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REVIEW

Burkholderia pseudomallei: A Multifaceted Threat and the Path Forward in Treatment and Prevention

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Abstract: *Burkholderia pseudomallei*, a gram-negative facultative intracellular bacterium, is the causative agent of melioidosis, a life-threatening infectious disease endemic to tropical and subtropical regions, particularly Southeast Asia and Northern Australia. Key risk factors such as diabetes, alcoholism, and socioeconomic challenges were identified as major contributors to disease susceptibility and treatment outcomes in melioidosis. Globally, melioidosis accounts for approximately 89,000 deaths annually and poses a significant public health concern, particularly in resource-limited settings. *B. pseudomallei* exhibits remarkable environmental resilience, thrives in soil and water, and is intrinsically resistant to various antibiotics. Its pathogenicity is mediated by diverse virulence factors, including type III and VI secretion systems, a protective capsule, lipopolysaccharide (LPS), and BimA-mediated actin-based motility, which facilitate intracellular survival, immune evasion, and systemic dissemination. This bacterium can cause a wide spectrum of clinical manifestations ranging from localized skin infections to severe septicemia, pneumonia, and neurological involvement. In certain cases, *B. pseudomallei* may persist in a latent state for years and reactivation is often triggered by immunosuppression. The treatment of melioidosis is challenging because of its intrinsic antibiotic resistance, necessitating a two-phase approach: an intensive phase with intravenous antibiotics, such as ceftazidime or meropenem, followed by a prolonged eradication phase using trimethoprim-sulfamethoxazole. However, relapse remains a concern, particularly in patients with poor adherence to the therapy. Preventive strategies, particularly in endemic regions, focus on minimizing environmental exposure through protective measures and safe water practices. Despite advancements in therapeutic approaches, there is an urgent need for novel treatment strategies, including bacteriophage therapy and vaccine development, to enhance melioidosis prevention and control. Understanding the complex pathogenic mechanisms of *B. pseudomallei* is essential to improve its clinical management and reduce its global burden.

Keywords: melioidosis, *Burkholderia pseudomallei*, antibiotic resistance, antibiotic therapy, bacteriophage therapy, vaccine development

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Introduction

Burkholderia pseudomallei (*B. pseudomallei*) is a gram-negative bacterium found in the environment and the causative agent of melioidosis, a severe infectious disease responsible for approximately 89,000 deaths globally each year.[1] *B. pseudomallei* is a motile facultative anaerobic bacterium that is a potentially fatal infectious disease endemic to tropical and subtropical regions, particularly Southeast Asia and northern Australia.[2–4] It was first identified in 1911 by Alfred Whitmore and Krishnaswami in Myanmar. Originally referred to as Whitmore's disease, melioidosis received its current name in 1921 when Stanton and Fletcher introduced the term while working in the Federated Malay States.[5,6] The earliest documented human cases of melioidosis were subsequently reported in Sri Lanka in 1927, followed by Australia in 1950 and Thailand in 1955, marking its recognition as a significant infectious disease in various tropical regions.[5,6] Taxonomically, *B. pseudomallei* belongs to the *Burkholderia* genus.[7]

It is an environmental saprophyte that thrives in soil and water, and exhibits remarkable resilience and adaptability.[8] Its ability to persist under diverse environmental conditions, along with antibiotic resistance, poses significant challenges to public health and infection control. *B. pseudomallei* exhibits resistance to multiple antibiotics including penicillin, ampicillin, first- and second-generation cephalosporins, gentamicin, tobramycin, streptomycin, macrolides, and polymyxins.[1] This bacterium is of particular concern because of its potential for severe infections, high mortality rates, and the difficulties associated with its diagnosis and treatment.[9]

B. pseudomallei is a neglected tropical disease with a significant burden on many developing countries.[1] Its high level of intrinsic antibiotic resistance and need for prolonged treatment regimens make managing the infection particularly challenging.[10] These factors highlight the urgent need for innovative therapeutic approaches to enhance current treatment strategies. In this context, alternative options such as bacteriophage therapy are gaining attention because of their potential to target drug-resistant strains. Furthermore, given the limitations of the existing interventions, the development of an effective vaccine remains a critical goal. This review highlights the pressing need to explore novel treatment options and outlines key strategies to guide future vaccine development, emphasizing Burkholderia pseudomallei as a multifaceted threat due to its intrinsic resistance, diagnostic challenges, and diverse clinical manifestations, with the aim of improving clinical outcomes and reducing the global impact of melioidosis.

