elbahr et al., 2022). Gastrointestinal anthrax is relatively rare but fatal if it is not treated in due time. The mortality rate reaches up to 25-60% through complications like septicemia and shock if left untreated (Pillai et al., 2015; Kanafani et al., 2003). Inhalational anthrax is a particularly dangerous infection due to its high mortality rate, even with treatment, that can reach up to 80% if the

Eman Fahad Alsehli, Yousra Khudran Alzahrani, Manal Ali Alsharif, Fares Hussain Fares Alsharif, Bandar Saleem Saeed Alsaedi, Majed Mohammed Alharbi, Ibrahim Ghalib Mohammed Alharbi, Mamdouh Mathhan Alrashidi, Eman Mohsen Nahhas, Nemat Nourullah Enaam Aldeen, Majed Badr Al-Mutairi, Omar Hamed Alsalemi, Najla Qabl Ayed Almutairi, Abdulnasser Ayed Alrashedi, Abdulla Matar Alsehli disease is advanced at the time of diagnosis (Pillai et al., 2015; Demirdag et al., 2003; Doğanay et al., 2010). This fast progression from initial mild symptoms to severe respiratory failure points out the importance of early recognition and aggressive treatment. Anthrax, which is caused by the bacterium Bacillus anthracis, is a serious public health issue in both endemic and nonendemic regions. The approach in diagnosis, treatment, and prevention varies with geographical presence of the disease and a particular clinical presentation.

6. Diagnosis of Anthrax

Diagnosis of anthrax can be made by various techniques: microscopy, culture, and molecular techniques. In the endemic regions, where one is likely to encounter an infected animal, suspicion based on clinical grounds in the form of cutaneous lesions or gastrointestinal distress is a must. For cutaneous anthrax, diagnosis is confirmed by Gram staining of samples from the lesion, which classically shows the presence of characteristic bacilli (Yilmaz & Yumuşak, 2015; Özer et al., 2019). PCR testing also has proven to be very sensitive for the detection of Bacillus anthracis, having a sensitivity of 100% compared to traditional microscopy, which is only at 60%, and its utility is found both in endemic and non-endemic settings (Ochai, 2024). A patient history that points to exposure to animal products is fundamental in suspected inhalation anthrax, as well as confirmatory tests such as blood cultures or serological assays (Sweeney et al., 2011).

7. Treatment of Anthrax

The treatment of anthrax depends on the type of illness: cutaneous, gastrointestinal, or inhalational. Antibiotics are the mainstay for all types of infections. Treatment for cutaneous anthrax will be with antibiotics like ciprofloxacin or doxycycline; treatment is usually 60 days long to avoid flare-up from spores still present in the body (Suggu & Konakanchi, 2020; Savransky et al., 2020). The quinolones, β -lactams, and protein synthesis inhibitors should be prescribed in combination to maximize the efficacy in systemic infections, particularly meningitis-related infections (Kaymaz, 2024). The threat of antibiotic resistance calls for judicious selection of treatment and possibly adjunctive therapies such as anthrax antitoxins that can neutralize the effects of anthrax toxins (Savransky et al., 2020; Weiss et al., 2015).

8. Prevention of Anthrax

Preventive measures against anthrax include vaccination and public health education, mainly in endemic regions where livestock vaccination is critical to controlling outbreaks. Vaccination of herbivorous animals in contaminated pastures is the major method of prevention (Rume et al., 2016). Post-exposure prophylaxis is a crucial intervention in non-endemic areas for individuals who are likely to have been exposed to anthrax spores, mainly by bioterrorism (Hendricks et al., 2014). The CDC has guidelines regarding post-exposure prophylaxis, which is directed towards the administration of antibiotics and vaccination to at-risk populations as soon as possible (Weiss et al., 2015; Hendricks et al., 2014). Aside from that, favorable environmental conditions for the

event of anthrax like soil and weather conditions have to be perceived while implementing the interventions (Fan, 2022).

