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Melioidosis Vaccines: Recent Advances and Future Directions

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Abstract

Melioidosis, caused by *Burkholderia pseudomallei*, poses a significant public health threat with mortality rates of 10-50% despite treatment. The pathogen's intrinsic antibiotic resistance, complex clinical presentations leading to delayed diagnosis, and potential as a bioterrorism agent underscore the critical need for an effective vaccine. Multiple vaccine platforms have been explored with varying success. Live-attenuated vaccines demonstrate robust immunogenicity but face safety challenges due to inherent pathogen virulence. DNA vaccines offer safety advantages and generate both humoral and cellular responses, though human immunogenicity remains suboptimal. Subunit vaccines provide enhanced safety profiles but require sophisticated adjuvants for adequate immune stimulation. Nanoparticle-based platforms have emerged as promising delivery systems enabling targeted antigen presentation and controlled release. Heterologous prime-boost strategies using sequential different platforms show potential for generating more robust immune responses. Key challenges impeding vaccine development include complex antigenic diversity across geographical strains, lack of established immune correlates of protection, limited understanding of natural immunity, absence of validated animal models, and complex regulatory pathways for biodefense-related vaccines. Future efforts must address these challenges through innovative approaches including structure-based antigen design, systems biology for optimal antigen combinations, development of predictive animal models, and establishment of immune correlates. Success requires sustained international collaboration and commitment to address this neglected tropical disease threatening global health security.

Keywords: *Burkholderia pseudomallei*, DNA vaccines, heterologous vaccination, live-attenuated vaccines, melioidosis, nanoparticle vaccines, subunit vaccines

1. Introduction

Melioidosis has become a global problem. It is caused by the environmental bacterium *Burkholderia pseudomallei*, which is mainly found in the soil and water of tropical and sub-tropical regions of the world[1,2]. In Southeast Asia and northern Australia, where *B. pseudomallei* is commonly found in the environment, melioidosis became highly endemic[1]. Persons with diabetes, chronic kidney disease (CKD), excessive alcohol consumption, those on corticosteroids, and other immunosuppressive therapies may have a high risk of developing melioidosis upon exposure to *B. pseudomallei*. This pathogen has an incubation period ranging from 1-21 days, with an average of 9 days[3,4]. To prevent relapse, melioidosis requires prolonged antibiotic therapy. The mortality rate remains high in some areas[2]. Based on the current situation, there is an urgent need for a melioidosis vaccine.

2. Epidemiology

Based on recent studies, *B. pseudomallei* is widely present in many countries of tropical regions, but mostly found in soil and surface water in Southeast Asia and northern Australia[4]. Melioidosis is not considered a contagious disease because person-to-person transmission is rare.

3. Why a Vaccine is Needed

3.1. High Burden of Disease

Many reports have suggested that highest incidence of melioidosis occurs in the Asia-Pacific region, as well as in other tropical countries. Rural populations and those who are in low socioeconomic groups, including agricultural workers in Asia, are at high risk of contracting melioidosis. Heavy rainfall and severe weather conditions are other factors for the increased burden of melioidosis[2].

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3.2. Treatment Difficulty

Studies have suggested that *B. pseudomallei* can become multi-drug resistant due to inappropriate use of antibiotics. Hence the need for a vaccine[5].

3.3. Biothreat Potential

The bioweapon potential of *B. pseudomallei* has been evaluated by both the US and the former USSR, though research is less extensive, compared to *B. mallei*. Due to its high mortality risk, it is designated a CDC Tier 1 Select Agent, challenging treatment even in non-endemic areas. Its property of environmental hardiness, ubiquitous distribution, and intrinsic antibiotic resistance make it an ideal bioweapon candidate[6].

4. Evolution of Vaccine Platforms: Key Advances and Emerging Trends

There are five major types of vaccines for melioidosis, which are depicted in Figure 1.