Microbiological Characteristics

B. pseudomallei belongs to the Burkholderiaceae family and shares phenotypic characteristics with its non-pathogenic relative *B. thailandensis*.[7,11] It is a rod-shaped, oxidase-positive, non-spore-forming organism capable of surviving under extreme conditions, including acidic and alkaline environments.[12,13] One of its unique characteristics is its ability to form biofilms, a critical survival strategy that enhances its persistence in both natural and clinical settings. Biofilm formation plays a key role in antibiotic resistance and chronic infections, making treatment more challenging.[14] Additionally, the bacterium can survive in nutrient-limited environments, further contributing to its persistence in the soil, water, and host tissues.[15]

Epidemiology and Geographic Distribution

Melioidosis is highly endemic in areas with heavy rainfall, particularly Thailand, Malaysia, Singapore, northern Australia, and parts of South America and Africa.[10] *B. pseudomallei* is primarily found in soil at depths of 10 cm or greater; however, during the rainy season, it can migrate from deeper layers to the surface, where it has the potential to proliferate.[8] The disease predominantly affects individuals exposed to contaminated soil or water, and transmission occurs via ingestion or percutaneous inoculation.[8] Transmission of *B. pseudomallei* from livestock to humans is exceptionally rare.[1,10]

Certain risk factors increase susceptibility to infection, including diabetes mellitus, chronic lung disease, chronic kidney disease, excessive alcohol consumption, and immunosuppression.[10,16,17] Because of its widespread presence in the environment and its potential for severe disease, *B. pseudomallei* is classified as a Tier 1 selective agent by the US Centers for Disease Control and Prevention (CDC), signifying its potential as a biothreatening pathogen.[18]

Melioidosis presents unique epidemiological and clinical challenges across different regions. In Southeast Asia, where the disease is endemic, environmental exposure plays a central role in transmission.[19] In contrast, the Middle East often reports imported cases due to the dynamic movement of migrant workers from endemic countries, particularly from South and Southeast Asia.[20] This distinction highlights the need for region-specific surveillance and diagnostic strategies. Additionally,

the clinical presentation of melioidosis can mimic several other infectious diseases, such as tuberculosis, pneumonia, or septicemia, making accurate diagnosis difficult.[1,21,22] This confounding nature contributes to underreporting and mismanagement, underscoring the urgent need for increased clinical awareness and improved diagnostic protocols globally.

Notably, melioidosis is a rare and often unfamiliar to both healthcare professionals and the general public in non-endemic areas like Saudi Arabia. A case report revealed that a case involving a 59-year-old Bangladeshi man with type 2 diabetes, who presented with pneumonia after returning from Bangladesh. He had experienced a three-week history of fever, cough, and shortness of breath. Initially, he was misdiagnosed and treated for pulmonary tuberculosis at another hospital. This case highlights the challenges in diagnosing melioidosis, especially in regions where awareness is low and the clinical presentation mimics other common conditions. Early recognition, particularly in patients with relevant travel history and risk factors like diabetes, is essential. Long-term antibiotic therapy and close outpatient monitoring are critical to prevent relapse.[23] Another study reported two imported cases of melioidosis involving individuals returning from endemic regions. The first case was a 26-year-old Saudi woman who developed fulminant sepsis shortly after returning from Thailand, while the second involved a 48-year-old woman with a prolonged history of fever. Blood cultures from both patients confirmed the presence of *B. pseudomallei*. These reports are significant, especially as *B. pseudomallei* has been classified by the Centers for Disease Control and Prevention (CDC) as a potential bioterrorism agent. Prior to these cases, no confirmed melioidosis infections had been documented in Saudi Arabia.[24]

Mode of Transmission

B. pseudomallei is an opportunistic environmental pathogen that infects humans and animals through multiple routes, including transmission when the bacterium enters the body through skin abrasions, cuts, or wounds after direct exposure to contaminated environments.[1,25] Respiratory exposure to contaminated dust or aerosols, particularly during extreme weather events, such as heavy storms, can lead to pulmonary melioidosis.[26] Although less common, the consumption of contaminated water or food may introduce bacteria into the gastrointestinal tract, leading to systemic infection.[27] Although rare, direct transmission through body fluids or congenital infections have been documented in isolated cases.[10] Hospital-acquired infections can occur because of exposure to contaminated medical equipment, fluids, or needles, although such instances are uncommon.[28,29] Notably, it has been reported that transmission of *B. pseudomallei* from a freshwater aquarium to a human. Given that many ornamental freshwater fish are imported from Southeast Asia, this discovery highlights a previously unrecognized route of infection that may carry important implications for the global aquarium trade.[30] Recently, *B. pseudomallei* was detected in a goat, indicating possible human–animal transmission. Phylogenetic analysis linked the strain to those found in local human cases. This potential zoonotic route emphasizes the importance of a One Health approach, with integrated surveillance, better diagnostic access, and greater awareness of animal infections.[31]