9. Brucellosis

Brucellosis is one of the most important zoonoses worldwide. This disease affects humans through direct or indirect exposure to infected animals through animal contact or contaminated products. It results from several species within the genus Brucella and four specific species that have been attributed to human brucellosis, which includes B. melitensis, Brucella abortus, Brucella suis, and Brucella canis. Of these, B. melitensis has an association primarily with sheep and goats, B. Abortus with cattle, B. suis with swine, and B. canis with dogs (Vishnu et al., 2015; Ali et al., 2016; Rubach et al., 2013; Mohammed et al., 2013). The species are claimed to be pathogenic to humans, and the clinical symptoms involve undulant fever, endocarditis, and many neurological diseases (Vishnu et al., 2015; Rubach et al., 2013; Mallik et al., 2023). The main reservoirs of Brucella species are domestic animals that are mainly responsible for causing infection in humans. These are cattle, sheep, goats, and swine, which represent the most significant reservoirs. Amongst the three commonly isolated species in human cases are B. abortus, B. melitensis, and B. suis (Ali et al., 2016; Rubach et al., 2013; Mohammed et al., 2013). Other reservoirs of B. are dogs. canis, though this species is less commonly associated with human infection than the others (Ye et al., 2021). The most common route of brucellosis transmission to humans is through the consumption of unpasteurized dairy products, direct contact with infected animals, or inhalation of aerosolized particles from infected materials (Shaw, 2023; Wáng et al., 2014).

In areas where livestock rearing prevails, such as the countryside of Pakistan, the disease of brucellosis is more likely as the human and their animals' lives have close association (Ullah et al., 2022). More than that, other types of wildlife can get their hands in the epiphytology of Brucellosis because a case has been cited earlier that buffaloes are also transmissible in some ecosystems involving eating bush meat (Assenga et al., 2015). Environmental contamination during calving and the handling of aborted materials from infected animals represent important routes through which the bacteria are transferred to humans. Assenga et al., 2015; Moreno, 2014. Brucellosis is caused by the genus Brucella. This zoonotic disease is transmitted primarily by direct contact with infected animals or their products. This disease is primarily spread in agricultural and occupational environments. Different factors, such as husbandry practices among animals, occupational exposure, and public awareness, may influence the brucellosis transmission dynamics.

Animal husbandry in an agricultural environment is one of the most critical factors involved in brucellosis transmission. Major risks of brucellosis transmission in small ruminants involved overstocking and promiscuous mixing of animals without separation pens for the diseased and sick ones. For instance, a case study in Karnataka, India, suggested that the risk of getting brucellosis in goat farms with less separative distance among the animals was relatively high, meaning there is a need for the implementation of biosecurity measures that can prevent the spread of the disease (Natesan et al., 2021). A well-established risk factor for animals and

humans in contact with contaminated materials that include aborted fetuses, as well as placental tissues, includes Getahun et al., 2022;, Sibhat et al., 2022. The most plausible exposure among farmers and the veterinarians would be direct handling of such materials without proper protection equipment.

Occupational exposure is another major route for brucellosis transmission. Most risky are people working in slaughterhouses, farms, and laboratories handling Brucella cultures. For instance, there have been documented outbreaks in various occupational exposures. For example, in China, there was an outbreak in a drug factory. Many unchecked livestock caused the rise in the disease (Zhan et al., 2016). Another reported outbreak that involved handling live attenuated Brucella vaccines occurred in a biological products company in Chongqing.

The incident brought the risk associated with occupational exposure to infected materials into focus (Zhou et al., 2022). Moreover, unpasteurized dairy products are at risk as well since most human brucellosis is acquired by ingestion of contaminated milk (Wang et al., 2015). Public awareness and education on brucellosis are the primary ways to curb its spread. Poor knowledge of zoonotic disease transmission among farmers is a factor that will enhance the spread of brucellosis. For instance, most farmers in Ethiopia indicated they did not know the risks involved with the handling of abortion materials and consumption of raw milk, which are among the most critical risk factors in the transmission of the disease (Getahun et al., 2022, Getahun et al., 2021). Such a lack of knowledge creates a culture of behaviors that foster the spread of brucellosis in communities, particularly in endemic areas (Sibhat et al., 2022).

Acute Brucellosis typically presents with sudden onset of symptoms, which may include intermittent fever, chills, weight loss, and fatigue. There is arthralgia and back pain, being common complaints in acute presentation (Patra et al., 2018, Roushan et al., 2016). The fever with acute brucellosis is characteristically undulant in nature, which means the intensity varies and might be associated with profuse sweating (Roushan et al., 2016, Malik et al., 2016). It is also possible that the infection has systemic manifestations, such as anorexia and splenomegaly, because the infection is systemic (Zhang et al., 2022). Laboratory tests characteristically present positive markers of inflammation, and even acute cases usually have characteristics of bacteremia (Qie et al., 2020, Liu & Zhao, 2017).

