Melioidosis in Global Perspective and Challenges for Surveillance

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Abstract

Over the past 40 years it has become apparent that melioidosis is not only highly endemic in southeast Asia and northern Australia but is also widespread elsewhere in the tropics. Modelling suggests that there could be as many as 165,000 cases in 79 countries around the world each year leading to some 89,000 deaths, with some 44% of these occurring in south Asia. In reality, far fewer cases than this are being diagnosed. There are, however, numerous obstacles to accurate surveillance, especially since this is an infection that predominantly affects the rural poor who are the last people to have access to good diagnostics. The potential for *Burkholderia pseudomallei* to be used as a bioweapon has had beneficial spin-offs, no matter how unlikely it is ever to be used in this way. Nonetheless, melioidosis deserves to be formally recognised as a neglected tropical disease in the hope that this will help to raise awareness, improve management, and reduce the avoidable death toll from this silent killer.

Introduction

For many decades melioidosis was regarded as a rare disease of little significance, confined to certain remote parts of the tropics. Over the past 40 years, it has emerged as an infection with important implications for global public health, both as an understanding of its true distribution and burden has grown and as its potential as a biothreat agent has been explored. In this chapter, I will briefly review the 'known knowns' and the 'known unknowns' as far as melioidosis is concerned, explore some of the obstacles to unraveling the latter, and finally consider whether melioidosis, which is so neglected that it is not even on the World Health Organisation's (WHO) list of Neglected Tropical Diseases, should be formally recognized as such.

Worldwide distribution and dissemination

Back in 1991, I reviewed what was then known about the worldwide distribution of melioidosis from literature [1]. At this time, it was clear that the disease was endemic throughout southeast Asia and in northern Australia, but there were tantalizing glimpses of endemicity elsewhere throughout the tropics. Over the ensuing 30 years, endemicity in many of these places has been confirmed by the detection of human or animal infections and the presence of *Burkholderia pseudomallei* in the environment. The situation was reviewed again in 2016, when 45 countries were identified as endemic and another 34 were highlighted as potentially endemic because of a favorable climate and environment for *B. pseudomallei* [2]. Since this paper was published, evidence supporting endemicity has been found in several of these 34 countries, including Nepal [3-6], Benin [7], Cameroon [8], Democratic Republic of Congo [9], Eritrea [10], Ghana [11,12], Mali [13], Nicaragua [14], St Kitts and Nevis [15], Trinidad and Tobago [16], the Federated States of Micronesia [17], and most recently the southern USA [18,19].

Whenever melioidosis is identified in a new location, the question inevitably arises as to whether it has long been present but unrecognized or whether it has been recently introduced, for example, by international travel of infected humans or animals or transported by contaminated products or objects. All of these are theoretically possible, but the extent to which they can lead to the establishment of new endemic foci is unknown. Infection in returning travelers is well described and extensively reviewed [20-22]. Infections in animals or fish imported from endemic areas into non-endemic areas have also been frequently reported and have sometimes given rise to considerable public health concerns and occasional human infections [23,24]. A striking recent example of melioidosis resulting from the importation of a contaminated product is the cluster of four cases, two of whom died, across the USA in 2021, which was eventually traced back to a contaminated aromatherapy spray manufactured in India [25].

The advent of modern genomic techniques has provided fascinating insights into the global dissemination and timelines of *B. pseudomallei* transmission. The degree of diversity amongst clinical and environmental isolates can reveal the length of time the organism has been present in a newly recognized environment [17]. It appears that the species originated in Australia [26], from where it has spread multiple times into Southeast Asia and thence onto Africa and the Americas, the latter around the time of the slave trade [27,28]. However, this is not one-way traffic: a particular sequence type of *B. pseudomallei*, ST562, appears to have been introduced from southern China into the Darwin region of northern Australia sometime around 1988, since when it has caused an increasing proportion of human and animal melioidosis in the Darwin area [29]. No doubt, the widespread application of whole genome sequencing to isolates from around the world will shed further light on the precise dynamics of *B. pseudomallei* spread in the future.

