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REVIEW ARTICLE **OPEN ACCESS**

Host Immune Response to *B. pseudomallei* Infection: Insights for Therapeutic Strategies and Vaccine Development

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ABSTRACT
Melioidosis, caused by the Gram-negative bacterium Burkholderia pseudomallei, presents a formidable challenge to global health due to its wide clinical spectrum and intrinsic resistance to many antibiotics. Understanding the intricate interplay between the host immune response and B. pseudomallei infection is critical for developing effective therapeutic strategies and vaccines. This review provides insights into the host immune response mechanisms, encompassing both innate and adaptive immunity, as well as the strategies employed by B. pseudomallei to evade immune surveillance and establish chronic infections. B. pseudomallei employs several strategies to evade host immunity, such as intracellular survival within macrophages, biofilm formation to protect against immune attacks, and modulation of the host cell environment. These mechanisms pose significant challenges for treatment and vaccine development. Therapeutic strategies focus on enhancing phagocytosis, modulating the immune response, targeting intracellular bacteria, and developing anti-biofilm agents. Vaccines, including those targeting the capsular polysaccharide (CPS) and conserved surface proteins, as well as live attenuated vaccines, hold promise for preventing melioidosis. Adjuvants to boost vaccine immunogenicity and strategies for immunization optimization are also under investigation.This comprehensive review underscores the importance of understanding the host immune response to melioidosis for developing effective therapeutic interventions and vaccines. Collaborative efforts across disciplines, including microbiology, immunology, and clinical research, are crucial for advancing our ability to combat this challenging infectious disease.
Keywords: *Melioidosis, Burkholderia pseudomallei, innate immunity, adaptive immunity*

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INTRODUCTION

Melioidosis is an infectious disease caused by the bacterium *Burkholderia pseudomallei*. It primarily affects humans and a wide range of animals, particularly in Southeast Asia and Northern Australia. Burkholderia pseudomallei and B. mallei, which were used as biological weapons in World War I, have been categorised by the US Centres for Disease Control and Prevention (CDC) as tier 1 select agents due to their potential to pose a biothreat (tier 1 select agents present "the greatest risk of deliberate misuse with the most significant potential for mass casualties or devastating effect on the economy, critical infrastructure; or public confidence"). Concerns about a potential public health threat are further heightened by the lack of a vaccine for either at this time [46, 41]

Etiology:

Melioidosis is caused by the gram-negative bacterium *Burkholderia pseudomallei*. It is commonly found in soil and water in endemic regions. The bacterium can infect humans and animals through direct contact with contaminated soil or water, inhalation of contaminated dust or aerosols, or through skin inoculation via cuts or wounds. The bacterium has various virulence factors that enable it to evade immune surveillance and cause disease in susceptible individuals [46, 29]

Global Distribution:

Melioidosis is endemic in Southeast Asia and Northern Australia, particularly in countries such as Thailand, Malaysia, Singapore, Vietnam, and Northern Australia. However, sporadic cases have been

reported in other regions, including South Asia, Africa, the Middle East, and the Americas. The disease is more prevalent in rural areas where there is increased exposure to soil and water. [35,10]

Manifestations:

Melioidosis can manifest in various forms, ranging from localized skin infections to severe systemic disease. The symptoms can be diverse and nonspecific, often resembling other infections. The incubation period is typically 1-21 days, but it can be longer in some cases. Skin Abscesses are the most common form of localized melioidosis, presenting as painful, pus-filled sores on the skin. Melioidosis can also cause severe pneumonia with symptoms like fever, cough, chest pain, and difficulty breathing.

Burkholderia pseudomallei can enter the bloodstream and cause septicemia, leading to high fever, headache, body aches, joint pain, and confusion.The bacteria can also spread to various organs such as the liver, spleen, kidneys, and brain, resulting in abscess formation and organ dysfunction.In severe cases, melioidosis can spread throughout the body, leading to multi-organ failure and a high mortality rate.