Chronic Brucellosis is represented by either an acute case of Brucellosis that was not received appropriate treatment or as a long-standing chronic mode of the disease where this started. The clinical sign may be more varied but less intense than that identified in the acute phases. Chronic brucellosis may be characterized by persistence of symptoms such as fatigue, recurring fever, and arthralgia; however, it can manifest with a more serious form of complication, including osteoarticular involvement mimicking other rheumatological conditions (Kundu & Rath, 2019). Patients may manifest spondylitis or sacroiliitis that complicates the diagnosis because its symptoms are like other chronic inflammatory diseases (Kundu & Rath, 2019). Neurological manifestations may be less common but are present and may include meningitis that can be both acute and chronic in nature (Kaya et al., 2011).

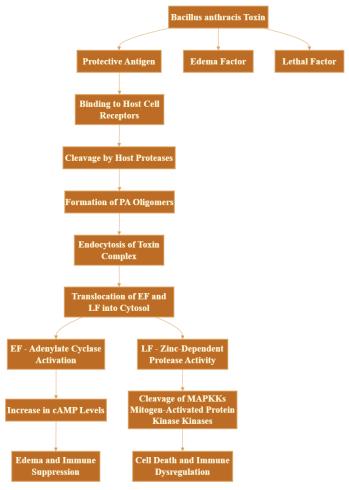


Figure 1. Mechanism of action of Bacillus anthracis toxin: Protective Antigen (PA) facilitates the entry of Edema Factor (EF) and Lethal Factor (LF) into the host cell cytosol. EF increases cAMP levels, causing edema and immune suppression, while LF cleaves MAPKKs, leading to cell death and immune dysregulation.

Relapsing Brucellosis presents a case of episodes of relapsing symptoms following a period wherein apparently the disease had vanished. This type may be confusing since it can be mistaken to resemble other chronic infectious conditions. Relapse is characterized by symptoms including recurrent fevers, fatigues, and pain in the joints that somewhat mimic the acute presentation but are less intense (Patra et al., 2018;, Roushan et al., 2016). The nature of the disease being relapsing highlights the relevance of proper treatment and surveillance. Incomplete treatment results in lingering infection followed by relapses (Stumpner et al., 2023). Brucellosis is a zoonotic infection caused by the species Brucella, which leads to various diagnostic challenges

Eman Fahad Alsehli, Yousra Khudran Alzahrani, Manal Ali Alsharif, Fares Hussain Fares Alsharif, Bandar Saleem Saeed Alsaedi, Majed Mohammed Alharbi, Ibrahim Ghalib Mohammed Alharbi, Mamdouh Mathhan Alrashidi, Eman Mohsen Nahhas, Nemat Nourullah Enaam Aldeen, Majed Badr Al-Mutairi, Omar Hamed Alsalemi, Najla Qabl Ayed Almutairi, Abdulnasser Ayed Alrashedi, Abdulla Matar Alsehli due to varied clinical presentations and because there are not many diagnostic approaches to the condition. Three key diagnostic methods for brucellosis include serologic testing, polymerase chain reaction (PCR), and culturing, with each having certain limitations.

Serological testing remains the most common and essential initial approach for diagnosis in brucellosis. The Rose Bengal test, or RBT, is a readily available rapid screening test that determines the presence of anti-Brucella antibodies. The reference method for serological diagnosis is the standard agglutination test, or SAT (Shome et al., 2017; Nenova et al., 2021). Other serological tests, such as ELISA, can distinguish between acute and chronic infections based on the presence of IgM and IgG antibodies (Shome et al., 2017; Sharififar et al., 2023). However, serological tests have poor sensitivity in the early stages of infection and may yield false-negative results due to cross-reactivity with other pathogens (Sharififar et al., 2023; Bozbaş et al., 2017). Serology is hence fundamental in screening, although it frequently needs confirmation by more definitive techniques.