Virulence Factors of Burkholderia Pseudomallei

Several key virulence factors contribute to *B. pseudomallei* pathogenicity The capsule protects bacteria against complement-mediated lysis and phagocytosis, thereby aiding immune evasion.[32] The Type III Secretion System (T3SS) injects effector proteins such as BopA and BopC into host cells, facilitating bacterial invasion and survival.[1] The Type VI Secretion System (T6SS) is involved in bacterial competition and host cell invasion.[25] Lipopolysaccharide (LPS) enhances resistance to host immune defenses, further supporting the persistence.[33] BimA protein, which drives actin-based motility, enables intracellular movement and cell-to-cell spread.[1] Finally, the formation of multinucleated giant cells (MNGCs) aids bacterial persistence and immune evasion, allowing bacteria to remain hidden within the host.[7,34]

Pathogenesis of Burkholderia Pseudomallei

B. pseudomallei is a motile, opportunistic, facultative intracellular saprophyte that derives energy from organic matter decomposition. It contains an extensive range of virulence factors and is inherently resistant to multiple antimicrobial drugs.[25] Its high adaptability allows it to cause diverse clinical manifestations based on the site of infection while also ensuring its persistence in both hosts and the environment. The pathogenic mechanism of *B. pseudomallei* involves a complex interplay between host cell invasion, intracellular survival, and pathogenesis *B. pseudomallei* involves inhibition of iNOS production by enhancing the expression of two negative regulatory cytokines: suppressor of cytokine signalling 3 (SOCS3)

and cytokine-inducible SH2-containing protein (CIS). Additionally, the bacterium employs superoxide (O2−)-and hydrogen peroxide (H2O2)-degrading enzymes to counteract oxidative stress and enhance survival.[35–38] The cytotoxic effects of *B. pseudomallei* on specific cell types vary depending on the strain. While some strains induce macrophage apoptosis, others trigger pyroptosis, a caspase-1-dependent inflammatory form of cell lysis.[39,40] The ability of *B. pseudomallei* to spread between cells along nerve roots may account for melioidosis-associated encephalomyelitis, characterized by brainstem involvement following nasal or throat infection and myelitis (spinal cord inflammation) resulting from skin infection of the limbs.[41] *B. pseudomallei* can persist in a latent state for prolonged periods, with reactivation and development of melioidosis occurring in response to immunosuppression and other host stress factors. Documented cases have latency periods ranging from 19 years to 29 years.[42–44] Additionally, the host immune response and selective pressure exerted by antibiotics can promote the emergence of resistance patterns that support the persistence of the infection. Multiple genotypes have been observed within a single infection, partly because of the genetic adaptation to the human host. This includes the inactivation of virulence and immunogenic factors as well as the deletion of pathways essential for environmental survival.[45]

The bacterium exploits host actin filaments via the BimA protein, thereby enabling actin-based motility. This allows it to propel itself into neighboring cells, thus avoiding extracellular immune surveillance.[46] Additionally, it induces the formation of multinucleated giant cells (MNGCs), which facilitate bacterial persistence and spread within the host tissues.[47] The infection progresses as *B. pseudomallei* spreads through the bloodstream, leading to bacteraemia.[48] Systemic dissemination results in the formation of abscesses in multiple organs, including the lungs, liver, spleen, and brain.[49,50] If untreated, the infection can escalate to septic shock and multi-organ failure, significantly increasing the mortality risk.[51]

Clinical Manifestations of Melioidosis

Melioidosis presents with a wide range of symptoms that vary according to the route of infection and disease severity. The primary clinical forms include acute myeloidosis (the most common presentation), such as pulmonary infection with fever, cough, chest pain, pneumonia, and lung abscesses.[52,53] Septicemic melioidosis: high fever, hypotension, bacteremia, multi-organ failure, and high mortality rates.[54] However, chronic melioidosis is less common. In chronic melioidosis, the symptoms persist for months to years and may mimic tuberculosis. The common signs include recurrent fever, weight loss, lung nodules, and chronic abscess formation.[21] It can also cause localized infections such as skin ulcers, abscesses, localized swelling, and fever. This can occur after direct inoculation through wounds.[55] Neurological melioidosis may manifest as brain abscesses, encephalitis, convulsions, or impaired mental status.[56]