In some instances, melioidosis can present as a chronic infection with intermittent symptoms that can persist for months or even years. This form of the disease is difficult to treat and may require prolonged antibiotic therapy.It's worth noting that melioidosis is more common in individuals with certain risk factors, such as diabetes, chronic kidney disease, or impaired immune function.Prompt diagnosis and appropriate antibiotic treatment are crucial for managing melioidosis. The choice of antibiotics may vary depending on the severity and presentation of the disease, and it often requires a prolonged course of treatment [25]

Epidemiology

The epidemiology of Melioidosis involves the study of the distribution, patterns, and determinants of the disease in populations.Melioidosis is primarily endemic in Southeast Asia and Northern Australia. The highest reported incidence is observed in countries such as Thailand, Malaysia, Singapore, Vietnam, and Laos. Northern Australia, particularly the Northern Territory and Queensland, also experiences a significant number of cases. However, sporadic cases have been reported in other regions, including South Asia, Africa, the Middle East, and the Americas.

The environmental reservoir of the causative bacterium, *Burkholderia pseudomallei*, plays a crucial role in the epidemiology of melioidosis. The bacterium is typically found in soil and surface water in endemic regions. Certain environmental conditions, such as heavy rainfall, high humidity, and monsoonal climates, are associated with increased transmission of the bacterium. [13, 31]

Occupational activities that involve exposure to soil and water increase the risk of acquiring melioidosis. Agricultural workers, rice farmers, construction workers, and military personnel deployed to endemic areas are at higher risk due to their increased exposure to contaminated environments.

Risk Factors:

Certain underlying conditions and risk factors can predispose individuals to melioidosis. Diabetes is a significant risk factor, and it is estimated that about 50% of melioidosis cases occur in individuals with diabetes. Patients with diabetes mellitus were three times more likely to develop melioidosis than patients with no diabetes. Renal impairment is associated with an increased risk of melioidosis. Individuals with chronic lung diseases such as chronic obstructive pulmonary disease (COPD) are at higher risk. Conditions such as HIV infection, cancer, and immunosuppressive therapy increase the susceptibility to melioidosis.

Melioidosis has been observed to exhibit seasonal patterns in certain endemic regions. In Northern Australia, cases tend to peak during the wet season, characterized by heavy rainfall and increased soil and water exposure [30,9]. It's important to note that the epidemiology of melioidosis is dynamic, and the distribution and incidence can change over time. Surveillance systems and improved diagnostic capabilities are essential for accurate monitoring and reporting of cases.

IMMUNE RESPONSE IN MELIOIDOSIS

INNATE IMMUNE RESPONSE

Early innate immune response has a vital role in identifying *Burkholderia pseudomallei*, the melioidosis-causing pathogen, and instigating an inflammatory reaction when it enters the body. The host innate immune response to B. pseudomallei, the causative agent of melioidosis, involves both pro- and anti-inflammatory responses that are dysregulated, allowing the bacteria to evade elimination. It was found that genes involved in immune response, stress response, cell cycle regulation, proteasomal degradation, cellular metabolism and signal transduction pathways were differentially regulated in mice with acute melioidosis [11]**.** While TLR2 and inflammatory responses were upregulated initially, cell death pathways were also activated, and the complement system was only activated after 24 hours, allowing uncontrolled bacterial spread. It was shown that *B. pseudomallei* inhibits NF-κB and IFN pathways through the virulence

factor TssM, suppressing the host inflammatory response [39]. The early innate response is characterized by production of pro-inflammatory cytokines like IL-18, as Wiersinga 2007 found IL-18 deficient mice were more susceptible to acute melioidosis. Genome-wide analysis of host responses during early infection in Chin 2010 revealed activation of inflammatory pathways and cell death mechanisms within 24 hours of infection, although these responses became suppressed by 42 hours, allowing uncontrolled bacterial growth. However, the complement system was not activated until 24 hours, suggesting a delay that may contribute to disease severity.

