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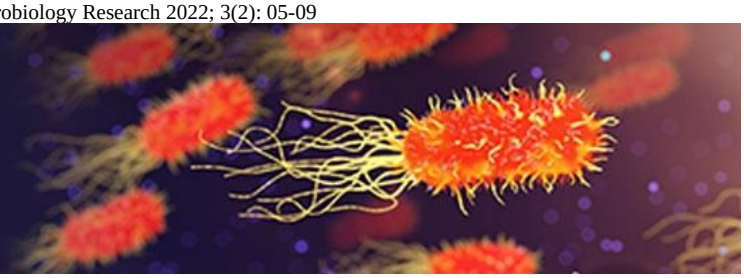

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Melioidosis: A life threatening tropical disease of public health significance

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Abstract
National and international public health agencies have been aware of a number of emerging and re-emerging zoonoses in recent years. These diseases are responsible of high morbidity as well as mortality both in humans and animals. *Burkholderia pseudomallei*, an environmental organism that is commonly found in the soil and water, is the cause of melioidosis. The disease mostly affects sheep, goats, and humans, with sporadic cases of infection in horses and subclinical disease in pigs. Southeast Asia, northern Australia, and the South Pacific are the regions with the highest prevalence of the disease, which is becoming endemic in tropical and subtropical regions of the world. Additionally, it is spreading to non-endemic regions. Currently, melioidosis is responsible to cause death of around 90,000 people annually. Transmission occurs through cutaneous abrasion and inhalation of contaminated dust. Humans contract the disease by soil-infected skin abrasions, contaminated drinking water or surface water, and aerosolization of these pathogens. Diabetes, renal failure, and alcoholism are the key risk factors of the disease. The disease has a wide range of acute and chronic local and systemic symptoms. The gold standard for diagnosing melioidosis is the isolation and identification of bacteria from the clinical specimens. Antibiotics, such as ceftazidime, imipenem, and meropenem are used to treat disease because of their broad spectrum of activity. Better coordination between veterinary and medical specialists, as well as general hygiene practices, are crucial for the prevention of this deadly infectious disease because there is now no vaccination available to immunize the susceptible population.

Keywords: *Burkholderia pseudomallei*, Life threatening, Melioidosis, Public health, Zoonosis

1. Introduction
Melioidosis, also known as Pseudo-malleus, Rodent glanders, Whitmore disease is a potential severe tropical disease that can affect both humans and animals, and is caused by *Burkholderia pseudomallei* (Pal, 2007; Kaestli *et al.*, 2007) [19, 22]. According to Inglis *et al.* (2004) [18] and Princess *et al.* (2017) [23], exposure to the contaminated soil or water is the cause of the infection. In areas where the disease is present, soil samples containing the bacterium are regularly isolated. The three most frequent modes of transmission are direct percutaneous abrasion, inhalation, and ingestion (Currie *et al.*, 2000; Pal, 2007) [11, 22].
Melioidosis is an infectious zoonotic disease reported mainly from the Asian countries (Pal, 2007) [22]. According to a recent survey released in 2016, South Asian nations are responsible for 44% of the world's melioidosis cases (Limmathurotsakul *et al.*, 2016) [21]. The epidemiology of disease is challenging because of the organism's environmental persistence, and there are significant differences in the organism's distribution in soil, how the disease manifests, and incidence rates among various places of endemicity (Roberta *et al.*, 2006) [25]. By using molecular typing to distinguish between strains, it is possible to understand the epidemiology of melioidosis. Due to pulsed field gel electrophoresis' great discriminative capacity, clonal relatedness has been the subject of multiple researches (Koonpaew *et al.*, 2008; Azura *et al.*, 2011) [20, 2].
There have been concerns that *B. pseudomallei* could be used as a biological weapon (Pal *et al.*, 2017) [22]. The CDC has identified melioidosis as a Category B potential bioterrorism agent. This may indicate that it is not too difficult to disseminate the agent. These substances are likewise linked to a low death rate and moderate morbidity. There will be a need for specific diagnostics in the event of an assault. The agent *Burkholderia pseudomallei* have a long half-life in the environment, lasting months. On the other side, heat can quickly kill it (CFSPH, 2016) [7].

The significance of melioidosis as an emerging and re-emerging bacterial zoonosis for public health concern is discussed in this article.