Diagnosis

The incubation period for acute melioidosis averages 9 days but can range from 1 d to 3 weeks, with more severe cases occurring after inhalation or aspiration of contaminated water. Disease severity and outcomes depend on risk factors, infection route, bacterial load, strain type, and specific *B. pseudomallei* virulence genes. The clinical presentation ranges from localized skin infections to fatal sepsis.[1,57] Melioidosis is significantly under-diagnosed on a global scale. Timely and precise identification of the disease is essential for successful treatment.[1,58] Although multiple diagnostic approaches exist, culture remains the definitive standard for the diagnosis of melioidosis. Although *B.pseudomallei* can grow on most routine laboratory media, it is often overlooked, mistaken for a contaminant, or misidentified as other bacteria (such as *Pseudomonas* spp.) unless laboratory personnel are trained to recognize its distinct characteristics.[59] Proper collection and submission of clinical samples to laboratories for the diagnosis of melioidosis is essential. Blood cultures are particularly important because of the high incidence of bacteremia. Additionally, culturing throat or rectal swabs can aid in detection.[60,61] Serological diagnosis of melioidosis remains challenging. Various assays have been developed to detect antibodies against *B. pseudomallei*, but many rely on poorly characterized antigens and lack international standardization or thorough validation. The most commonly used method is the indirect hemagglutination test, a simple assay for detecting antibodies against *B. pseudomallei*. However, in endemic regions, background seropositivity rates are often high, likely due to repeated exposure to *B. pseudomallei* or related organisms.[54] Multiple PCR assays with a high specificity for *B. pseudomallei* have been developed and evaluated in a limited number of clinical studies. Among these, the T3SS gene cluster is the most promising. However, the sensitivity of PCR in blood samples is influenced by bacterial concentration, which can affect detection accuracy.[62,63] CT scans and X-rays help to assess internal organ involvement.[1]

Treatment and Antibiotic Resistance

Early diagnosis and prompt *B. pseudomallei*-specific antibiotic therapy are vital for melioidosis treatment. In well-equipped settings, mortality is approximately 10%, but in resource-limited endemic regions, it exceeds 40% owing to delayed diagnosis and limited intensive care.[64] Most *B. pseudomallei* isolates from primary infections shared consistent antimicrobial susceptibility patterns. They respond to β-lactams like ceftazidime, meropenem, and co-amoxiclav, though their bactericidal effectiveness varies. Although doxycycline, chloramphenicol, and trimethoprim-sulfamethoxazole are generally effective, they are only bacteriostatic agents. Although piperacillin, ceftriaxone, and cefotaxime show in vitro activity, their clinical efficacy is limited.[65–67] *B. pseudomallei* exhibits resistance to penicillin, ampicillin, first- and second-generation cephalosporins, and aminoglycosides, such as gentamicin, tobramycin, and streptomycin. It is resistant to macrolides and polymyxins.[68] Surgical drainage is often required for isolated large abscesses such as those found in the liver, muscles, or prostate. However, it is typically unnecessary or impractical for multiple small abscesses affecting organs, such as the spleen, liver, or kidneys.[69] Since melioidosis is not a contagious disease, patient isolation or special precautions are generally unnecessary in endemic regions.[10,28,70]

Following the initial intensive phase of treatment, a prolonged course of oral antibiotics is essential to eliminate residual bacteria and prevent disease recurrence or relapse. Trimethoprim–sulfamethoxazole is considered the first-line choice for eradication therapy, whereas alternatives such as co-amoxiclav or doxycycline may be used when necessary.[1,7]

Extending the duration of the initial intensive therapy in patients with severe melioidosis has played a key role in reducing mortality rates in areas with advanced healthcare facilities.[1] A retrospective study following the Royal Darwin Hospital melioidosis treatment guidelines, which recommend the length of intravenous therapy based on disease severity, has demonstrated the benefits of this approach. In this study, critically ill patients received a median of approximately four weeks of intensive intravenous treatment, with a remarkably low relapse rate of only 1.2%. While poor adherence to eradication therapy remains a challenge, often due to patients skipping doses or discontinuing antibiotics after hospital discharge, a study suggested that prolonging the initial intensive phase of treatment significantly lowers the risk of relapse.[71,72]

Notably, *B. pseudomallei* has the ability to remain dormant in the body for extended periods, with reactivation occurring years later. One remarkable case involved a patient who presented with cutaneous melioidosis 62 years after being exposed during his time as a prisoner of war in Thailand, highlighting the bacterium's potential for long-term latency.[73] Recurrent melioidosis affects approximately 5% to 25% of patients and carries a mortality rate of around 25%. Due to its chronic nature, treatment typically involves an intensive phase of intravenous antibiotics—such as ceftazidime or meropenem, for 10 to 14 days, followed by an eradication phase using oral trimethoprim-sulfamethoxazole for 3 to 6 months. Ensuring patient adherence to this prolonged regimen is essential, as poor compliance has been identified as a key factor contributing to disease recurrence—the most serious complication of melioidosis.[18,74,75]