Disease burden

The 2016 modeling paper by Limmathurotsakul *et al.* has become one of the most widely cited papers in the field, as it contains the best estimate we have of the total global melioidosis burden – 165,000 human cases (95% credible interval 68,000–412,000) and 89,000 (36,000–227,000) deaths per year worldwide [2]. Notably, some 44% of these cases were predicted to occur in South Asia, particularly India. When further analyzed to estimate the burden in terms of disability-adjusted life years (DALYs), this equated to 4.6 million DALYs (uncertainty interval 3.2–6.6) or 84.3 per 100 000 people (57.5–120.0), the majority of which was accounted for by the high mortality rate [30].

Nonetheless, like any model, this study was based on a series of assumptions, particularly about the features of an environment that make it suitable for the survival of *B. pseudomallei* in soil and water, which may or may not prove to be correct. Our understanding of the complex interactions between the bacterium and the physical, chemical, and biological characteristics of its various ecological niches is rudimentary. So it would not be surprising if some of the projections proved to be wrong. This is at least partly due to the difficulty of detecting *B. pseudomallei* reliably in environmental samples, and the need to consider the extreme structural complexity and micro-niches within soil [31]. Assumptions about the proportion of the exposed population who become infected and die may also be wrong. So the model needs to be continually refined as more data become available.

In fact, the number of cases that have been reported, either through national surveillance systems or in the literature, falls well short of the number of cases predicted by the modeling, as a series of national and regional reviews published in 2019 clearly demonstrate [32]. This is particularly marked for India, where a less than a thousand cases were identified from the literature and local records, as opposed to more than 50,000 cases annually nationwide predicted by the model, a dramatic discrepancy. In countries with well-resourced healthcare systems and mandatory surveillance, such as Singapore and Australia, however, the number of cases reported comes far closer to the numbers predicted by the modeling

So whether the numbers from the model are anywhere near the truth remains to be determined. The extent to which melioidosis can pass below the radar is amply illustrated by the example of the Lao People's Democratic Republic (Laos). This country lies across the Mekong River from northeast Thailand, where melioidosis has been known to be highly endemic for many years [33]. When a research collaboration was established in 1999 between the University of Oxford and Mahosot Hospital in the capital, Vientiane, melioidosis had never previously been diagnosed in Laos. Within 2 years, cases had begun to be recognized [34], and by 2017, 1539 cases had been microbiologically confirmed [35]. It is highly unlikely that the disease had not existed within Laos before 1999, and whilst, of course, it is possible that factors such as climate change and an increased prevalence and longer survival of patients with predisposing conditions such as diabetes mellitus might have led to a genuine increase in melioidosis incidence, it is far more likely that the disease was simply being missed. Since most of these 1539 cases were diagnosed in Vientiane, the only city that at that time had a comprehensive diagnostic microbiology service, it is also likely that many cases of melioidosis are still being missed elsewhere within Laos.

Barriers to Surveillance

There are multiple barriers to gaining accurate data on the number of cases of melioidosis in each country, as illustrated in Figure 1.

