Personal View

A call to action: time to recognize melioidosis as a neglected tropical disease

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Abstract

Melioidosis is a tropical infection caused by the soil bacterium *Burkholderia pseudomallei*. Despite the significant impact of this often-overlooked pathogen on both the healthcare systems and economies of numerous low- and middle-income countries around the globe, melioidosis is not officially classified as a neglected tropical disease (NTD) by the World Health Organization (WHO). Melioidosis causes a higher estimated disease burden and mortality than many other recognized NTDs, with deaths primarily occurring amongst the rural poor in low- and middle-income countries. Fortunately, the impact of melioidosis in a region can be reduced once awareness is established of its known or suspected endemicity. In this Personal View we provide evidence in support of official recognition of melioidosis as an NTD. We urge member states to request WHO to revisit their NTD list and appeal to government and philanthropic organizations to establish programmes in endemic countries to control melioidosis in order to reduce its global health burden.

Melioidosis is a tropical infectious disease caused by the Gram-negative bacterium *Burkholderia pseudomallei.*[1,2] As *B. pseudomallei* is an environmental bacterium living in contaminated soil or water, inoculation, inhalation or ingestion of the organism from environmental sources may prompt localised infection leading to dissemination via the bloodstream, after which a broad clinical spectrum of disease can become apparent, ranging from pneumonia, intra-abdominal abscesses (e.g. spleen, liver, prostate) and fulminant sepsis to less common manifestations, such as infections of the musculoskeletal system or the central nervous system.[1,2] The disease primarily affects adults (median age of 50 years) with underlying comorbidities, of which diabetes is the most notable and present in about 50% of cases.[1,3]

Melioidosis is widely recognized as endemic in Southeast Asia and northern Australia, but it is increasingly reported from elsewhere. A modelling study predicted the disease to be far more common throughout the tropics than is generally appreciated and evidence continues to emerge of confirmed or probable endemicity in new areas.[4] Melioidosis is listed by the United States Centers for Disease Control and Prevention (CDC) as a Tier 1 Select Agent due to its biothreat potential.[5] Moreover, the disease is statutorily notifiable in a number of both endemic and non-endemic countries indicating that it is recognized as an important and high-impact disease despite its omission from the list of neglected tropical diseases (NTDs) established by the World Health Organization (WHO).

The initial NTD list with 13 diseases established in 2005 was later expanded to account for additional diseases impacting on global public health and nowadays comprises 20 diseases and disease groups that, according to WHO, disproportionately affect more than 1 billion of the poorest people on the globe.[6-8] Recently the WHO published a new road map for NTDs for the years 2021 to 2030.[9] Melioidosis, however, is so neglected that it is not even classified as an NTD despite estimates supporting it causing a much larger health burden and mortality than many officially recognized NTDs.[3,10,11]

Here we argue for the recognition and classification of melioidosis as an NTD.

Global distribution and burden of melioidosis

Continuing research efforts are helping to map the true distribution and burden of melioidosis, although these face many difficulties, as discussed below.[4,12]

Modelling estimates

Modelling has estimated that there were approximately 165,000 cases of melioidosis causing 89,000 deaths per year globally in 2015.[4] A subsequent study published in 2019 estimated the global burden of melioidosis as 4·64 million disability-adjusted life years (DALYs), which is higher than that of many NTDs, such as intestinal nematode infections (4·56 million DALYs), leptospirosis (2·90 million DALYs), dengue (2·86 million DALYs) and schistosomiasis (2·63 million DALYs) (**Figure 1**).[3] Years of life lost contributed roughly 99% of this number as a result of the high mortality rate of melioidosis.[3] However, the number of DALYs per 100,000 individuals varied considerably between countries as a result of differences in both incidence and mortality rates. For example, it was 8·7 in Australia compared to 212·6 in Thailand.[3] This is just one illustrative example of the global disparity in melioidosis that is so characteristic of NTDs.