Prevention and Control Measures

Awareness of melioidosis among the general population in developing tropical regions remains low, and preventive measures are often overlooked or not consistently practiced.[76] In northern Australia, annual public health guidelines are provided, particularly for high-risk individuals, advising them to minimize direct contact with the soil and water at the beginning of the rainy season.[1] In Thailand, prevention guidelines for melioidosis advise residents, farmers, and visitors to use protective equipment such as boots and gloves when handling soil or water, consuming only bottled or boiled water, and limiting outdoor activities during heavy rains or dust storms.[77] In low- and middle-income countries, boiling water before drinking is recommended to prevent melioidosis. In high-income settings, UV light treatment can also be an effective method for disinfecting water contaminated with *B. pseudomallei*, particularly in households with individuals at higher risk.[78]

A recent modelling study suggests that melioidosis causes approximately 2,800 deaths annually in Thailand, with the highest burden concentrated in the northeastern region. Despite being endemic across the country, the disease remains under-recognized, partly due to limited awareness among rural populations and frequent misidentification of *B. pseudomallei* as a contaminant in microbiology laboratories. The Thailand Melioidosis Network, established in 2012, has collaborated with the Ministry of Public Health to reduce disease impact; however, incidence remains alarmingly high. Over 2,000 culture-confirmed cases are reported yearly from general hospitals with microbiology labs in Northeast Thailand, where the mortality

rate reaches around 35%. In 2015, when a single hospital independently reported 107 melioidosis-related deaths, dramatically increasing national figures. This discrepancy highlights that the currently reported cases are likely only a fraction of the true burden. Strengthening laboratory capacity, enhancing clinician-lab communication, and adopting accurate point-of-care diagnostics like lateral flow antigen detection assays are urgently needed.[79–81]

B. pseudomallei, accounts for a significant proportion of the global disease burden, with South Asia contributing approximately 44%. Within this region, Bangladesh and Sri Lanka are recognized as endemic zones, while sporadic cases have emerged from Nepal and a limited number of imported cases have been documented in Pakistan. In recent years, India has seen a noticeable rise in reported melioidosis cases. The bacterium resides naturally in soil and transmits to humans through breaks in the skin, inhalation of dust particles, or consumption of contaminated water. Unfortunately, due to its clinical resemblance to other tropical infections, melioidosis is frequently misdiagnosed or overlooked, resulting in delayed treatment. Compounding the issue, laboratory identification often confuses *B. pseudomallei* with *Pseudomonas* species, or dismisses it as a contaminant. Additionally, the low sensitivity of blood cultures contributes to underdiagnosis. This combination of clinical unfamiliarity and diagnostic challenges has led to a false perception that melioidosis is a rare condition. Preventive strategies should focus on minimizing exposure to contaminated soil, particularly in endemic regions, and ensuring access to safe and clean drinking water.[82,83]

Although India is recognized as an endemic region—particularly in its southern and eastern coastal areas—recent years have seen an emergence of sporadic cases in North Indian states such as Rajasthan and Gujarat. These reports underscore the presence of multiple risk factors in regions not previously considered endemic, including a high burden of diabetes, widespread alcohol use, and large rural populations involved in paddy farming. Additionally, the impact of climate change—particularly frequent flooding and waterlogging in urban areas—has increased human exposure to contaminated soil, potentially facilitating the spread of the bacterium. Given that melioidosis was historically unrecognized in northern India, it is critical to raise awareness among clinicians and microbiologists to improve early detection, appropriate testing, and timely treatment.[84]

Of note, the epidemiology of melioidosis is influenced by climate change, which alters patterns of human exposure to *B. pseudomallei*, the causative organism. It has been detected that environmental factors such as intense rainfall and sustained cloud cover correlate with the presence of *B. pseudomallei* in the soil and a rise in melioidosis cases, likely due to elevated soil moisture. A notable increase in infections has been reported following extreme weather events—such as typhoons in Taiwan and cyclones in Northern Australia—underscoring a strong link between melioidosis incidence and severe weather. Additionally, indirect consequences of such events, including water seepage and localized flooding, enhance the spread and human contact with the bacterium. In Western Australia, long-term surveillance revealed that melioidosis cases often occurred in areas impacted by tropical cyclones, with distinct *B. pseudomallei* genotypes identified, suggesting multiple sources of infection rather than airborne transmission from a single point Continued investigation into the environmental and geographic factors influencing the spread of *B. pseudomallei* will be critical in understanding and mitigating the effects of climate change on melioidosis epidemiology.[26] Another instance of potential import-related exposure was reported in a woman diagnosed with *B. pseudomallei* bacteremia. Upon investigation, three PCR-positive samples were collected from her freshwater home aquarium containing imported tropical fish. Whole-genome sequencing revealed a genetic match between the environmental samples and the patient's isolate, suggesting that the aquarium environment or imported fish may have served as the source of infection and highlighting a possible risk of melioidosis linked to imported aquatic products.[85]