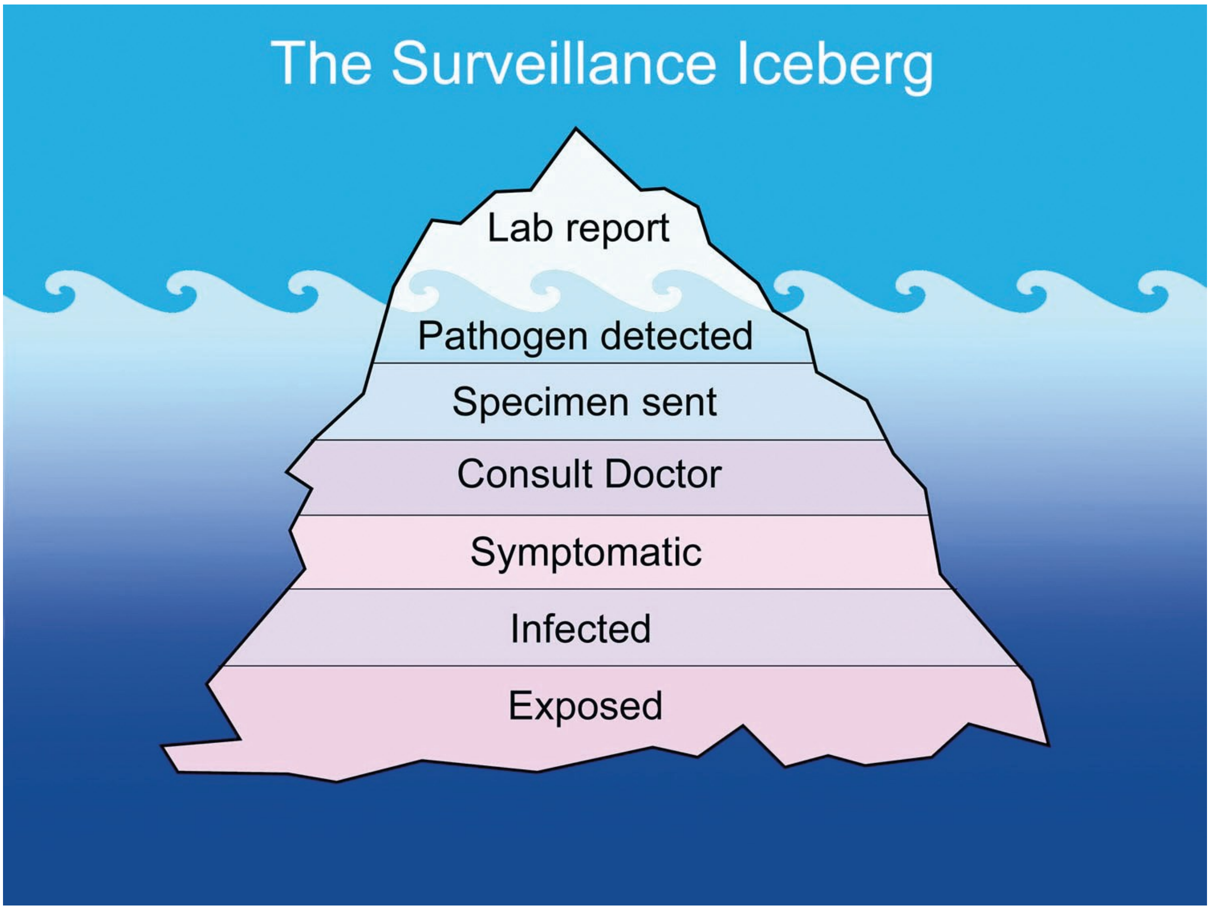

Fig. 1. The surveillance iceberg, showing the cases of an infection reported to national surveillance systems or in the literature, may represent only a small proportion of the total number of cases occurring.

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The first barrier is access to healthcare. Trained healthcare workers are unevenly distributed, and diagnostic laboratories even more so, and they are especially scarce in the remote rural areas where melioidosis patients are likely to live. Even if laboratories do exist, in countries where patients have to pay for diagnostic tests, poor subsistence rice farmers are unlikely to be able to afford to pay for these.

Secondly, awareness of melioidosis is poor in many countries, amongst both clinicians and laboratory staff (and even more so amongst the general public) [36]. Even if physicians know of the disease, the clinical manifestations of melioidosis are many and varied, giving rise to the nickname 'the great mimicker (or imitator)' [37], so diagnosis on clinical grounds alone is unreliable, meaning that laboratory confirmation is necessary for accurate diagnosis and surveillance. However, since laboratory staff are often not trained in the identification of environmental organisms such as *B. pseudomallei*, the literature is littered with instances in which the diagnosis has been missed or delayed, often with fatal results, even when appropriate samples had been taken and the organism had been isolated but either dismissed or misidentified [38-41].

