Melioidosis and *Burkholderia pseudomallei*: progress in epidemiology, diagnosis, treatment and vaccination

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Purpose of review
Melioidosis and its causative bacterium *Burkholderia pseudomallei* are being found in unexpected locations and bacterial genotyping is providing new insights into global spread and where and how individuals are being infected. This review summarizes recent studies covering the epidemiology, diagnosis, treatment, and prevention of melioidosis.

Recent findings
Whole-genome sequencing of *B. pseudomallei* from patients and environmental sampling is informing the phylogeography of *B. pseudomallei* at regional, continental, and global levels, while also defining the epidemiology for individual cases. The situation in Africa remains the most unresolved, while the evolving story of *B. pseudomallei* in the Americas may establish that *B. pseudomallei* is endemic in parts of southern USA. Guidelines for diagnosis and treatment of melioidosis are well established, and published mortality has decreased from 50% or higher to 10% or lower in some countries but access to laboratory and therapeutic resources are not available or are extremely limited in many melioidosis-endemic regions.

Summary
The enormous clinical diversity of melioidosis and the complexities of laboratory diagnosis and of treatment make it a sentinel disease for highlighting the continuing global disparities in access to and provision of healthcare.

Keywords
bacterial genotyping, biothreat, *Burkholderia pseudomallei*, emerging infectious diseases, melioidosis, neglected tropical diseases

INTRODUCTION

Melioidosis remains an enigmatic disease, and the global footprint of the causative soil and water bacterium, *Burkholderia pseudomallei*, continues to be redefined. What remains unclear is how much of this is an unmasking of endemic *B. pseudomallei* in regions where it has long been present but limited clinical and laboratory resources have precluded culture and identification; and how much represents more recent expansion of *B. pseudomallei* endemicity through anthropogenic and even climate-related drivers.

The listing of *B. pseudomallei* as a tier-1 select agent by the United States of America Centers for Disease Control and Prevention (CDC) underpins much of the funding for global research efforts, including innovations in diagnostics and development of potential vaccine candidates. Since the resurgence of interest in melioidosis, which began with the work from northeast Thailand commencing in the 1980s [1], there have been sequential comprehensive reviews [2–8].

This article focusses on selected new data published in 2021 and 2022, relating to the epidemiology, diagnosis, treatment, and prevention of melioidosis. It complements another recent review highlighting: the connection between melioidosis and global increases in the noncommunicable diseases diabetes and chronic kidney disease; the importance of a One Health approach given the known animal

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KEY POINTS

- The map of global distribution of *B. pseudomallei* remains to be completed and this and regional and global case numbers of melioidosis will only be accurately defined by increased support for improved laboratory services in known and suspected endemic locations.
- The situation across Africa remains the most unclear, while an evolving story of *B. pseudomallei* in the Americas may well soon establish that *B. pseudomallei* is indeed endemic in parts of southern USA. What remains unclear is to what extent there is ongoing spread of *B. pseudomallei* beyond historical locations and how quickly that is happening, rather than simply increased surveillance unmasking *B. pseudomallei* presence in locations not previously recognized as being endemic.
- Whole-genome sequencing of *B. pseudomallei* from patients and environmental sampling is informing the phylogeography of *B. pseudomallei* at regional, continental, and global levels, while also defining the epidemiology for individual cases.
- Evidence is accumulating for spread of melioidosis through global trade and for the link between case numbers and anthropogenic factors such as environmental perturbation from construction and agriculture and farming animals.
- With resources for rapid diagnosis, early implementation of best antibiotics, and state-of-the-art intensive care facilities for managing severe sepsis, mortality in melioidosis can be under 10%. However, such resources are just not available or are extremely limited in many melioidosis-endemic regions.

susceptibility to melioidosis and links to global trade; and the strong predictions that climate change and other anthropogenic drivers will increase melioidosis globally [9▪].