2. Etiology and Host Spectrum

The disease's causative agent, *Burkholderia pseudomallei*, is a small, gram-negative, oxidase-positive, motile, aerobic bacillus with sporadic polar flagella and bipolar "safety pin" pattern on staining (Dance, 1991) [13]. The organism has a diameter of 0.4 to 0.8 nano meter and may propel itself by means of its flagella. The bacteria may flourish in a variety of artificial nutritional conditions, particularly those that contain betaine and arginine (Haase *et al.*, 1997) [16]. The bacterium can enter and grow in phagocytic and epithelial cells. Type III (gene cluster Bsa, *Burkholderia* secretion apparatus) and type VI protein secretion systems, as well as a polysaccharide capsule, are some of the most important virulence factors (Galyov *et al.*, 2010) [15]. Sunlight has the ability to inactivate *B. pseudomallei*. It can be killed by dry heat of 160ºC-170ºC (320ºF-338ºF) for at least an hour or moist heat of 121ºC (249ºF) for at least 15 minutes (Rovid, 2016) [26]. *Burkholderia pseudomallei* can endure up to 8 weeks in water at room temperature, 7 months in muddy water, and 30 months in laboratory soil (Thomas *et al*., 1981) [29]. Humans, zoo animals, dogs, cats, horses, pigs, sheep, goats, alpacas, camels, rats, rabbits and pigeons are all susceptible to disease, although cattle are rarely affected (Bergin and Torenbeeck, 1991; Choy *et al.*, 2000;Pal, 2007) [3, 10, 22].

3. Transmission

It is believed that the infection is opportunistic and spreads more through the environment than it does from animal to animal (for example, through contaminated soil and surface waters). The most common methods of infection are inhalation, ingestion of soil, wound contamination, inoculation through the skin, and swallowing of infected corpses or soil. According to reports, transplacental infections in goats have caused abortions. It's probable that host-to-host sexual transmission and other types of transmission will occur (Merck, 2012) [28]. Because rodents have a long course of the disease and infected animals transmit the organism in their feces, rodents are significant reservoirs of infection (Radostitis *et al*., 2006) [24].

Human infections are typically spread through contact with contaminated soil or water by mucous membranes or non-intact skin. Additionally, infections have happened when people inhaled contaminated dust or water droplets, or when they aspirated or ingested contaminated water. Although transmission from one person to another is highly uncommon, it has happened in cases of sexual transmission and transmission from melioidosis patients to family caregivers. Vertical transmission from an infected mother to her newborn has also been shown to occur. Contaminated blood-drawing equipment has resulted in nosocomial transmission. Meat or milk consumption has been linked to infections in some cases (CFSPH, 2007; CDC, 2012) [6, 5]. On a few occasions, laboratory workers have been exposed via inhalation or percutaneous inoculation (Schlech 1981) [27]. Animal products like milk can get contaminated when an animal is infected, which can cause human diseases in humans who consume the contaminated milk (Limmathurotsakul *et al.*, 2012) [21].

4. Clinical Signs

4.1. In Humans

Depending on the inoculating dose, the mechanism of infection, and host risk factors, the incubation period for melioidosis can range between 1 and 21 days. Renal insufficiency, diabetes, and alcoholism are the main risk factors. Clinical manifestations of disease range from the localized cutaneous abscesses to extensive infection with septic shock and pneumonia in patients (UPMC, 2011) [30]. Single or many painful nodules or abscesses, lymphangitis, lymphadenopathy, a high temperature, and malaise are the symptoms of acute cutaneous melioidosis, which can quickly proceed to septicemia. In both acute and chronic types, there are abscesses that form in numerous organs, including the brain, lungs, pleura, peritoneum, liver, spleen, kidneys, prostate, bones, muscles, and skin (Currie *et al.*, 2010) [11].

4.2. In animals

Depending on the site of infection, signs within a species might range from acute to chronic. Possessing a subclinical infection is extremely common. Possible symptoms include fever, anorexia, or enlarging of the glands. Suppurative or caseous nodules or abscesses, which can appear in any organ tissue and have a variety of symptoms, may be related to an infection. Without any indication of an active infection at the site of the injection, disease brought on by percutaneous injection frequently reveals itself at a distance. Animals frequently experience damage to their lungs, spleen, liver, and lymph nodes, but any organ could be affected (Rovid, 2016) [26].