PCR has become one of the most significant molecular diagnostic tools for brucellosis, showing greater sensitivity and specificity than traditional culture techniques. Several studies have found that PCR is able to detect Brucella DNA in different samples, including blood and milk, and sensitivities up to 90% have been reported (Gülbaz & Kamber, 2016; Mohammed et al., 2013). The rapidity of PCR results allows for timely diagnosis and treatment, which is particularly important given the potential complications of untreated brucellosis (Garshasbi et al., 2014; Islam et al., 2018). In addition, PCR in association with serological tests has been proposed to improve sensitivity, particularly when the serological results are negative or inconclusive (Mohammed, 2017; Bashiri et al., 2013). Culture remains the gold standard for diagnosing brucellosis since it facilitates the isolation of pathogens. However, it takes time and, in some cases, returns negative in a patient with prior antibiotic use or has chronic infection (Bozbas et al., 2017; Mohammed et al., 2013). Blood culture can be very specific, and sensitivity can vary widely; hence reported rates range between 17% to 85%, which again depends on the time frame of the disease and sample types (Bozbas et al., 2017). Therefore, even though it is very important to diagnose using culture, the diagnosis becomes more effective if accompanied by serological and molecular techniques.

10. Treatment Protocols for Brucellosis

Management is antibiotic therapy, and specific treatment regimens are recommended by WHO. The gold standard regimen is a combination of rifampicin and doxycycline for six weeks or streptomycin combined with doxycycline for two to three weeks (Hamdi & Ghalimah, 2019). Which antibiotic regimen to choose would be up to the clinical presentation of the disease and severity at presentation. For instance, a regimen of doxycycline and rifampicin, combined with an aminoglycoside, is recommended for the treatment of brucellosis with prosthetic devices for 8-12 weeks (Tsyba et al., 2018). However, even a combination of oral regimens is associated with failure of treatment and relapse: from 4.6% to 24% orally, which requires careful follow up and monitoring (Xu et al., 2021). Diagnostic challenges also face treatment since serological tests result in false negatives at the initial stages of infection (Sharififar et al., 2023). Practitioners

are therefore advised to repeat serological tests after a few weeks if initially negative to avoid delays in treatments that may cause complications. Additionally, clinical guidelines should be followed since deviation from them may result in mistreatment and poor patients' outcomes (Namuwonge, 2023).

11. Preventive measures against brucellosis

Preventive measures must be undertaken in the prevention of brucellosis spread, especially within endemic areas. Vaccination of livestock, especially adult sheep, is one strategy; however, the current rates of immunization are not at a level that would bring the disease prevalence under control (Gong et al., 2023). Moreover, rigorous animal husbandry practices, such as the elimination of seropositive animals and strict quarantine measures, are crucial in reducing the risk of transmission (Zhang et al., 2014). It has crucial preventive roles in public health education since most infections happen in communities that have contact with domestic animals (García-Juárez et al., 2012). Awareness on the handling of cattle safely and also vaccination among farmers and pastoralists can greatly help decrease disease transmission risk among brucellosis (Asakura et al., 2022). In addition, healthcare facilities should have better diagnostic capabilities for the early and accurate detection of cases that will be effectively managed and controlled (Bodenham et al., 2020).

Table 2: Clinical Presentations and Outcomes of Anthrax and Brucellosis

Disease	Forms	Clinical	Complications	Mortality	References
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Anthrax	Cutaneous	Black necrotic eschar, localized edema	Sepsis, compartment syndrome	<1% (with treatment)	Pillai et al., 2015; Demirdag et al., 2003
	Inhalational	Flu-like symptoms, respiratory distress, mediastinal hemorrhage	Shock, systemic infection	~80% (late diagnosis)	Greene et al., 2002; Pillai et al., 2015
	Gastrointest inal	Abdominal pain, bloody diarrhea, vomiting	Severe dehydration, septicemia	25-60% (without treatment)	Kanafani et al., 2003; Khariri et al., 2019
Brucellosis	Acute	Undulant fever, night sweats, arthralgia	Endocarditis, hepatosplenomegaly	<5% (if treated promptly)	Patra et al., 2018; Roushan et al., 2016
	Chronic	Persistent fatigue, arthritis, neurological symptoms	Spondylitis, sacroiliitis, chronic meningitis	Increased morbidity without treatment	Kaya et al., 2011; Kundu & Rath, 2019