It was found that IL-18, which stimulates IFN-γ, was elevated in melioidosis patients and improved survival in mice, indicating its importance in host defense [45]. However, it was showed that IFN-mediated signaling, while dominant in the host responses to both melioidosis and TB, did not distinguish between these diseases [17]. Few researchers found dysregulation of TNF-α and IFN-γ in chronically infected mice across multiple *B. pseudomallei* strains, suggesting these could serve as biomarkers. [1]. [18] showed downregulation of immune response genes and epigenetic regulators in melioidosis patients compared to sepsis patients, which could also indicate disease and distinguish it from other infections.

Aschenbroich *et al*. (2016) summarized that *B. pseudomallei* and the related B. mallei modulate the innate immune system to evade intracellular killing, but the specific mechanisms remain unclear. A better understanding of how these pathogens dysregulate host immune responses could identify new vaccine and therapeutic targets.

Burkholderia pseudomallei, elicits a strong innate immune response in humans that helps determine the outcome of infection. Multiple studies have found that melioidosis patients and individuals with subclinical exposure to *B. pseudomallei* generate robust antibody[3,42,] and cell-mediated [16,4] immune responses to the pathogen. Specifically, melioidosis patients produce IgG, IgA and IgM antibodies against *B. pseudomallei* antigens throughout infection, with IgG1 and IgG2 being the predominant IgG subclasses [42]. Although all patients generate these antibodies, IgG and IgG1/IgG2 levels correlate well with clinical outcomes, suggesting they may be useful for monitoring infection status and treatment [42]. Individuals with subclinical melioidosis also mount strong cell-mediated responses, including lymphocyte proliferation and interferon-gamma production, which may protect against disease progression [4, 47]

Cytokines like interleukin-18 (IL-18) and tumor necrosis factor-alpha (TNF-α) are crucial components of the early innate response to B. pseudomallei. IL-18 levels are elevated in melioidosis patients and promote interferon-gamma production, which is essential for controlling infection [47]. Mice lacking IL-18 experience accelerated mortality and increased bacterial burdens upon *B. pseudomallei* challenge, indicating IL-18 is protective [47]. TNF-α is also upregulated in melioidosis, and dysregulation of TNF-α and interferon-gamma is a common host response across different *B. pseudomallei* strains [1]**.**

The innate response to melioidosis differs between diabetic and non-diabetic individuals. Diabetic patients rely more on antibodies and double-negative T cells for survival, whereas non-diabetic patients depend more on NK cells, CD8+ T cells and granzyme B [19]. IL-15, IL-18 and CX3CR1 are also linked to outcome in melioidosis, with excessive IL-15 and IL-18BP reducing survival, and CX3CR1 expression on lymphocytes improving survival [19].

In summary, the host innate immune response to melioidosis involves a mix of inflammatory and anti-inflammatory responses that are improperly regulated, allowing the bacteria to thrive intracellularly. Certain cytokines like IFN-γ and TNF-α, as well as other immune regulators, are dysregulated across multiple studies, suggesting they could serve as biomarkers or therapeutic targets. However, the specific mechanisms by which *B. pseudomallei* modulates the host immune response remain to be fully elucidated.

ADAPTIVE IMMUNE RESPONSE

The adaptive immune response to melioidosis, caused by the bacterium *Burkholderia pseudomallei*, involves both humoral and cell-mediated immunity. Several studies found that melioidosis patients and individuals exposed to *B. pseudomallei* develop antibodies against the bacterium, including IgG, IgA and IgM [42, 31]. IgG1 and IgG2 were the predominant IgG subclasses [42]. Although antibody levels were high in melioidosis patients, they did not always correlate with disease severity or outcome [42]

Cell-mediated immunity also plays an important role in the adaptive immune response to B. pseudomallei. T cells, especially CD4+ and CD8+ T cells, proliferate in response to *B. pseudomallei* antigens in melioidosis patients and exposed individuals [4,16,31]. This T cell proliferation was accompanied by production of interferon-gamma (IFN-γ), a key cytokine in the immune response to intracellular pathogens [4, 16]. Mice deficient in IFN-γ were more susceptible to *B. pseudomallei* infection, demonstrating its importance in controlling the infection**.**