Notably, it has been evaluated oral antibiotic prophylaxis against aerosolized *Burkholderia pseudomallei* in mice. Co-trimoxazole, doxycycline, and amoxicillin/clavulanic acid were tested as pre- and post-exposure treatments. Co-trimoxazole showed 100% protection when given before or within 24 hours post-infection, while doxycycline was moderately effective. Amoxicillin/clavulanic acid was least effective. Findings highlight co-trimoxazole's potential for managing laboratory exposure or bioterrorism-related melioidosis.[86] On the other hand, it has been assessed the monoclonal antibody Ps6F6 targeting the bacterium's exopolysaccharide in mice. Pre-infection treatment with Ps6F6 improved survival and reduced spleen bacterial load over 30 days. Ps6F6 modulated cytokine responses, showing a brief IFN-γ spike and minor IL-12 increase, with no IL-10 and reduced TNF-α. While Ps6F6 offered partial protection, it did not achieve sterilizing immunity.[87]

In many low- and middle-income countries where melioidosis is endemic, prevention efforts must go beyond clinical interventions to consider the broader socioeconomic context. The high cost of prolonged antibiotic therapy often places a significant financial burden on patients, leading to treatment discontinuation and poorer health outcomes. These economic challenges underscore the importance of integrating affordability and universal health coverage into national infection control strategies. Strengthening public health systems, ensuring access to cost-effective antibiotics, and expanding community-level education are all essential components in preventing disease recurrence and improving adherence to treatment. A comprehensive approach that includes financial risk protection and health system support is vital to ensure equitable access to both existing therapies and any future treatment innovations. Additionally, Prevention efforts in low-resource settings should prioritize raising awareness, improving access to diagnostics and treatment, and addressing environmental exposure risks. Official recognition and targeted support could significantly reduce the impact of melioidosis in these vulnerable communities.[82,88–90]

Effective prevention of melioidosis requires a comprehensive approach involving both community engagement and government support. Such strategies are currently being evaluated in ongoing studies in northeast Thailand.[1] Post-exposure prophylaxis is advised after high-risk laboratory exposure to *B. pseudomallei*, involving a 21-day course of trimethoprim-sulfamethoxazole, or alternatives like doxycycline or co-amoxiclav if needed.[91]

Future Direction

B. pseudomallei, the causative agent of melioidosis, poses significant treatment challenges due to antibiotic resistance and prolonged therapy duration, prompting interest in finding new approaches to address this issue, including phage therapy, combination therapy, and vaccines.

Combination Therapy

Recently, the efficacy of finafloxacin against *B. pseudomallei* was assessed in vitro and in vivo. In a BALB/c mouse model of inhalational melioidosis, finafloxacin, either alone or in conjunction with doxycycline, demonstrated superior bacterial control compared with doxycycline alone. When treatment was postponed to 36 h after infection, finafloxacin demonstrated enhanced survival. Overall, finafloxacin appears to be a promising treatment for *B. pseudomallei* infections.[92] Moreover, one study explored the synergistic effects of combining silver nanoparticles (AgNPs) with the conventional antibiotics ceftazidime, imipenem, meropenem, and gentamicinagainst three *B. pseudomallei* isolates. These combinations exhibited strong antibacterial activity, with the greatest enhancement observed for gentamicin with AgNPs. SEM analysis confirmed significant bacterial damage at bactericidal concentrations. These findings highlight antibiotic–AgNP combinations as a promising strategy for combating melioidosis.[93] A systematic review and network meta-analysis were conducted to evaluate treatments for severe melioidosis and eradication therapy. Patients treated with ceftazidime plus TMP-SMX had the lowest mortality rate. For eradication, TMP-SMX for 20 weeks was the most effective, with minimal recurrence and few adverse effects.[94] Another systematic review analyzed the use of co-trimoxazole in the eradication phase of melioidosis and evaluated its dosage, duration, combinations, efficacy, and safety. Data from 40 studies showed lower relapse and mortality rates with co-trimoxazole monotherapy than with combination therapy.[95] A case report showed that A 58-year-old female farmer with poorly controlled diabetes, metastatic breast cancer, and chemotherapy-induced pancytopenia showed no improvement with antibiotics alone. However, adding nivolumab as an adjunct therapy led to significant improvement, highlighting a potential new approach for refractory melioidosis.[96] A case study indicated that a 60-year-old male with hematogenous melioidosis septic arthritis of the hip was successfully treated with intravenous meropenem and oral trimethoprim-sulfamethoxazole. However, after prematurely stopping the treatment, the patient developed septic arthritis of the elbow. This was managed with surgical debridement and intensive antibiotics, followed by a six-month eradication phase. The patient recovered completely, highlighting the need for strict adherence to treatment to prevent relapse.[96]