Relapsing	Recurrent fever,	Long-term systemic	Higher risk	Stumpner et
	joint pain,	inflammation	with	al., 2023;
	weakness		incomplete	Malik et al.,
			treatment	2016

12. Other Zoonotic Bacterial Infections

12.1. Epidemiology and Transmission

Leptospirosis is one of the most common diseases in tropical and subtropical regions, which results from Leptospira spp. It is normally acquired through contact with infected water or soil, especially in cases involving agricultural activities (Sateia et al., 2017). The mode of transmission happens when people are in direct contact with infected animals or their excreta. Typical sources of infection for humans involve flooding and engaging in recreating activities in the water. Contrasted, the disease Yersinia pestis or the plague, is essentially spread from animal-infected organisms through insect bites of infected flea and direct physical contact. Besides this, direct inhalation of respiratory droplets may lead to transmission (Sateia et al., 2017). Plague is endemic in some parts of the globe, especially in Africa, Asia, and the Americas; the outbreaks are sporadic and associated with rodent infestations (Sateia et al., 2017).

The epidemiological profile of tularemia or Francisella tularensis is complex, and its mode of transmission occurs through ticks via bites, direct contact, and the inhalation of aerosolized droplets. Tularemia often presents in connection with wildlife like rabbits and rodents. Reemergence into new geographic areas is a known feature and has occurred recently in Austria and France (Seiwald et al., 2020; Chavanet et al., 2011). Q fever, which is mainly caused by Coxiella burnetii, is essentially transmitted through the inhalation of aerosols contaminated with infected livestock or their products (Rahravani et al., 2022). Epidemiology of Q fever differs from region to region and has been reported to be occurring in areas where livestock farming is practiced, emphasizing the importance of animal reservoirs in the transmission of disease (Rahravani et al., 2022; Monteiro et al., 2021).

12.2. Clinical Manifestations

Regarding clinical presentation, these diseases occur with symptoms that vary in presentation and make it challenging to establish a diagnosis. It primarily manifests by symptoms like flu with the onset of fever, chills, and myalgia and may rapidly evolve into a severe state of renal failure or complications from hemorrhaging (Sateia et al., 2017). There are three types of plague - bubonic, pneumonic, and septicemic and pneumonic has the worst outcomes with unrelenting death rates unless treated (Sateia et al., 2017). Tularemia has several clinical forms, including ulceroglandular, glandular, and typhoidal. Disease manifestations range from mild fever and lymphadenopathy to significant respiratory distress in pneumonic disease (Seiwald et al., 2020; Esmaeili et al., 2021). The typhoidal form of the disease can cause systemic illness with a presentation like typhoid fever and thus requires exact diagnosis and treatment (Nakamura et al., 2018; Maurin, 2024). Q fever often occurs in association with acute febrile illness, pneumonia,

or hepatitis, and subsequently may lead to chronic complications of disease such as endocarditis among predisposed subjects (Monteiro et al., 2021; Bayakhmetova, 2023).

Clinical manifestations and modes of transmission differ distinctly if compared to both anthrax and brucellosis, another pair of zoonoses. Anthrax, by Bacillus anthracis, may be cutaneous, inhalational, or gastrointestinal, and inhalational anthrax is especially deadly (Sateia et al., 2017). Brucellosis, caused by Brucella spp, usually has undulant fever, sweats, and arthralgia, which are often related to unpasteurized dairy products or direct contact with infected animals (Sateia et al., 2017). Both anthrax and brucellosis have epidemiologic features often linked with a specific occupational exposure farm-related or exposure to animal products; it is unlike the generalized environmental and wildlife exposures that leptospirosis, tularemia, and Q fever entail (Sateia et al., 2017).