IL-18, a cytokine that stimulates IFN-γ production, was also shown to be important in the immune response to *B. pseudomallei*. Plasma IL-18 levels and monocyte IL-18 mRNA levels were elevated in melioidosis patients [47]. Mice deficient in IL-18 were more susceptible to lethal *B. pseudomallei* infection, with higher bacterial burdens and more severe organ damage [47]. This indicates that IL-18 helps improve

the early antimicrobial host response in melioidosis.
The host immune response to the bacterial infection melioidosis, caused by *Burkholderia pseudomallei*, involves both innate and adaptive immunity. [16] found that patients who survived melioidosis developed cell-mediated immunity against B. pseudomallei, indicating an adaptive T cell response is important for protection. Supporting this, [4] found that individuals with subclinical melioidosis who did not develop disease had stronger T cell responses to *B. pseudomallei* compared to those with clinical melioidosis.
Both type 1 and type 2 interferon responses are elicited in melioidosis, according [17], who found interferon-mediated signalling dominated host responses to both melioidosis and tuberculosis. They also found an 86-gene signature thought to be specific for tuberculosis was also present in melioidosis patients, indicating some similarity in host responses. However, [18] found some differences in gene expression between melioidosis patients and those with sepsis from other causes. Certain immune response genes like IL8 and epigenetic regulators were downregulated in melioidosis patients compared to other sepsis patients, suggesting they could serve as diagnostic biomarkers.
In summary, the host adaptive immune response to melioidosis involves T cell activation and production of interferons, although the early innate response is also crucial for controlling infection. A delay in complement activation and suppression of some inflammatory responses may contribute to disease severity. Differences in gene expression profiles could help distinguish melioidosis from other causes of sepsis. A combination of innate and adaptive immune responses, as well as rapid diagnosis and treatment, are required for effective host defense against this potentially deadly disease.
So, both humoral and cell-mediated immunity are required to control *B. pseudomallei* infection. Antibodies, CD4+ and CD8+ T cells, IFN-γ, and IL-18 all contribute to the adaptive immune response in melioidosis. A deficiency or dysregulation in any of these imune components can lead to severe, life-threatening disease. Continued research on the immune response to *B. pseudomallei* may identify new prevention and treatment strategies for this neglected tropical disease.

IMMUNE EVASION MECHANISM

Melioidosis, caused by the bacterium *Burkholderia pseudomallei*, is a potentially fatal disease endemic to Southeast Asia and northern Australia. *B. pseudomallei* is adept at evading the host immune system through various mechanisms, allowing it to persist intracellularly and chronically infect its host.
Several studies found elevated levels of cytokines and other immune markers in melioidosis patients, indicating activation of the immune system. However, this immune activation is ineffective at clearing the infection. [3] and [16] found melioidosis patients demonstrate cell-mediated immune responses and lymphocyte proliferation against *B. pseudomallei* antigens. Yet, [3] found individuals with subclinical melioidosis actually had stronger cell-mediated responses, suggesting the immune system may play a role in determining disease outcome. Iliukhin (1980) found laboratory animals developed immunity against reinfection with *B. pseudomallei*, but golden hamsters showed no such response, indicating sensitivity to infection depends on individual immunity levels.
B. pseudomallei is adept at modulating the host immune response to its advantage. [47] found interleukin-18 (IL-18), a cytokine important for inducing interferon-gamma (IFN-γ) production, was elevated in melioidosis patients. However, IL-18 knockout mice were more susceptible to *B. pseudomallei* infection, suggesting IL-18 plays a protective role, and *B. pseudomallei* may suppress its effects. Brown (1991) found IFN-γ and soluble IL-2 receptors were elevated in melioidosis patients, indicating immune cell activation, but soluble CD8, a marker of cytotoxic T cell activation, was unchanged, suggesting *B. pseudomallei* may selectively activate certain immune pathways.
Aschenbroich (2016) proposes that *B. pseudomallei* exploits host immune signaling pathways to thrive intracellularly, evade killing, and establish chronic infection. A better understanding of how these pathogens manipulate the host immune system may reveal new vaccine targets to counter these effects and prevent melioidosis.
While the host immune system responds to *B. pseudomallei* infection, the pathogen is adept at selectively modulating the immune response to its advantage, allowing it to persist in the host and cause chronic or fatal disease. A vaccine that can counteract B. pseudomallei's immune evasion mechanisms may be key to preventing melioidosis.
B. pseudomallei expresses many proteins on the surface of infected erythrocytes that help the pathogen evade detection. For example, it was found that the *B. pseudomallei* protein RIFIN binds to inhibitory receptors on immune cells, suppressing their activation. Additionally, *B. pseudomallei* flagellin proteins trigger host pathogen recognition receptors like TLR5 and NLRC4, but the pathogen has developed ways to avoid the immune responses activated by these receptors. [44] showed that while TLR5 and NLRC4 help control *B. pseudomallei* infection in the lungs, mice deficient in both receptors were not more susceptible, indicating the pathogen can evade each individual receptor.