Goats frequently get mastitis, and aortic aneurysms have been observed. Sheep are more susceptible to respiratory diseases, which can manifest as fever, persistent coughing, respiratory distress, and muco-purulent nasal and ocular discharge. The signs of CNS disease in cattle, horses, sheep, and goats include circling, lack of coordination, blindness, nystagmus, and spasms. Asymptomatic lesions are frequently found in the spleens of slaughtered pigs. The septic arthritis and osteomyelitis can cause lameness. After acute fulminating infections or when vital organs are damaged, fatalities are common (Finklesteien, 2018) [14].

In horses with melioidosis, symptoms, such as limb weakness, oedema, and lymphangitis, as well as mild colic, diarrhea, coughing, and nasal discharge, have all been reported. Before developing papular, early skin infections may mimic fungal eczema. Dogs can get acute, subacute, or chronic infection. In acute cases, septicemia with a fever, severe diarrhea, and fulminant pneumonia are prevalent. The subacute patients may experience a cutaneous lesion with lymphangitis and lymphadenitis; untreated cases might progress to septicemia. The signs of a chronic infection that can affect any organ include anorexia, myalgia, limb oedema, and skin abscesses (Merck, 2012) [28].

5. Epidemiology

Meliodosis can occur in a variety of tropical and subtropical environments. Most endemic regions are located between latitudes 20ºN and 20ºS. The disease is endemic in Southeast Asia, China, the Indian subcontinent, and some regions of Australia. It has been documented in the Caribbean, the Middle East, South America, Singapore, and Taiwan. Africa's situation is precarious. Despite isolated cases being reported in the past from a few African

countries, melioidosis is not a disease that is frequently documented in Africa (CFSPH, 2016) [7]. Since 2012, melioidosis cases in India, which were formerly sporadic, have become endemic (Princess *et al.*, 2017) [23]. The infections in horses, monkeys, and other animals transported with insufficient oversight have recently been reported from France and Spain (Wiesinga *et al.*, 2012) [32]. Isolated cases in the US have also been reported in Georgia and Hawaii, but most have been connected to international travel. Clinical infection is a very uncommon occurrence. In endemic locations, 5% to 20% of agricultural workers have antibodies to *B. pseudomallei*, but they have not manifested the disease. In places with high humidity or warmth, outbreaks and cases are more likely to occur during the rainy season or following periods of heavy rainfall (CFSPH, 2011) [7].

Environmental sampling has been widely used to detect the presence of *B. pseudomallei* in an effort to identify the geographical distribution of the organism and related risk of infection, according to an epidemiological study about the distribution of virulent strains and the source of melioidosis infection (Brook *et al.*, 1997; Vuddhakul *et al.*, 1999) [4, 31]. In order to connect isolates to a common polluted source during outbreak investigations, genotyping of environmental and clinical isolates is crucial (Currie *et al.*, 2001) [11]. Understanding the epidemiology of melioidosis can be accomplished by molecular typing, which provides a very discriminatory tool for differentiating strains. Pulsed field gel electrophoresis (PFGE) has been used in several studies to study the clonal relatedness due to its high discriminative power (Koonpaew *et al.*, 2008; Azura *et al.*, 2011) [20, 2].

6. Diagnosis

Patients from endemic areas who come with fever, a fulminant respiratory infection with tachypnea, pulmonary infiltrates that resemble tuberculosis, cutaneous or subcutaneous pustules, or necrotic lesions should be evaluated for melioidosis (Cheng, 2010) [9]. The gold standard method is to isolate and identify the organism from lesions and discharges. The bacterium grows readily on standard diagnostic media like MacConkey's agar and blood agar. This method can be made more sensitive and specific by using Ashdown's agar, a selective media. The colony of *Burkholderia pseudomallei* is characterized by an earthy odor. Indirect hemagglutination and complement fixation are two effective serologic screening methods. Some species can be diagnosed using agglutination tests, indirect hemagglutination, immunofluorescence, and enzyme immunoassays. In serologic assays, cross-reactions with *Burkholderia thailandensis* might happen, leading to false-positive results in exposed animals. Despite the fact that chronically infected animals cannot have their antibody titers measured, new techniques based on DNA probes and PCR have been created. Using specific primers for conserved regions of the 16s rRNA, 16S-23S rRNA intergenic spacer, flagellin, and lipopolysaccharide, *B. pseudomallei*, *B. mallei*, and *B. thailandensis* can be differentiated from one another (AAZVIDC, 2013) [1].