Finally, even if the patient has managed to see a doctor who has sent appropriate samples and the laboratory has isolated and correctly identified the organism, it may or may not be captured by local surveillance systems. Even in countries where mandatory laboratory-based surveillance systems exist, official data regarding melioidosis can be grossly misleading. For example, it has been known since the mid-1980s that melioidosis is highly endemic in Thailand, especially in the northeast of the country [33]. Nonetheless, when Hantrakun and colleagues reviewed 7126 laboratory-confirmed cases between 2012 and 2015, they found major discrepancies between the laboratory data and what was being reported through the National notifiable diseases surveillance system (NNDSS), particularly over-reporting of cases based on serology, which is notoriously inaccurate, and dramatic under-reporting of deaths [42]. Even in a country like the UK, where melioidosis is not endemic and the number of cases seen is small, and where notification of the isolation of *B. pseudomallei* by laboratories became mandatory under the Health Protection (Notification) Regulations 2010, O'Connor *et al.* found that only 19 of 46 (41.3%) patients with culture-confirmed melioidosis diagnosed in the UK between January 2010 and July 2019 had been notified [43].

Biothreat potential

B. pseudomallei is one of the bacteria that has been considered as an agent that might be used as a weapon, either by terrorists or by state actors. It was classified as a 'Category B critical biological agent for public health preparedness' by Rotz *et al.* in 2002 [44], and more recently as a 'Tier 1 Select Agent' by the US Department of Health and Human Services and Department of Agriculture (https://www.selectagents.gov/sat/list.htm). The reasons for this are several fold. First, *Burkholderia mallei*, the causative agent of glanders, which is effectively a clone of *B. pseudomallei* that has become adapted as a pathogen of equines in association with the loss of large sections of its genome [45], was used as a weapon against horses by German agents during World War I [46]. Secondly, *B. pseudomallei* is known to be infectious by inhalation, and in animal models, the infectious dose can be extremely low. Thirdly, it is intrinsically resistant to antibiotics and difficult to treat. Additionally, as an environmental saprophyte that is widespread in tropical environments, it would be relatively easy to obtain. On the other hand, there appears to have been little research done into its weaponization, at least as far as is known from information in the public domain, although it was undoubtedly an agent of interest to Biopreparat, the Soviet biological weapons programme [47]. It would certainly not be as easy to aerosolize as a spore-forming organism like *Bacillus anthracis* and, as an opportunistic pathogen with a predilection for people with underlying conditions such as diabetes mellitus, its impact on whole populations is difficult to predict. This topic has been extensively reviewed [46].

Nonetheless, whether or not *B. pseudomallei* is likely ever to be used as a weapon, the attention paid to the organism undoubtedly increased after its classification as a Select Agent, as did the funding devoted to melioidosis research, so this has not been without its benefits to melioidosis as a real-world public health problem.

Melioidosis as a Neglected Tropical Disease

Suppose the predictions from the model of Limmathurotsakul *et al*. are anywhere near accurate. In that case, the annual global mortality from melioidosis is comparable to that of measles and higher than some infections that are far better known, such as leptospirosis and dengue [2]. The overall disease burden would be considerably higher than that of many diseases that are formally classified as NTDs by the WHO and falls primarily on the poor rural working in agriculture [30]. It is certainly greatly under-diagnosed and therefore inappropriately treated, but if picked up early and treated correctly, the mortality can be reduced from around 50% to less than 10% [48]. This recently led several of us to call for WHO to recognize melioidosis as an 'official' NTD in the hope that this would further raise the profile of the infection and result in it being given higher priority by local and global health agencies [49].

Conclusions

Whatever the true burden and distribution of melioidosis eventually proves to be, there is no doubt that it is currently grossly under-recognized and under-reported. It fulfills the criteria for a neglected tropical disease, and it is long overdue that it should be formally recognized as such. Only better surveillance, improved access to diagnostics, better education of clinicians and laboratory staff in its recognition and management, and the implementation of effective preventive measures will help to reduce the unnecessary suffering and death toll from this silent killer.