A study reveals that the folate biosynthesis enzyme FolE2 is nonessential under normal conditions but is critical in the presence of subinhibitory trimethoprim. Screening identified ten FolE2 inhibitors, including DHL, which formed a lethal combination with trimethoprim. X-ray crystallography confirmed DHL's mechanism-based inhibition of DHL. This

combination outperforms Bactrim against *B. pseudomallei* while sparing beneficial gut bacteria and offering a targeted antimicrobial strategy.[97]

Notably, one study evaluated combinations of antibiotics and antimicrobial peptide (AMP) combinations against *B. mallei, B.pseudomallei, Yersinia pestis, Francisella tularensis*, and *Bacillus anthracis*. Checkerboard MIC assays showed that tetracycline-AMP combinations enhanced susceptibility in multiple strains, whereas novobiocin-AMP improved the sensitivity across all five strains. These findings highlight the potential of antibiotic-AMP combinations to combat biothreats, warranting further in vivo studies.[98] After screening 400 compounds from Pathogen Box, seven showed inhibitory effects, including auranofin, rifampicin, miltefosine, MMV688179, and MMV688271. Auranofin, MMV688179, and MMV688271 significantly reduced persister populations, suggesting their potential for repurposing as melioidosis treatments, and highlighting alternative therapeutics to combat *B. pseudomallei* persistence.[99] Recently, a study investigated the effects of fluoxetine (FLU) on *B. pseudomallei* planktonic and biofilm growth of B. pseudomallei. FLU exhibited MICs of 19.53–312.5 μg/mL, eradicated growing and mature biofilms at 19.53–312.5 μg/mL and 1250–2500 μg/mL, respectively, and enhanced the antibiofilm activity of antimicrobial drugs. These findings suggest FLU's potential in melioidosis treatment, warranting further research.[100] Recently, the role of extracellular DNA (eDNA) in *B. pseudomallei* biofilm resistance and its impact on antibiotic efficacy have been explored. DNase I combined with ceftazidime significantly inhibited biofilm formation and reduced viable biofilm cells by 3–4 logs. Confocal imaging confirmed the effectiveness of DNase I for biofilm disruption and enhanced ceftazidime activity. DNase I with chitosan-ceftazidime further eradicated planktonic and biofilm-forming cells. These findings highlight DNase I as a potential strategy for enhancing antibiotic susceptibility in biofilm-associated melioidosis infections.[101] LPC-233, a potent LpxC-targeting antibiotic, was evaluated for the treatment of *B. pseudomallei* infections in a murine aerosol exposure model. Oral and intraperitoneal administration of LPC-233 (≥30 mg/kg) significantly improved survival compared with that of the vehicle and outperformed ceftazidime. It also reversed infection-induced weight loss more rapidly, suggesting a faster action. However, similar tissue burdens across the treatment groups indicate the need for both intensive and prolonged therapy for complete bacterial clearance.[102]

Vaccine

Notably, one study explored a gold nanoparticle (AuNP)-based subunit vaccine to elicit both humoral and cell-mediated immunities. Immunization with AuNP-conjugated antigens, including OpcP and OpcP1 with LPS, provided significant protection, whereas a combined nanovaccine (AuNP-Combo2-LPS) provided complete protection. The vaccine induced a strong TH1-skewed immune response, promoting macrophage uptake and antigen-specific TH1-TH17 cytokine profiles. This approach offers a promising vaccine strategy against *B. pseudomallei* and a platform for enhancing the immune responses.[103] Another study explored subunit vaccines by using key protective antigens. A capsular polysaccharide (CPS) from *B. pseudomallei* was conjugated to CRM197 and Hcp1 and TssM proteins were purified. Immunization in mice induces strong IgG and T-cell responses. Notably, a combination of CPS-CRM197 and Hcp1 provided 100% survival against a lethal *B. pseudomallei* challenge, with 70% of survivors completely clearing the infection. These findings offer valuable insights into the development of an effective vaccine.[104]

Phage Therapy

One study investigated phage therapy using phage C34, which was isolated from seawater and categorized as a Myoviridae virus. Phage C34 lysed 39.5% of *B. pseudomallei* clinical strains and improved A549 cell survival from 22.8% to 41.6% when applied before infection. In a mouse model, phage treatment rescued 33.3% of infected mice and significantly reduced the bacterial load in the spleen. These results suggest that phage therapy is a promising approach against *B. pseudomallei* infections.[105] Another study demonstrated the clinical potential of a *B. pseudomallei* phage isolated from Hainan, China, which was capable of lysing 24/25 clinical isolates. Phage vB_BpP_HN01 improved A549 cell viability (up to 96.8%) and significantly reduced mortality (10%) and bacterial load. This study highlights vB_BpP_HN01 as a promising alternative for the treatment of melioidosis because of its strong lytic activity, stability, and protective efficacy.[106] In a study addressing phage specificity issues linked to O-antigen diversity, 145 phage samples from soil and water in Thailand were screened using two biosafe strains representing major serotypes. Ten phages