Verification of endemicity across the globe

Isolation of *B. pseudomallei* from both environmental and clinical samples provides unequivocal confirmation of melioidosis endemicity. Mapping of the presence of *B. pseudomallei* in a country where bacterial culture of clinical samples is not routinely available, as is the case in many of the rural tropical locations where melioidosis is most likely to exist, may alternatively be conducted using a combination of serosurveillance and environmental sampling, such as a study conducted in Gabon.[13] Unfortunately, isolation of *B. pseudomallei* from environmental samples is fraught with difficulty, presenting an obstacle to establishing the true distribution of melioidosis.[14] Nonetheless, there is good evidence for endemicity in at least 45 countries spanning Southeast and South Asia, Australia, Pacific and Indian Ocean island nations, sub-Saharan Africa, Central and South America and the Caribbean, as summarised in several reviews.[4,15-20] For reasons discussed below, however, the number of cases that are currently being recognised falls well short of the modelling estimates in most countries known to be melioidosis-endemic.[4]

Efforts are underway to verify the presence of melioidosis in some of the 34 countries suspected from the modelling study to harbour *B. pseudomallei* but where it has not yet been recognized.[4] Evidence suggesting endemicity has already been obtained in some new geographies; including the Horn of Africa,[21] Federation of St. Kitts and Nevis,[22] Micronesia,[23] and Trinidad and Tobago.[24] Ascribing melioidosis endemicity can, however, be

particularly difficult, since patients often have complex travel histories and latent periods of many years after infection can occur before clinical disease in some cases.[1,25,26] In addition, while geospatial modelling had predicted that the southern USA would be receptive for *B. pseudomallei*,[4] evidence for autochthonous cases of melioidosis in the USA has been lacking until the recent report of a resident of Texas, without a history of travel to melioidosis endemic areas, whose *B. pseudomallei* isolate was genetically closely related to other isolates from the Americas.[27] Furthermore, review of the genotype of a historical case from the same county in Texas, that had previously been incorrectly attributed to infection in Asia during World War II, showed a related genotype.[28] This suggests that *B. pseudomallei* is indeed endemic in the continental USA, although whether this reflects recent introduction is unknown, and environmental confirmation is still required.[27] Additionally, it demonstrates the potential for spread of *B. pseudomallei* across the globe, which itself is predicted to accelerate with global climate change and increasing travel.[29]

Neglected status of melioidosis

The reason why melioidosis is neglected reflects a combination of the populations affected, a lack of awareness among healthcare workers, a lack of microbiology services in the regions most affected, complexities in detection and diagnosis of the bacterium, deficiencies in current surveillance systems, and a lack of epidemic potential. Moreover, it might be challenging to add another pathogen to surveillance systems in low- and middle-income countries due to a lack of resources. Unfortunately this results in the disease being regarded as of low priority for national and international public health programmes, with allocation of very limited funds to melioidosis research, creating a vicious circle of under-recognition.

Populations affected

Melioidosis primarily affects the rural poor in low- and middle-income countries: it is estimated that >99% of deaths from melioidosis occur within these countries.[4] The current burden of melioidosis is not only higher in these countries but is also expected to rise with the global pandemic of diabetes mellitus, which increases the risk of melioidosis by at least 12-fold and which is growing particularly in low- and middle-income tropical countries.[1,30-32] The majority of the poorest people on the globe work in the agricultural sector,[33] hence in melioidosis-endemic areas they face a disproportionate “double burden” from both

increasing diabetes prevalence and exposure to the environmental bacterium *B. pseudomallei*.[30,31]

Lack of awareness among clinicians

In many melioidosis-endemic areas, clinicians may not consider the disease in their differential diagnoses, with potentially serious consequences. For example, in a recent retrospective Malaysian study, a majority of patients with melioidosis did not initially receive melioidosis-appropriate antibiotics owing to a lack of clinical suspicion.[34]

Lack of microbiology services in regions most affected

The availability of laboratory facilities and trained personnel is a key issue. Pathology and laboratory medicine (including but not limited to medical microbiology) are vital services to support optimal healthcare but laboratory services are frequently absent or under-developed in low- and middle-income countries, particularly in the more remote and rural areas where melioidosis patients tend to live.[35]

Even where laboratories do exist, laboratory staff unfamiliar with *B. pseudomallei* frequently misidentify the organism as '*Pseudomonas* species' or dismiss it as a contaminant.[36] Even new automated identification systems, such as MALDI/TOF mass spectrometry, also systematically misidentify *B. pseudomallei* if the appropriate database is not installed.[37] Again, this may have damaging consequences, highlighting the importance of increased awareness.[38]

Difficulties of detection and diagnosis

The current diagnostic gold standard is culture and isolation of *B. pseudomallei* from any clinical specimen.[1] However, it is common for patients presenting with community-acquired sepsis in developing tropical countries to receive empirical antibiotic treatment without the appropriate clinical specimens being collected for bacterial culture. Furthermore, no point-of-care test for a reliable, affordable, rapid diagnosis of melioidosis is currently commercially available.[1,2,39,40]