12.3. Diagnosis and Surveillance

Advanced biosensors have been engineered as nano-biosensors to allow rapid zoonotic bacterial detection for quick intervention. Technologies, based on nanomaterials, allow such systems to operate sensitively and specifically enough for prompt identification of pathogens of concern for public health (Ahangari et al., 2022). This shift is toward even more effective methodologies in diagnosis, which can be made deployable to many varied settings, especially in the field, in which lab resources may be quite limited. Besides biosensors, techniques such as molecular biology in diagnosing pathogens can be included, like the Real-time PCR and the 16S ribosomal RNA polymerase chain reaction. These methods have high specificity and sensitivity for the detection of bacterial DNA. They are invaluable in the identification of pathogens such as Brucella canis and Capnocytophaga canimorsus, which are generally difficult to culture (Rasool, 2023; Lam et al., 2023). With direct detection from clinical samples, it saves a considerable amount of time in terms of reaching an actual diagnosis and improves the handling of zoonotic infections, especially in immunocompromised patients who are likely to have severe consequences (Lam et al., 2023).

On top of that, there are also epidemiological studies along with better diagnostic protocols, which have helped identify some of the emerging zoonotic pathogens. For example, the discovery of novel pathogens causing diseases such as lymphadenitis has been improved by the updated diagnostic strategies that involve both conventional culture methods and advanced molecular technologies (Oršolić, 2023). The combination of these methods does not only help identify previously known pathogens but also leads to the identification of novel zoonotic agents that expands our knowledge of the dynamics of zoonotic diseases. Another factor influencing diagnostic practices is the incorporation of One Health principles, which emphasize the interconnectedness of health among humans, animals, and the environment. This holism encourages multidisciplinary collaboration, increasing the strength of surveillance and control measurements of zoonotic disease (Overgaauw et al., 2020). With this reasoning, diagnostic methods are created with a perspective of being One Health, so that application is possible in veterinary and environmental settings alike.

Public health surveillance systems are crucial in tracking outbreaks of zoonotic bacterial diseases through a multi-faceted approach integrating data from the human, animal, and environmental

health sectors. This integration is necessary for early detection and effective response to zoonotic diseases, which are pathogens that can be transmitted between animals and humans. The "One Health" concept emphasizes the interrelatedness of these domains and calls for collaborative efforts among various disciplines, including epidemiology, microbiology, and veterinary science, to enhance surveillance capabilities and public health outcomes (Menon & George, 2021; Kobuszewska, 2024; Roess et al., 2018).

One of the main methods used in public health surveillance is syndromic surveillance, which enables the detection of unexpected diseases by using broader case definitions. The ability to detect emerging zoonoses is one of the prime qualities of such surveillance systems as exemplified by the incidental discovery of Rickettsialpox by a system designed to monitor anthrax cases in New York City (Vrbova et al., 2010). Systematic reviewing of surveillance systems for emerging zoonoses indicates that catching the different data points enhances rates and helps the response strategy (Vrbova et al., 2010; Halliday et al., 2012). Additionally, incorporation of wildlife monitoring into surveillance frameworks is necessary since wildlife often acts as reservoirs of zoonotic pathogens. In this regard, public health officials can monitor the status of wildlife populations for any signs of infection, hence gaining insights into potential spillover events that may cause human outbreaks (Ojeyinka, 2024).

Timely exchange of epidemiological data and laboratory results across sectors and geographic levels is also effective in zoonotic disease surveillance. This intersectoral partnership is important to determine and address disease threats early on before they become more complex public health issues (Menon & George, 2021; Elton et al., 2021; Martins et al., 2015). In other words, for example, absence of reportable zoonotic diseases in some areas will not allow early detection of diseases and their transmission from animals to humans without check (Allen, 2011). These include setting effective reporting systems across agencies and improving communication between agencies. Enhancing zoonotic disease surveillance in such aspects is not without the economic implications because a long-term investment, though pricey at first instance, will turn out to be more affordable when one looks at an overall cost-effectiveness within public health. By limiting the spread of zoonotic diseases in animals, public health systems prevent these pathogens from affecting humans; the consequence is a decreased human case load, leading to less expenditure on health and an improved community's overall health status (Elton et al., 2021; Martins et al., 2015). Even decision making within those areas lacking surveillance data may rely on prioritizing zoonoses by applying a tool known as the one health zoonotic disease prioritization tool by Rist et al., (2014).