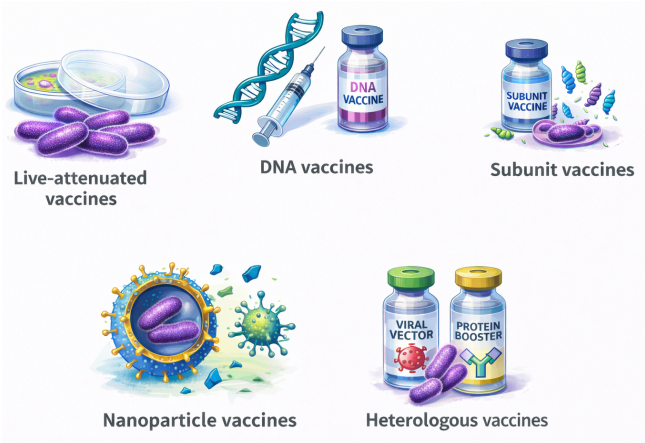

Figure 1: Melioidosis vaccines

4.1. Live-attenuated Vaccines (LAV)

A study showed that immunization of mice with live-attenuated *B. pseudomallei* mutants can induce a strong immune response, conferring long-lasting protection and is highly cost-effective in combating melioidosis[1]. Another study reported that LAV mutants can alter cellular metabolism and transport of biomolecules[7]. This study revealed that LAV faces many challenges against *B. pseudomallei*, including failure to demonstrate sterilizing immunity against chronic infections.

4.2. Heterologous Vaccines

Potential vaccine candidates using non-pathogenic strains are also being actively explored. A Russian study in guinea pigs showed that *Burkholderia thailandensis*, a species closely related to *B. pseudomallei*, gave approximately 50% protection against melioidosis. Another Russian study in mice reported that heterologous immunization against tularemia, plague, and salmonellosis conferred protection against melioidosis and extended survival time[5].

4.3. DNA Vaccines

DNA vaccines are another cost-effective strategy against melioidosis. These vaccines deliver genes encoding specific antigens, which subsequently stimulate cellular and humoral immune responses against pathogens. A recent study evaluated a plasmid DNA vaccine expressing *B. pseudomallei* flagellin (FliC). This DNA vaccine candidate was tested in mice, which showed that a single intranasal dose of pVAX-hTPA-FliC was more effective than dermal delivery. However, ultimately only 53% of mice receiving pVAX-hTPA-FliC survived. Further studies are needed to determine the optimal dose, route of delivery, and efficacy of DNA vaccines, as these are new for melioidosis[8].

4.4. Subunit Vaccines

Subunit vaccines are so-called because they use only a specific bacterial antigenic component (subunit). Subunit vaccines are currently being developed for melioidosis, instead of using live bacteria, as these vaccines have been found to be more promising than LAVs[8]. Since subunit vaccines only use a specific antigenic determinant of the bacterium, it is much safer and more targeted, compared to using the whole microbe that has been traditionally used. The duration of protection conferred by subunit vaccines may vary. For example, polysaccharide-based subunit vaccines confer short-lived protection in infants, whereas protein-subunit vaccines, such as tetanus and hepatitis B vaccines, provide long-lasting protection. A study in mice evaluated different types of subunit vaccines. The study showed that the lipopolysaccharide (LPS)-based vaccine conferred the highest protection. However, the LPS vaccine was not protective against all the strains, upon inhalation challenge[1].

4.5. Nanoparticle Vaccines

Recently, a melioidosis vaccine candidate has been developed using reverse vaccinology and gold nanoparticles. Three proteins (FlgL, hemagglutinin, Hcp1) were selected and combined with bacterial LPS to create gold nanoparticles (AuNPs). It was shown that the combination of the three proteins with LPS conferred 100% protection compared to 90% protection, when only the FlgL protein was used in the formulation[8]. Another melioidosis vaccine candidate has been developed using nanoparticles, biopolymers, and liposomes. This vaccine formulation incorporated a potent adjuvant that generated a robust immune response[7].

5. Key Challenges

Melioidosis remains a neglected yet formidable infectious disease, particularly across endemic regions of South, Southeast Asia, and northern Australia. Despite significant advances in the understanding of immunopathogenesis of *B. pseudomallei*, no licensed vaccine is currently available. Major challenges include difficulty in establishing immune correlates of protection, strain diversity, durability of immunity, and safety concerns in vulnerable populations.

6. Conclusion

Recent progress in subunit, live-attenuated, glycoconjugate, and other vaccine platforms have demonstrated encouraging preclinical efficacy, especially in eliciting balanced humoral and cellular immune responses that are essential for protection against this intracellular pathogen. Advances in antigen discovery, adjuvant systems, and delivery technologies have further strengthened rational vaccine design. Integrated efforts combining translational immunology, systems biology, standardized animal models, and multicentric clinical collaborations will be crucial. With sustained efforts, the development of a safe, effective, and accessible melioidosis vaccine will likely become a reality in the foreseeable future.

Disclosure

The AI tool, ChatGPT (free version) was used to create the image presented in Figure 1.

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