B. pseudomallei also directly inhibits immune responses. For instance, [37] reviewed how *B. pseudomallei* secretes factors that manipulate host cell processes and disable parts of the immune system. Specifically, *B. pseudomallei* uses a type III secretion system to inject effector proteins into host cells that suppress phagocytosis and the production of reactive oxygen species. The pathogen also interferes with antigen presentation to avoid detection by T cells.

However, the host is still able to mount some immune responses against B. pseudomallei. [18] found that melioidosis patients had different expression of certain immune response genes compared to patients with other infections, indicating the host can recognize *B. pseudomallei* as a distinct pathogen. A study also showed that guinea pigs and mice developed immunity against *B. pseudomallei* after infection, exhibiting signs of allergic responses, antibody production, and increased phagocytosis. Still, golden hamsters remained highly susceptible, highlighting how *B. pseudomallei* potently evades immunity in some hosts.

In summary, *B. pseudomallei* has developed mechanisms to evade host immunity by expressing surface proteins that inhibit immune cells, secreting effectors that suppress immune responses, and interfering with antigen presentation. However, some hosts are still able to mount adaptive immune responses against B. pseudomallei, though susceptibility varies significantly between host species. A greater understanding of how *B. pseudomallei* so effectively evades and suppresses the host immune system may help identify new therapeutic targets for this deadly disease.

CURRENT APPROACHES FOR THERAPEUTICS AND VACCINE

ANTIBIOTIC TREATMENT STRATEGIES

Melioidosis, caused by the bacterium *Burkholderia pseudomallei*, is a life-threatening disease endemic to tropical regions that requires intensive treatment. The primary therapeutic strategy involves an initial acute phase of intravenous antibiotics, typically ceftazidime or meropenem, followed by an eradication phase of oral antibiotics for up to 20 weeks [12]**.** The conventional oral regimen includes a combination of chloramphenicol, doxycycline and trimethoprim-sulfamethoxazole [8], though doxycycline alone may be insufficient [8].

Amoxicillin-clavulanic acid shows promise as an alternative oral option and was found to be effective for 67% of patients in one study [38]. The beta-lactam imipenem may be comparable to ceftazidime for acute severe melioidosis [36]. The ideal treatment strategy remains unclear, though, and melioidosis continues to have a high mortality rate, in part due to the bacteria's intrinsic antibiotic resistance**.**

Researchers propose investigating repurposed drugs that target the immune response to melioidosis, such as those that balance cytokines or inhibit virulence factors [21]. *B. pseudomallei* is able to manipulate the host immune system, replicate intracellularly, and form biofilms, so drugs affecting these mechanisms could provide new treatment options [21]. With increasing antibiotic resistance, alternative strategies are urgently needed.

.The current standard of care involves an initial acute phase of intravenous antibiotics, typically ceftazidime or imipenem, for at least 10-14 days to prevent death from overwhelming sepsis [36,12]. This is followed by an eradication phase of 3-6 months of oral antibiotics, usually trimethoprim-sulfamethoxazole, to eliminate any remaining bacteria and prevent relapse [12]. While this treatment can be effective, melioidosis has a high mortality rate and the long duration of antibiotics poses challenges.