References

1. Dance DAB. Melioidosis: the tip of the iceberg? Clinical microbiology reviews 1991; 4(1): 52-60.
2. Limmathurotsakul D, et al. Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis. Nature Microbiology 2016; 1: 15008.
3. Parajuli S, et al. Bilateral Non Granulomatous Anterior Uveitis from Melioidosis Case Report. Acta Scientific Ophthalmology 2020; 3.8: 03-05.
4. Kuijpers SC, et al. Primary cutaneous melioidosis acquired in Nepal - Case report and literature review. Travel Med Infect Dis 2021; 42: 102080.
5. Bhandari PB, et al. A Fatal Case of Cerebral Melioidosis. Medical Journal of Shree Birendra Hospital 2019; 18(2): 64-68.
6. Abu Khattab M, et al. Melioidosis an Imported Infection in Qatar: Case Series and Literature Review. Advances in Infectious Diseases 2022; 12(02): 175-92.
7. Ombelet S, et al. Blood culture surveillance in a secondary care hospital in Benin: epidemiology of bloodstream infection pathogens and antimicrobial resistance. BMC infectious diseases 2022; 22(1).
8. Bousquet A, et al. Accidental exposure to Burkholderia pseudomallei: awareness is also needed for urine specimens. Clin Microbiol Infect 2020; 26(2): 265-66.
9. Shongo MY-P, et al. Melioidosis and sickle cell disease: Description of a rare association. Theory and Clinical Practice in Pediatrics 2020; 3(1): 57-62.
10. Almog Y, et al. A Burkholderia pseudomallei Infection Imported from Eritrea to Israel. The American journal of tropical medicine and hygiene 2016; 95(5): 997-98.
11. Oduro G, et al. On the Environmental Presence of Burkholderia pseudomallei in South-Central Ghana. Applied and environmental microbiology 2022; 88(12): e0060022.
12. Mabayoje DA, et al. Melioidosis Manifesting as Chronic Femoral Osteomyelitis in Patient from Ghana. Emerging infectious diseases 2022; 28(1): 201-04.
13. Dicko AA, et al. Mélioïdose cutanée : A propos d'un cas au Mali. Revue Malienne d'Infectiologie et de Microbiologie 2022; 17(1): 97-99.
14. Pasupneti T, et al. Disseminated melioidosis in a patient from Nicaragua. IDCases 2021; 26: e01318.
15. Canales R, et al. MELIOIDOSIS IN A BOTTLENOSE DOLPHIN (TURSIOPS TRUNCATUS) AFTER A HURRICANE IN THE CARIBBEAN ISLANDS. J Zoo Wildl Med 2020; 51(2): 443-47.
16. Hogan C, et al. Melioidosis in Trinidad and Tobago. Emerging infectious diseases 2015; 21(5): 902-04.
17. Nolen LD, et al. Differentiating New from Newly Detected: Melioidosis in Yap, Federated States of Micronesia. The American journal of tropical medicine and hygiene 2019.
18. CDC Health Alert Network. Melioidosis Locally Endemic in Areas of the Mississippi Gulf Coast after *Burkholderia pseudomallei* Isolated in Soil and Water and Linked to Two Cases – Mississippi, 2020 and 2022. 2022. https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjgoID27a_5AhXxRkEAHY3sC2gQFnoECBAQAQ&url=https%3A%2F%2Fwww.emergency.cdc.gov%2Fhan%2F2022%2Fpdf%2FCDC_HAN_470.pdf&usg=AOvVaw0EHqQWY5IUIWfTpi5PZka_ (accessed 05/08/22 2022).
19. Cossaboom CM, et al. Melioidosis in a Resident of Texas with No Recent Travel History, United States. Emerging infectious diseases 2020; 26(6): 1295-99.
20. Dan M. Melioidosis in Travelers: Review of the Literature. J Travel Med 2015; 22(6): 410-4.
21. Birnie E, et al. Melioidosis in travelers: An analysis of Dutch melioidosis registry data 1985-2018. Travel Med Infect Dis 2019: 101461.
22. Saidani N, et al. Melioidosis as a travel-associated infection: Case report and review of the literature. Travel Med Infect Dis 2015; 13(5): 367-81.
23. Ryan CW, et al. Public health response to an imported case of canine melioidosis. Zoonoses Public Health 2018; 65(4): 420-24.
24. Dawson P, et al. Human Melioidosis Caused by Novel Transmission of Burkholderia pseudomallei from Freshwater Home Aquarium, United States(1). Emerg Infect Dis 2021; 27(12): 3030-35.
25. Gee JE, et al. Multistate Outbreak of Melioidosis Associated with Imported Aromatherapy Spray. N Engl J Med 2022; 386(9): 861-68.
26. Pearson T, et al. Phylogeographic reconstruction of a bacterial species with high levels of lateral gene transfer. BMC biology 2009; 7: 78.
27. Sarovich DS, et al. Phylogenomic analysis reveals an Asian origin for African *Burkholderia pseudomallei* and further supports melioidosis endemicity in Africa. mSphere 2016; 1(2).