Table 1 Comprehensive Summary of the Different Strategies Explored for Combating B. Pseudomallei

Approach	Key Findings	Reference
Combination Therapy	• Finafloxacin combined with doxycycline showed better bacterial control and survival outcomes in murine models.	[68]
	• Silver nanoparticles (AgNPs) enhanced antibiotic efficacy, especially with gentamicin.	[93]
	• Ceftazidime + TMP-SMX had the lowest mortality rates for severe melioidosis therapy.	[96]
	• Nivolumab adjunct therapy improved refractory melioidosis cases.	[97]
	• FolE2 inhibitors (eg, DHL) enhanced trimethoprim efficacy.	[98]
	• Antibiotic + antimicrobial peptide (AMP) combinations improved susceptibility in *B. pseudomallei* and related biothreat pathogens.	[99]
	• Screening 400 compounds identified potential repurposed drugs, including auranofin and rifampicin.	
	• DNase I improved antibiotic efficacy against *B. pseudomallei* biofilms.	[101]
	• LPC-233, targeting LpxC, outperformed ceftazidime in murine models but required prolonged therapy.	[102]
Vaccine	• A gold nanoparticle-based subunit vaccine (AuNP-Combo2-LPS) provided complete protection and induced a strong immune response.	[103]
	• A subunit vaccine using CPS-CRM197 and Hcp1 achieved 100% survival and bacterial clearance in murine models.	[104]
Phage Therapy	• Phage C34 lysed 39.5% of *B. pseudomallei* strains and improved survival in A549 cells and mouse models.	[105]
	• Phage *vB_BpP_HN01* lysed 24/25 clinical isolates and significantly reduced bacterial load and mortality.	[106]
	• Screening 145 phages led to the isolation of ΦPK23V1, which infected 83.3% of *B. pseudomallei* strains despite O-antigen diversity.	[107]
	• Phage ΦBp-AMP1 infected all 11 tested *B. pseudomallei* strains and may serve as a therapeutic or diagnostic tool.	[108]

overcame O-antigen differences, leading to the isolation of 22 candidates. One adaptively mutated phage, ΦPK23V1, demonstrated broad infectivity, targeting 83.3% of *B. pseudomallei* strains across both serogroups. Although ΦPK23V1 is lysogenic and unsuitable for therapeutic use, this study provides valuable insights into *B. pseudomallei* phage-host interactions and the role of tail fiber genes in infection.[107] Gatedee et al showed that the bacteriophage ΦBp-AMP1, a Podoviridae family member with a ~45 Kb genome, was isolated from the environment and infected all 11 tested *B. pseudomallei* strains but not related species. Thus, it may serve as a potential tool for the treatment or diagnosis *B. pseudomallei* infections[108] (Table 1).

In addition to antimicrobial and vaccine-based strategies, exploring host-targeted therapies offers a promising complementary approach to managing melioidosis. By modulating the host immune response, such therapies can potentially enhance pathogen clearance and improve outcomes in severe or refractory cases.[109] For instance, a recent case reports diabetic cancer patient with disseminated melioidosis showed no response to antibiotics alone. However, the addition of nivolumab, an immune checkpoint inhibitor, led to marked improvement, highlighting its potential as an adjunct therapy for severe, treatment-resistant melioidosis.[110] Future research should further investigate immunomodulators, cytokine therapies, and strategies to strengthen host defenses, particularly in high-risk populations such as those with diabetes or immunosuppression.[112]

Conclusion

Addressing the global burden of melioidosis requires a multifaceted approach that includes enhanced diagnostic capabilities, effective antimicrobial therapies, and targeted preventive strategies. This review underscores the confounding clinical presentation of melioidosis, which often mimics other diseases, leading to misdiagnosis and delayed treatment—particularly in resource-limited settings. Significant research gaps remain, including the need for affordable, rapid diagnostics, understanding zoonotic transmission pathways, and the development of context-specific treatment protocols. Additionally, high treatment costs and limited access to prolonged antibiotic therapy pose challenges in endemic regions. Reinforcing these gaps and prioritizing the development of novel therapeutics and vaccines are crucial to improving patient outcomes and mitigating the global impact of this neglected tropical disease.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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