7. Treatment

7.1. In humans

Broad spectrum antibiotics like ceftazidime, meropenem, or imipenem with cilastatin should be used to treat patients with severe melioidosis as a first line of treatment. All doses should be adequately adjusted in patients with renal impairment. If these medications are unavailable, treatment with co-amoxiclav and cefoperazone sulbactam has been shown to be effective, though professional advice should be sought. Depending on the infection site and clinical response, the duration of intravenous therapy will vary; nevertheless, all patients should plan on receiving treatment for at least 14 days. The recommended oral "eradication" regimen for a total of 20 weeks of treatment includes doxycycline and co-trimoxazole, or co-amoxiclav if doxycycline and/or co-trimoxazole are contraindicated (particularly for children and pregnant women). Extended intensive phase parenteral therapy is used to treat deep-seated infections such osteomyelitis, several undrained abscesses, or CNS infections. Patients with mild infections can receive 12 to 20 weeks of treatment just from oral antibiotics. Despite the fact that the combined treatment lowers recurrence, it is linked to more adverse effects (HPA, 2008) [17].

7.2. In Animals

Due to the nature of the infection and the potential for human exposure, it is unlikely that farm animals will receive treatment (Chaowagul, 2000) [8]. *B. pseudomalleus* is susceptible to some antibiotics, but it is naturally resistant to many drugs, including those that are frequently used to treat bacterial infections. Pharmaceutical treatments may also lose their effectiveness with time, sometimes producing an unsatisfying cure and increasing the risk of recurrence if treatment is stopped in animals. Three steps, including post-exposure prophylaxis, induction, and eradication, make up the medical treatment, which will last at least four months. The treatment regimens are identical to those now used in people. Because treatment can be expensive and time-consuming and because it might not completely eradicate the virus, some animals are slaughtered rather than treated. It might be illegal to treat diseased animals in some locations (AAZVIDC, 2013; Rovid, 2016) [1, 26].

8. Prevention and control

Typically, melioidosis is acquired from the exposure to the environment, particularly soil or water. As a result, avoid coming into contact with much dirt or animals. People with skin breaks should avoid recurrent contact with soil or surface water in endemic areas. This is especially important during rainy seasons. As well avoid drinking raw sheep or goat milk. Chlorine should be used to sterilize water from suspicious sources. Trimethoprim-sulfamethoxazole 2×960 mg/day for 3 weeks is advised for post-exposure prophylaxis. Wearing gloves and routinely cleaning their knives are recommended for those who process meat. Veterinarians should take precautions to prevent exposure when working with sick animals or obtaining diagnostic samples, such as wearing gloves and protective clothes. In hospitals, standard precautions should be taken to avoid the spread of disease through bodily fluids and blood. Animal necropsies should be conducted with care. For those who are immunocompromised or suffer from a chronic disease like diabetes or kidney disease, this is extremely important. To prevent infection, a wound that has become contaminated by soil or water needs to be properly cleaned with disinfectant soap and water. There is no FDA-approved vaccination against melioidosis (Radostitis *et al.*, 2006; CFSPH, 2011; Rovid, 2016) [24, 7, 26].

9. Conclusion

The bacterium *Burkholderia pseudomallie* is the cause of the bacterial disease meliodosis, an emerging public health concern with life-threatening potential. The infection has been observed in a number of animal species as well as in humans. The contact between diseased skin and contaminated soil or water is the main ways of transmission of meliodosis. An accurate diagnosis of melioidosis requires the assistance of a well equipped laboratory. Critical care, early diagnosis, and appropriate antibiotic treatment all contribute to better management and lower mortality rates. Since there is now no vaccine available, serious efforts should be undertaken to develop a vaccine that is affordable, effective, and safe so that it may be utilized to immunize the susceptible population in low-resource nations all over the world. Additional research on the pathogenesis, molecular epidemiology, and diagnostic is emphasized.

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11. Contribution of authors

All the authors contributed equally. They read the final version, and approved it for the publication.

12. Conflict of interest

The authors declare that they do not have conflict of interest.

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