EPIDEMIOLOGY

The known and modelling-predicted global presence of *B. pseudomallei* and case numbers and mortality from melioidosis was published in 2016 [10]. Melioidosis was known to be endemic in 48 countries, but case numbers were considered to be substantially underreported in all but three; Australia, Brunei Darussalam and Singapore. In further 34 countries, melioidosis was predicted to be endemic but had not yet been reported. Predicted global annual case numbers for 2015 was estimated at 165 000 (95% credible interval for the model was 68 000–412 000 cases annually), with a predicted 89 000 deaths annually (95% credible interval for the model was 36 000–227 000 deaths annually). Inroads have subsequently been made in filling in the gaps of confirmed endemicity, but confirmation of the predicted case numbers and deaths remains problematic. Much of the uncertainty may still be attributed to the continuing lack of or limited access to microbiological laboratory diagnostic facilities and concomitant disease-reporting systems, but it is also possible that the global cases numbers and mortality are substantially lower than the estimated numbers. The ongoing disparity in access to laboratory resources has been documented in a review of diagnosis of melioidosis and tuberculosis from Papua New Guinea, where the divide between urban and rural capabilities is stark and reflects the reality of much of the Asia Pacific region and elsewhere globally [11▪].

Africa

Efforts continue to establish the extent of *B. pseudomallei* and melioidosis in Africa. The first WHO African Melioidosis Workshop was held in Lagos, Nigeria, in March 2019. A review of the meeting documented the countries with confirmed melioidosis cases and the plans for supporting improved case finding through initiatives, including the African Sepsis Alliance [12▪]. The most recent example of unmasking of melioidosis in Africa is from Ghana, where, in addition to a reported case of chronic melioidosis osteomyelitis [13], *B. pseudomallei* has been recovered from a formal soil sampling study of a rice farm in south-central Ghana [14]. Preliminary environmental sampling from Cameroon, however, recovered no *B. pseudomallei* [15].

South Asia

There continue to be reports from South Asia filling in the gaps of melioidosis-endemic locations, epidemiology and clinical manifestations and environmental associations with presence of *B. pseudomallei*. A cluster of 10 cases with 4 deaths occurred in eastern Sri Lanka in 2015 after an extreme weather event, with genomic analysis of *B. pseudomallei* showing genetic diversity and that the cluster was nonclonal despite four of the isolates being multilocus sequence type (MLST) ST594 [16]. Further evidence of the biogeographic and genetic diversity of *B. pseudomallei* in Sri Lanka was provided by the analysis of 310 clinical isolates, with the variable presence of selected genetic markers raising intriguing questions about the origins of *B. pseudomallei* in Sri Lanka, both ancient and potentially more recent introductions [17▪].

Informative case series have been published from Tamil Nadu [18], Kerala [19] and Karnataka [20] in southern India and Odissa in eastern India [21]. An extensive soil sampling study from southwest India showed the wide environmental distribution of *B. pseudomallei* but with considerable differences in abundance between sites and within single sites, the highest abundance during the rainy season and the presence of *B. pseudomallei* linked to nutrient-depleted habitats [22▪].

A retrospective review of all *B. pseudomallei* detected at a tertiary care hospital in Dhaka, Bangladesh reported 68 patients with melioidosis over 21 years, concluding that melioidosis remains largely unrecognized by healthcare policy makers and should be included as a notifiable disease in the national surveillance system of Bangladesh [23].

A recent review of melioidosis in India and South Asia describes in detail the difficulties in clinical recognition and laboratory diagnosis of melioidosis and the formidable challenges of addressing these as well as in establishing effective prevention programs [24▪].