Newer treatment strategies aim to improve outcomes by shortening treatment, reducing toxicity, and increasing affordability and access. Amoxicillin-clavulanic acid has been proposed as an alternative oral regimen that is safer, cheaper, and may allow for shorter treatment, though optimal dosing is still unknown [38]. Other approaches target the pathogenesis of the disease, such as blocking virulence mechanisms or modulating the immune response to reduce inflammation. For example, Laws 2019 proposes adjunctive immunomodulatory therapies to rebalance the cytokine response in melioidosis.

The increasing availability of *B. pseudomallei* genome sequences has enabled new drug discovery efforts. [40] review strategies to develop new antibiotics as well as host-directed therapies for melioidosis and the related disease glanders. These include targeting bacterial type II and III secretion systems, quorum sensing, capsule and lipopolysaccharide synthesis, and host pathways such as caspases that are manipulated during infection. Monoclonal antibodies, such as those targeting capsular polysaccharide, are also being investigated.

In summary, the current recommended treatment for melioidosis involves prolonged intravenous and oral antibiotic regimens, typically with ceftazidime, meropenem, and doxycycline. However, treatment is difficult, mortality remains high, and better options are still needed. Repurposed immune-modulating drugs and alternative antibiotics show promise for improved therapeutic strategies. Overall, continued research is critical for combating this challenging disease.Alsowhile ceftazidime and trimethoprim-sulfamethoxazole remain the mainstay of melioidosis treatment, new therapeutic strategies aim to improve outcomes through shorter, safer, and more affordable regimens as well as novel host-directed

and pathogenesis-based therapies currently in preclinical development. Continued research and clinical trials are still needed to determine optimal treatment strategies and bring new lifesaving therapies into clinical practice, especially in resource-poor settings.

VACCINE DEVELOPMENT STRATEGY

There are several promising vaccine candidates for melioidosis currently in development. Multiple research groups are pursuing structure-based epitope design to identify immunogenic *B. pseudomallei* antigens for vaccine formulations [14]. A 2014 meeting of melioidosis experts recommended testing all available epitopes in animal models and combining multiple epitopes onto a single scaffold to stimulate both arms of the immune system [23].

Live attenuated and subunit vaccines have shown promise in animal studies but have not yet demonstrated long-term survival after lethal challenge [27, 15]. An early Russian study found live attenuated *B. pseudomallei* strains provided statistically significant protection in moderately susceptible animals but not highly susceptible ones; a F. tularensis-based bivalent vaccine also showed promise.

A recent study found that a subunit vaccine combining *B. pseudomallei* capsular polysaccharide and recombinant proteins (CPS-CRM197 and AhpCC57G) stimulated high antibody and T cell responses and provided 70% survival in mice after high-dose inhalational challenge [33]. CPS-CRM197 alone also stimulated high anti-CPS antibody responses [5]. Another group found the proteins Hcp1 and TssM stimulated robust T cell responses and, when combined with CPS-CRM197, provided 100% survival and sterilizing immunity in mice after inhalational challenge [5].

A cost-effectiveness analysis found melioidosis vaccines could be cost-effective, especially in high-risk groups like diabetics, even with only partial immunity [28]. Diabetic and respiratory challenge models will be key to evaluating melioidosis vaccine candidates, as these reflect common routes of natural infection [28].

The development of an effective vaccine against melioidosis has been an ongoing challenge, but recent progress provides hope. Multiple vaccine strategies have been explored, including live attenuated, whole cell killed, subunit, plasmid DNA, and dendritic cell vaccines [28,43]. Live attenuated vaccines, while the most immunogenic in animal models, are unlikely to be suitable for humans due to safety concerns [32]. Killed and subunit vaccines have shown promise and continue to be refined [28, 43]

A cost-benefit analysis found that even a partially effective vaccine could be cost-effective, especially if targeted at high-risk groups like diabetics in endemic areas [28]. The ideal vaccine would provide both humoral and cell-mediated immunity, as melioidosis can be acquired through multiple routes of exposure [28]. While vaccine research has largely focused on biodefense, vaccines could have significant public health impact in highly endemic areas like Thailand and northern Australia [28,24]

Multiple studies have evaluated vaccine candidates in mouse models, but few have used models that accurately reflect natural infection in humans, including diabetic or inhalational models [28]. Heterologous vaccines, like one using Francisella tularensis, have shown promise, as have certain attenuated *B. pseudomallei* mutants, but more research is needed, especially in models that better reflect human disease [24]. Ongoing research continues to identify new potential antigens for subunit vaccines.