12.4. Treatment and Management

Zoonotic bacterial infections become a very threatening public health issue which demands adequate antimicrobial therapy. Standard treatment algorithms of such infections usually involve the application of a wide spectrum of antibiotics that is strongly required in the management of various pathogens involved in zoonoses. Still, choosing this kind of therapy obliges the implementation of antimicrobial stewardship principles that would not increase the risks of antimicrobial resistance (Cantas & Süer, 2014; "Antimicrobial Resistance and Zoonotic Pathogens", 2023). Administration for the treatment of zoonotic bacterial infection comprises broad-spectrum antibiotics. Such includes classes, which include fluoroquinolones, beta-

lactams, aminoglycosides, and macrolides. Their efficacies are against a variety of microorganisms, including agents that cause infections such as those of Campylobacter, Salmonella, and Escherichia coli (Shin & Park, 2018; Karp et al., 2017). Ideally, such use of antibiotics should follow the process of culture and sensitivity tests for selection of therapy in an appropriately responsive mode toward the selected pathogen. This ensures effective therapy with minimal opportunities for development of resistance (Cantas & Süer, 2014; "Antimicrobial Resistance and Zoonotic Pathogens", 2023).

Apart from traditional antibiotics, the interest in alternative therapies such as antimicrobial peptides and bacteriocins is increasing, and they show promising activities against resistant strains of zoonotic bacteria. Such compounds may offer an adjunct approach to traditional antibiotics to possibly overcome some of the constraints posed by antibiotic resistance (Madhi et al., 2021). More research studies on nanotechnology-based innovative strategies are coming to light, including some that are applied to the targeted drug delivery mechanism. This may improve the performance of antimicrobial agents on zoonotic infections ("Innovative Strategies for the Control of Zoonotic Diseases by using Nanotechnology", 2023).

Another major step is that of preventive measures that also may come in terms of biosecurity interventions implemented at the farm level that will help in reducing the zoonotic bacteria transmitted from the livestock to human. They may help greatly reduce infections as a result of pathogen causations, such as that seen with C. burnetii, that are some of the notable zoonotic agents (Youssef et al., 2021). Thus, preventive and antimicrobial therapy must work in concert for effective control. Further, the rapidly increasing threat of AMR complicates the time horizon of treatment of zoonotic infections. It is in veterinary medicine and agriculture where antibiotics are misused and the emergence of AMR is attributed to, thereby challenging healthcare professionals to push for the responsible use of antibiotics ("Antimicrobial Resistance and Zoonotic Pathogens", 2023; "Zoonoses and AMR: Silent Spreader of Superbug Pandemic", 2023). Continuous surveillance and monitoring of antimicrobial resistance patterns are crucial to inform treatment decisions and develop appropriate public health strategies (Karp et al., 2017; Ma et al., 2021).

The use of AMR greatly complicates treatment for zoonotic diseases, or those diseases whose causes can be transmitted from animals to human beings. AMR greatly raises the chance of failure of treatment significantly for zoonotic pathogens, mainly through reducing the effectiveness of conventional antimicrobial treatments. The phenomenon has significant public health concerns in the contemporary setting as it reflects a relationship between human, animal, and environmental health-an interrelation oft described using the One Health approach. One direct implication of AMR in the context of zoonotic infections is reduced efficacy of commonly used antibiotics. For instance, the resistance of Campylobacter jejuni and Campylobacter coli to fluoroquinolones is extremely high in some member states; therefore, these agents could not be recommended anymore for empirical use in humans infected with disease-causing agents from poultry ("EU Summary Report on antimicrobial resistance in zoonotic and indicator bacteria from humans, animals and food in 2013", 2015). This is an example of direct transfer from the infections in the food animals to the treatment options and demonstrates a stressful position of

Eman Fahad Alsehli, Yousra Khudran Alzahrani, Manal Ali Alsharif, Fares Hussain Fares Alsharif, Bandar Saleem Saeed Alsaedi, Majed Mohammed Alharbi, Ibrahim Ghalib Mohammed Alharbi, Mamdouh Mathhan Alrashidi, Eman Mohsen Nahhas, Nemat Nourullah Enaam Aldeen, Majed Badr Al-Mutairi, Omar Hamed Alsalemi, Najla Qabl Ayed Almutairi, Abdulnasser Ayed Alrashedi, Abdulla Matar Alsehli keeping a close eye on such AMR while having alternative therapeutic approaches for its treatment.