Americas

The most dynamic region for evolving melioidosis epidemiology is the Americas, with ongoing unmasking of endemic disease and intriguing suggestions of movements of *B. pseudomallei* northwards into new environments over recent decades. Whole-genome sequencing and molecular phylogeny studies of clinical and environmental *B. pseudomallei* from defined clinical scenarios and geographical locations are informing the regional, continental and global population structure of *B. pseudomallei*. Analysis of *B. pseudomallei* genomes from the state of Ceara in northeast Brazil has shown the complexities of such analyses, with surprising genetic diversity but isolates still falling within a distinct subclade of Western Hemisphere *B. pseudomallei* [25]. Similarly diverse genotypes have been described from Colombia [26]. A notable finding in Brazil is a relatively high proportion of cases of melioidosis occurring in children, with severe disease and high mortality [27▪]. Further studies are required to ascertain if and why childhood melioidosis may be more severe in Brazil than reported elsewhere, with analogies to the situation in rural Papua New Guinea [11▪].

The global modelling of *B. pseudomallei* predicted that the southern USA could well be endemic for *B. pseudomallei* [10]. While *B. pseudomallei* has yet to be recovered from the natural environment in the USA, soil and water sampling efforts continue as a bacterial isolate from a recent autochthonous case in Texas has a distinctly Western Hemisphere genotype [28▪].

Investigations led by the US CDC have shown the power of classical 'shoe leather' outbreak case investigation combined with modern pathogen genomic studies to pinpoint the source of unexpected cases of melioidosis. A cluster of four nontravel-associated cases of melioidosis in Georgia, Kansas, Minnesota, and Texas were found on whole-genome sequencing of *B. pseudomallei* to be caused by the same strain of *B. pseudomallei* that was recovered from an aromatherapy spray product imported from India [29▪]. Two cases were fatal, including a child co-infected with SARS-CoV-2, who had disseminated melioidosis, including extensive brain involvement. The potential for infection with SARS-CoV-2 to activate melioidosis from latency or accelerate clinical disease in melioidosis has been postulated [30,31], analogous to reports of melioidosis following influenza [32]. The other child from the cluster had severe melioidosis encephalomyelitis and survived but remained wheelchair-bound and nonverbal 3 months after discharge. Of note, the outbreak strain of *B. pseudomallei* has the uncommon $bimA_{Bm}$ variant of the *bimA* gene, which encodes the autotransporter protein (BimA) that mediates actin-based motility. Recent analysis of melioidosis cases from across northern Australia has confirmed the previous finding that patients infected with the $bimA_{Bm}$ variant gene are more likely to present with brainstem encephalomyelitis and more commonly die or have long-term disability [33,34].

In a second investigation, another melioidosis case in the USA with no international travel history was linked by genotyping of environmental *B. pseudomallei* to infection from a freshwater home aquarium that had contained imported tropical fish [35▪].

Southeast Asia

Thailand remains the country reporting by far the most numbers of melioidosis cases, with the majority coming from the northeast provinces of Ubon Ratchathani and Khon Kaen. In a prospective study of community-acquired sepsis from Ubon Ratchathani, the three commonest bacterial pathogens recovered from blood cultures were *Escherichia coli, B. pseudomallei* and *Staphylococcus aureus*, respectively, with a substantially higher mortality in the patients with melioidosis [36]. Studies of *B. pseudomallei* using genomics, transcriptomics and gene knockout assays have provided important novel insights into the evolution and survival of *B. pseudomallei* in harsh environments, supporting the hypothesis that nutrient-limited conditions have been the common selection pressure acting on this species [37▪].

Melioidosis was first described in Myanmar in 1911, but it was not recognized as a continuing cause of sepsis in that country for decades until recently. A nationwide soil study has confirmed the widespread presence of *B. pseudomallei* in Myanmar [38], but a study from Yangon has shown that the burden of tuberculosis is far greater than that of melioidosis [39].

A study from northern Cambodia reported 355 children with culture-confirmed melioidosis over 10 years, with bacteraemia and presentation with pneumonia being risk factors for death [40▪]. The study describes the challenges of diagnosis and treatment of melioidosis, but the decreased mortality compared with a prior study from the same hospital very likely reflects a focus on improved diagnostic capability and therapeutic guidelines.