Classification of melioidosis into distinct clinical categories will help in evaluating new treatments and vaccine efficacy [22]. Recent discoveries about B. pseudomallei's mechanisms of virulence and intracellular survival may aid in developing new therapies and vaccines [22]. New selective media and molecular techniques improve diagnosis and distinguish *B. pseudomallei* from near neighbours [22].

Table 1. Various reported vaccines developed to regulate the *B. pseudomallei* infection.

Vaccine Type	Antigens	Response	Reference
Nanoparticle based vaccines	The B. pseudomallei-derived OMVs (M9 OMVs) include proteins linked to intracellular survival but are not harmful to live cells.	Mice that have been immunised show high resistance to lung infection, comparable to that seen with a live attenuated vaccine, and this resistance is accompanied by an increase in IgG, CD4+, and CD8+ T cells.	[2]
Nanoglycoconjugate Vaccines	The lipopolysaccharide (LPS) from *Burkholderia thailandensis* served as an additional antigen and was	This sophisticated multicomponent glycoconjugate vaccine formulation can protect	[40]

	covalently linked to several nanoglycoconjugates using predicted immunogenic protein candidates, Hcp1, FlgL, OpcP, OpcP1, OmpW, and hemagglutinin.	against deadly *B. pseudomallei* infection by inducing both humoral and cell-mediated responses.	
Nanoglycoconjugate Vaccines	Hcp1 was joined to lipopolysaccharide (LPS), and two more new proteins were added to the surface of a gold nanoparticle (AuNP).	Animals given AuNP glycoconjugate vaccinations produced significant antibody titers against specific proteins and polysaccharides. Importantly, following a fatal challenge with B. pseudomallei, immunised rats receiving the AuNP-FlgL-LPS alone or in combination showed up to 100% survival and decreased lung colonisation.	[26]
Manno-HeptopyranoseHexasaccharide Glycoconjugate	The innocuous Hc domain of the tetanus toxin was connected to the homopolymer of unbranched 1- 3 linked 2-O-acetyl-6-deoxy-d-manno-heptopyranose that was created.	Developed natural capsule-specific IgM and IgG responses and were resistant to infection by *B. pseudomallei* strain K96243 at concentrations more than 120 LD50.	[34]
Glycoconjugated vaccines	CPS-CRM197 was created by covalently attaching the 6-deoxyheptan capsular polysaccharide (CPS) from *B. pseudomallei* to the recombinant CRM197 diphtheria toxin mutant (CRM197).	High-titer IgG and opsonizing antibody responses were obtained after immunising against CPS-CRM197.	[5]
Vectored	Alternative subcellular targeting flagellin DNA vaccines	Compared to the empty vector, C57BL/6 vaccine-treated mice demonstrated a 10-fold reduction in bacterial burdens in the lungs and other distant organs.	[20]
Bacterial subunits	Combination of BPSL2765, a protein known to trigger immunological responses, and three genes from E. coli, BPSL1897, BPSL3369, and BPSL2287.	Mice that were immunised with the combination of the chronic stage antigens displayed improved protection against experimental disease in mice as compared to animals who were only immunised with capsular polysaccharide or LolC protein.	[7]

In summary, while no licensed vaccine yet exists, multiple promising strategies are being explored. Continued research into virulence mechanisms, clinical classification, and new treatments will all support vaccine development. Melioidosis vaccine research is an active area, with multiple promising subunit candidates in development. Future work should focus on combining epitopes to stimulate both B and T cell responses, improving models to better reflect natural infection, and progressing candidates to clinical trials, especially in endemic areas where a vaccine could have substantial public health impact. Targeting high-risk groups in endemic areas could make even a partially effective vaccine cost-beneficial. The ideal vaccine will provide both humoral and cell-mediated immunity to this challenging disease.