Another kind of health threat from this zoonotic aspect emerges as MDR strains of zoonotic bacteria like *Escherichia coli* itself. These are the resistant strains, more especially Enterohemorrhagic which is usually located within pastoral communities and remains among the biggest causatives of diarrhea in human beings particularly those aged below two years, because children usually consume animal-source products without the due observation of hygiene during and after food preparation and cooking processes(Walusansa et al., 2019; Walusansa et al., 2020). The animal-source transmission to humans within food chains implies the crucial aspect of using combined surveillance as well as control systems with the purpose of minimizing further spread of AMR. Another important consideration is the function of companion animals in AMR spread. For example, there are certain species within the Staphylococcus intermedius group that are notorious pathogens of pets and have also been recognized as potential zoonotic agents harboring methicillin resistance (Edwards et al., 2019). The occurrence of such resistant bacteria in the bodies of companion animals adds treatment complexity and threatens transmission to humans, thereby escalating the AMR problem.

Further to this, there is the environmental aspect of AMR. The horizontal spread of resistant pathogens within the food chain and the environment continues to facilitate the persistence of AMR in many ecosystems, which have an equal impact on both wildlife and human health (George, 2019). This requires an integrated approach to fight AMR; hence, it should cross sectors to come up with strategies that will help the community in managing zoonotic diseases effectively (Robbiati, 2023; "One Health Approach: Combating Antimicrobial Resistance and Zoonotic Diseases in a Connected World", 2023).

12.5. Prevention and Control Strategies

Public health awareness is one of the critical preventive measures against zoonotic infections. Education programs geared towards high-risk groups will be efficient in reducing incidence rates of zoonotic diseases. For instance, a report showed that community attitudes and practices on animal birth products ought to change as they handle them in the wrong ways, hence boosting the mode of transmission for zoonotic agents (Alemayehu et al., 2021). Public health programs that promote hygiene and good practices in the handling of animals and animal products will be able to prevent some of the zoonoses from occurring (Wajed et al., 2021). The ecological conditions of zoonotic infection would be understood, where availability of rodents around man habitat increases the risk by means of companion animals, like Staphylococcus spp. (Amoah, 2023). In addition to education, biosecurity measures inhibit zoonotic diseases that include vaccination of livestock with typical zoonotic agents: brucellosis and tuberculosis.

Preventive measures of spillover of zoonotic via monitoring and controlling animal health are essential as it has proved that if "test and slaughter" is implemented, spillover of tuberculosis is reduced drastically (Abrantes et al., 2023). In addition, proper hygiene and sanitation in agricultural fields, for example, cleaning of animal dwellings and proper disposal of animal excreta significantly reduce the load of the bacteria in the environment ("Animal Ecology Enhances Farmers' Zoonotic Bacterial Occupational Diseases at High Altitude Area", 2021). The

other preventive measure is the one health approach, which recognizes interconnectivity between human, animal, and environmental health. This can help promote collaborations between veterinary medicine, public health, and environmental science approaches in integrated ways for the management of zoonotic risk (Cantas & Süer, 2014). For example, the awareness of how zoonotic pathogens spread from wild and domestic animals may be an opening avenue to improved management practices that have low possibilities of breaking out ("Zoonotic Diseases: Emerging Threats to Public Health and Livestock Production", 2023).

Conclusion

Anthrax and brucellosis are zoonotic bacterial infections characterized by severe damage to human, animal health, and the environment. An interdisciplinary approach should be used when managing them due to their profound links with socioeconomic determinants, agricultural practices, and environmental conditions. While there has been marked progress in diagnostic technologies and treatment regimens, the emergence of the challenge of antimicrobial resistance calls for careful stewardship and alternative therapies. Preventing the risks by means of vaccination of the livestock or enhanced hygiene and public education against the diseases turns out to be crucial. Even the robustness of the surveillance mechanism and integration of innovative diagnosis tools can enhance the capabilities of responding appropriately to challenges. Only global coordination involving relentless and cumulative input, drawing on scientific research, public health initiatives, and interventions that modify policy, will sufficiently control zoonotic infections from bacteria. A future without such infections, where in agriculture productivity and ecological stability coexist with the achievement of healthier living conditions.

Author contributions

All authors participated in the study for manuscript review, text editing, data collection, table and figure creating, and involved in the final approval for the manuscript submission to journal for publication.

Conflict of Interest

The authors declare they don't have any conflict of interest.

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