A study of 510 patients with melioidosis from northern Malaysia showed very high rates of bacteraemia (86.8%), persisting high mortality (50.1%) and emphasized the importance of diabetes as the major risk factor for melioidosis (69.8%) [41]. A study from Sarawak in Malaysian Borneo confirmed the previous finding of predominantly gentamicin-susceptible *B. pseudomallei* (65% of clinical isolates) [42▪]. Although this has important implications for laboratory clinical and environmental study diagnostic culture methods, there were no clinical or outcome differences between patients with and without gentamicin-susceptible *B. pseudomallei*. The gentamicin-susceptible *B. pseudomallei* were mostly from the high-incidence rural interior of Borneo, and further studies are required to elucidate their environmental niches.

Environmental studies from Laos have shown the important association between rivers and *B. pseudomallei* [43] and an unexpected finding that the highest concentrations of *B. pseudomallei* were observed between 100 and 200 cm below the soil surface [44▪]. It was concluded that for comprehensive environmental studies, collecting samples down to the water table is critical, with groundwater persistence considered an important controlling factor for the presence of *B. pseudomallei* in soil. A study sampling surface runoff from drain catchment areas throughout urban Vientiane, Laos showed detection of *B. pseudomallei* in drainage areas throughout the capital, with a high level of genetic diversity on whole-genome sequencing, confirming that the bacterium has been long-established and endemic in Laos [45].

Australia

Studies continue in the three tropical cities of northern Australia. A sharp rise in case numbers in Cairns, far north Queensland has been linked to urban development and in particular the construction of a large motorway on the city's southern outskirts during 2011–2017 [46▪]. The importance of melioidosis as a disease of socioeconomic disadvantage was established in analysis of the Cairns cohort, with socioeconomic disadvantage having a greater independent association with in-hospital death than age, indigenous status, bacteraemia and the classical risk factors for melioidosis, such as diabetes [47▪]. A 21-year analysis of seasonal and weather data confirmed the marked wet season predominance of melioidosis (and leptospirosis) [48]. Further south in Townsville, Queensland, melioidosis cases showed similar demographics and clinical presentations to Cairns and Darwin, Northern Territory [49].

The Darwin prospective melioidosis study described the epidemiological, clinical and laboratory data for 1148 patients with melioidosis over 30 years and supports the concept of melioidosis as an opportunistic infection, with all but 16% of cases having clinical risk factors and mortality under 10% when resources enable early diagnosis, specific antimicrobial therapy, and state-of-the-art intensive care [50▪]. Activation from latency represented only 3% of cases, 9% presented with chronic melioidosis (symptoms for 2 months or longer) and 88% were acute melioidosis from recent infection, with an estimated median incubation period of only 4 days (range 1–21 days). Genotyping of *B. pseudomallei* from cases and the environment has provided new insights into local and regional dispersal of *B. pseudomallei*, with the surprising finding of introduction and spread of an Asian *B. pseudomallei*, ST562, into northern Australia [51▪]. Targeted environmental sampling linked cases to their specific infecting events, with genomically matched clinical and environmental *B. pseudomallei* pairs supporting all three modes of infection: percutaneous inoculation, inhalation and (rarely in Australia) ingestion [52▪]. Similar analysis from northern Vietnam linked three deaths in children from one family to likely ingestion of *B. pseudomallei*-contaminated water from a borehole on their property, which was damaged, presumptively allowing rainy season ingression of *B. pseudomallei* from soil [53▪]. Another environmental study was undertaken in India from the backyard of two siblings with melioidosis [54].

DIAGNOSIS

Culture of *B. pseudomallei* remains required for confirmation of melioidosis. Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) is increasingly used for bacterial colony identification, but current systems

continue to sometimes misidentify *B. pseudomallei,* most commonly as *Burkholderia thailandensis* [29▪]. With appropriate spectra added, sensitivity and specificity of MALDI-TOF MS approaches 100% [55].

Molecular methods for identification of *B. pseudomallei* continue to evolve, but sensitivity of directly testing clinical samples remains inferior to culture [56–58]. One new potential diagnostic target studied is the *Burkholderia* invasion protein D (BipD) [59].