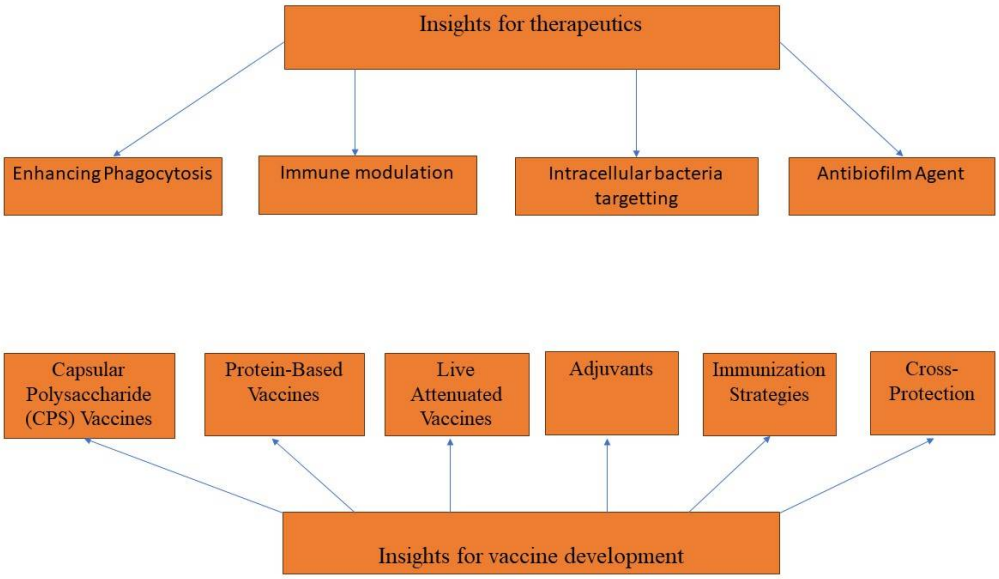

Fig 1: Insights for therapeutics and vaccines development

INSIGHTS FOR FUTURE

INSIGHTS FOR THERAPEUTICS

1. Enhancing Phagocytosis: Developing therapies or drugs that boost the phagocytic activity of macrophages and neutrophils can be beneficial in early infection control.
2. Immune Modulation: Modulating the host immune response to improve its effectiveness in clearing the infection is an active area of research. This includes enhancing T-cell responses and cytokine production.
3. Intracellular Bacteria Targeting: Identifying and developing drugs that can specifically target and kill intracellular *B. pseudomallei* can be effective against chronic infections.
4. Anti-Biofilm Agents: Research into compounds that disrupt the biofilms formed by *B. pseudomallei* can improve antibiotic penetration and treatment efficacy.

INSIGHTS FOR VACCINE DEVELOPMENT

1. Capsular Polysaccharide (CPS) Vaccines: Developing vaccines targeting the CPS, while addressing antigenic variation, is a potential approach to providing protection against melioidosis.
2. Protein-Based Vaccines: Identifying and characterizing conserved surface proteins for vaccine development is a promising strategy.
3. Live Attenuated Vaccines: Developing live attenuated vaccines that are safe for use in humans and provide protection against *B. pseudomallei* is an ongoing area of research.
4. Adjuvants: Investigating adjuvants that can enhance the immune response to vaccines is crucial for vaccine development.
5. Immunization Strategies: Determining the appropriate vaccination schedule and target populations for vaccines is important for disease prevention.
6. Cross-Protection: Research on whether immunity to closely related Burkholderia species can provide cross-protection against *B. pseudomallei* is ongoing.

In conclusion, comprehending the host immune response to melioidosis is essential for developing therapeutic strategies and vaccines. These approaches must consider the complexity of the disease, including B. pseudomallei's ability to evade the immune system, its intracellular survival mechanisms, and the formation of biofilms. Collaboration among researchers, healthcare professionals, and policymakers is crucial for addressing the challenges posed by melioidosis.

Conflict of Interest

There is no conflict of interest

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