

meliodosis is considered highly endemic. By contrast, South Asia is predicted to bear 44% of the overall burden, because large populations live in areas contaminated with *B. pseudomallei*. Our estimates suggest that melioidosis is severely underreported in the 45 countries in which it is known to be endemic and that melioidosis is likely endemic in a further 34 countries which have never reported the disease.

The large numbers of estimated cases and fatalities emphasise that the disease warrants renewed attention from public health officials and policy makers.

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Why is melioidosis difficult to treat? - Insights into pathogenesis



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Abstract: Largely due to its recognition as a biological threat agent, current knowledge on melioidosis, caused by the Gram-negative bacterium *Burkholderia pseudomallei*, has increased tremendously in the last decade. In this talk, recent insights will be given on our understanding on the molecular characterization of *B. pseudomallei* and the immunology of melioidosis.

The genome of *B. pseudomallei* is composed of two chromosomes of which the largest part represents the *B. pseudomallei* core genome, whereas the remaining accessory genome has been associated with bacterial virulence. Virulence factors, most notably quorum sensing, type III secretion system, lipopolysaccharide and other surface polysaccharides, flagella and various factors essential for the intracellular life cycle of *B. pseudomallei*, have been further characterized. These so called microorganism associated molecular patterns (MAMPs) are recognized by pattern recognition receptors (PRRs) such as Toll-like receptors and NOD-like receptors (NLRs). The neutrophils play a critical in host defense, which is initiated by the TLRs. The proinflammatory immune response – including the activation of coagulation – is further ignited by the release of various damage associated molecular patterns (DAMPs) such as calprotectin and the nucleosomes which are also recognized by PRRs.

Severe melioidosis can probably be seen as the clinical manifestation of a PRR mediated dysregulation of the immune response to invading *B. pseudomallei*. *B. pseudomallei* employs numerous tactics to evade the immune response. Studies on host–pathogen interactions in melioidosis have identified a whole range of potential new treatment targets which will be discussed.

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Challenges in diagnosis and management of melioidosis



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Abstract: For many years it has been clear that melioidosis is endemic in parts of SE Asia and northern Australia, but over the past 25 years, the melioidosis iceberg has been emerging. Within known endemic areas, cases are being recognized with increasing frequency. New endemic areas are also being identified, particularly in Africa and the Americas, but also in Asia. In Laos, for example, the first case of melioidosis was diagnosed as recently as 1999, but since then more than 900 cases of culture-positive melioidosis have been diagnosed in a single laboratory, although this is just the tip of a national iceberg.

Worldwide, the disease undoubtedly remains under-diagnosed, especially in the Indian sub-continent. The two main barriers to the diagnosis of the disease, which has its biggest impact on the rural poor, are access to high quality diagnostics, and the lack of awareness and familiarity of clinical and laboratory staff. Clinical diagnosis is difficult due to the protean manifestations of the disease. Where microbiology laboratories exist, the mainstay of diagnosis remains culture. The organism is easy to grow as long as the site of infection can be sampled, but laboratory technicians unfamiliar with the organism may discard it as a contaminant. An important clue is resistance to aminoglycosides and colistin combined with susceptibility to co-amoxiclav, although regional variants have recently been described. Latex agglutination or lateral flow tests are useful for screening suspect isolates, and the latter may be used for rapid diagnosis directly on clinical samples. Molecular tests such as PCR have not yet found a role in routine diagnosis. Available serological tests also lack sensitivity and specificity.

Current treatment regimens, comprising an initial parenteral phase with either ceftazidime or a carbapenem followed by a prolonged oral eradication phase with co-trimoxazole or co-amoxiclav, are based on strong evidence from a series of clinical trials conducted in Thailand. Several questions remain unanswered, however, such as the optimal duration of each phase and the role of adjunctive treatment.

Even with optimal antibiotic therapy the mortality in developing countries remains disappointingly high.

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