Serological diagnosis of melioidosis remains problematic because of both low sensitivity early in infection and the presence of antibodies from prior exposure being common in melioidosis-endemic regions, making specificity for diagnosing active infection (melioidosis) low. Recently the development of ELISAs for melioidosis has evolved as an alternative to the long-term standard indirect hemagglutination assay (IHA). Such ELISAs have used recombinant or crude extract antigens, including O-polysaccharide (OPS), haemolysin co-regulated protein 1 (Hcp1) [60▪], outer membrane protein (ompA), chaperonin molecule (GroEL) and flagellin fragments, with a chimeric fusion protein rGroEL-FLAG300 showing promise [61].

A point-of-care lateral flow immunoassay (Active Melioidosis Detect LFA) has been developed for direct detection of the *B. pseudomallei* capsular polysaccharide (CPS) antigen in clinical samples [60▪,62]. A review of 8 studies from diverse countries and analysis of the assay on clinical samples from 232 patients with culture-confirmed melioidosis from Australia showed potential for use as a rapid diagnostic for testing serum and urine from those with severe sepsis who may have melioidosis and for testing sputum and pus samples from clinically relevant scenarios [63▪]. A bacteriophage tail fibre-based latex agglutination assay for rapid detection of *B. pseudomallei* infection has also recently been described [64].

TREATMENT

Treatment guidelines for melioidosis are well defined, both the antibiotics recommended and the length of therapy for each of the intensive and eradication phases of treatment [6,7,65▪]. The vast majority of primary isolates of *B. pseudomallei* have a standard antimicrobial sensitivity profile that enables confidence with empirical therapy as per guidelines [66▪,67▪]. Nevertheless, in patients on therapy for melioidosis, variant selection and mutation-driven acquired resistance in *B. pseudomallei* can develop through diverse mechanisms that continue to be elucidated [66▪,67▪,68,69]. The new EUCAST (European Committee on Antimicrobial Susceptibility Testing) guidelines for reporting of antimicrobial susceptibilities for *B. pseudomallei* requires an understanding of the terminology, to avoid misinterpretation of dosing recommendations (I = use increased doses) as resistance to ceftazidime and trimethoprim/sulfamethoxazole [70▪].

New antimicrobials continue to be evaluated, with the siderophore cephalosporin cefiderocol being highly active *in vitro* against *B. pseudomallei* but with resistance found in a minority of isolates [71]. Novel products for potential future development include synthetic agents incorporating silver nanoparticles [72,73] and antimicrobial compounds that would act by binding to *B. pseudomallei* disulphide-bond-forming proteins (Dsbs), such as DsbA [74].

VACCINES

Steady progress continues in the development and assessment of vaccines for melioidosis, but there remains no licensed vaccine currently available [75]. Outer membrane vesicles (OMV) derived from *B. pseudomallei* are highly effective immunogens, and immunization of mice with enhanced OMV derived from infection-mimicking conditions provided significant protection against pulmonary infection [76▪]. Other OMV vaccine candidates are also being assessed [77–79]. Live attenuated vaccines show robust immune responses in a mouse model, eliciting both humoral and cellular immunity with the potential to protect against inhalational melioidosis [80▪]. An in-vitro model using priming of human T cells by dendritic cells has been developed, which can assess components of *B. pseudomallei* for utility in potential subunit vaccines [81].

CONCLUSION

Although the global distribution of *B. pseudomallei* and melioidosis case numbers and mortality require ongoing surveillance for clarification and quantification, the burden of disease justifies calls for melioidosis to be formally included by WHO as a neglected tropical disease [82▪]. Guidelines for diagnosis and therapy are well established and with resources for rapid diagnosis, early implementation of best antibiotics, and state-of-the-art intensive care facilities for managing severe sepsis, mortality can be under 10%. However, in many of the regions where melioidosis is endemic, such resources are just not available or are extremely limited.

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Conflicts of interest

There are no conflicts of interest.

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