28. Chewapreecha C, et al. Global and regional dissemination and evolution of Burkholderia pseudomallei. Nat Microbiol 2017; 2: 16263.
29. Meumann EM, et al. Emergence of Burkholderia pseudomallei Sequence Type 562, Northern Australia. Emerg Infect Dis 2021; 27(4): 1057-67.
30. Birnie E, et al. Global burden of melioidosis in 2015: a systematic review and data synthesis. Lancet Infect Dis 2019; 19(8): 892-902.
31. Manivanh L, et al. Burkholderia pseudomallei in a lowland rice paddy: seasonal changes and influence of soil depth and physico-chemical properties. Sci Rep 2017; 7(1): 3031.
32. Global Burden and Challenges of Melioidosis. Basel: MDPI; 2019.
33. Suputtamongkol Y, et al. The epidemiology of melioidosis in Ubon Ratchatani, northeast Thailand. International journal of epidemiology 1994; 23(5): 1082-90.
34. Phetsouvanh R, et al. Melioidosis and Pandora's box in the Lao People's Democratic Republic. Clin Infect Dis 2001; 32(4): 653-4.
35. Dance DAB, et al. Melioidosis in the Lao People's Democratic Republic. Trop Med Infect Dis 2018; 3(1).
36. Chansrichavala P, et al. Public awareness of melioidosis in Thailand and potential use of video clips as educational tools. PLoS ONE [Electronic Resource] 2015; 10(3): e0121311.
37. Yee KC, et al. Melioidosis, the great mimicker: a report of 10 cases from Malaysia. The Journal of tropical medicine and hygiene 1988; 91(5): 249-54.
38. Muthumbi EM, et al. Population-Based Estimate of Melioidosis, Kenya. Emerging infectious diseases 2019; 25(5): 984-87.
39. Wu B, et al. Misidentification of Burkholderia pseudomallei, China. Emerging infectious diseases 2021; 27(3): 964-66.
40. Nguyen HB, et al. Case of misdiagnosed melioidosis from Hue city, Vietnam. Iranian journal of microbiology 2022.
41. Greer RC, et al. Misidentification of Burkholderia pseudomallei as Acinetobacter species in northern Thailand. Trans R Soc Trop Med Hyg 2019; 113(1): 48-51.
42. Hantrakun V, et al. Clinical Epidemiology of 7126 Melioidosis Patients in Thailand and the Implications for a National Notifiable Diseases Surveillance System. Open Forum Infect Dis 2019; 6(12): ofz498.
43. O'Connor C, et al. Imported melioidosis in the United Kingdom: Increasing incidence but continued under-reporting. Clinical Infection in Practice 2020: 100051.
44. Rotz LD, et al. Public health assessment of potential biological terrorism agents. Emerg Infect Dis 2002; 8(2): 225-30.
45. Nierman WC, et al. Structural flexibility in the Burkholderia mallei genome. Proceedings of the National Academy of Sciences of the United States of America 2004; 101(39): 14246-51.
46. Dance DAB. Melioidosis and glanders as possible biological weapons. In: Fong I, Alibek K, eds. Bioterrorism and infectious agents: a new dilemma for the 21st century. New York: Springer; 2005: 99-145.
47. Alibek K. Biohazard : the chilling true story of the largest covert biological weapons program in the world, told from the inside by the man who ran it: First edition. New York : Random House, [1999] ©1999; 1999.
48. Currie BJ, et al. The Darwin Prospective Melioidosis Study: a 30-year prospective, observational investigation. The Lancet Infectious diseases 2021; 21(12): 1737-46.
49. Savelkoel J, et al. A call to action: time to recognise melioidosis as a neglected tropical disease. The Lancet Infectious Diseases 2022; 22(6): e176-e82.