Deficiencies in current surveillance systems

Diagnosis of melioidosis requires laboratory confirmation. In some countries, such as Laos, there is no laboratory-based surveillance system and so melioidosis goes largely unrecognised at a national level.[41] In Thailand, where melioidosis is well known amongst clinicians, the official surveillance system has until recently failed to identify the true burden of melioidosis, particularly in terms of mortality.[42,43] Even in non-endemic countries such as the UK, where laboratory-based surveillance is well developed and notification of melioidosis is mandatory, a recent study showed that 41·3% of cases of melioidosis were not notified to the national surveillance system.[44]

Lack of epidemic potential

One of the most important reasons for its neglect is the fact that melioidosis does not spread readily from person to person.[1,45] This means that explosive outbreaks of infection, such as those seen with COVID-19 or Ebola, do not occur, although the disease continues to kill many thousands of people in endemic areas every year. The limited risks of inhabitants of high-income, non-endemic countries acquiring this potentially fatal disease naturally has also contributed to the low priority accorded to melioidosis.[45,46]

Global funding for melioidosis

Melioidosis is truly neglected compared to other NTDs when comparing funds available for research and development (R&D). Global investment in 2016 for melioidosis non-biodefence R&D has been estimated to be less than US$ 4 million.[3] In comparison, R&D investment was estimated by the WHO to be considerably higher for some diseases with a comparable or even a lower DALY burden (**Figure 1**).[3] For example, US$ 788 million, 283 million, and 244 million were invested in dengue, intestinal nematode infections, and schistosomiasis, respectively.[3]

Interestingly, the greatest boost to the profile and funding of melioidosis came when it was listed as a potential biothreat agent in the United States, resulting in significant investment in melioidosis research and to some extent the loss of its "orphan status".[46] Despite this capital injection, the initial concerns about bioterrorism appear to be diminishing, particularly in the context of the current COVID-19 pandemic. In addition, although cases of melioidosis imported into non-endemic countries across Europe are being reported with increasing frequency, the overall numbers remain low and the availability of

better diagnostic resources and treatment options mean that the high mortality rates seen in resource-limited countries are not observed.[44,47,48] Altogether, the previous injection of biodefence-driven funding for melioidosis research has undoubtedly moved the field forward, particularly in high-income countries, but in reality this has had limited impact on incidence and mortality in most melioidosis-endemic regions.[49]

Compliance of melioidosis with the WHO criteria for NTDs

We have assessed melioidosis against the WHO criteria for defining NTDs in **Table 1**.[50] In our opinion it satisfies every criterion. It disproportionately affects the rural poor in low- and middle-income countries across the globe, displaying high mortality rates, which we believe justifies a coordinated global response. The national and global health impact can be reduced by increasing basic public health measures alongside sustainable improvement of healthcare facilities and investment in R&D (**Table 2**). However, the process of adopting a new NTD requires member states to submit a request to the WHO Country and Regional Office(s).[50] A pre-requisite for this is either an efficient routine surveillance system that captures melioidosis or R&D funding that enables endemic countries to recognise their true burden of melioidosis. In practice, large parts of the scientific community already informally classify melioidosis as an NTD, as is reflected by the fact that the journal *PLOS Neglected Tropical Diseases* includes melioidosis within their list of NTDs because of its global public health impact.[7]

Benefits of including melioidosis as an NTD

It is our belief that the recognition of melioidosis as an NTD by WHO would help to encourage the inclusion of melioidosis in the national public health strategies of many endemic countries. We have summarised the approaches as part of the roadmap 2021-2030 to combatting the worldwide melioidosis burden in **Table 2** and believe that preventative measures in combination with enhanced case management will undoubtedly lead to a decrease in global morbidity and mortality from melioidosis, as has occurred over the past decades in northern Australia.[51,52]

Raised awareness and surveillance at governmental level

The improvement of surveillance should be a priority on the agenda of governments in order to map and monitor the health impact of melioidosis. Furthermore, government organizations have a key role to play in driving the sustainable improvement of laboratory facilities and in implementing disease-specific awareness, prevention and management campaigns. Improved diagnosis of melioidosis could be piggy-backed onto other programmes aimed at strengthening diagnostic microbiology within melioidosis-endemic countries, such as that being implemented by the UK Fleming Fund with the overall aim of improving detection, prevention and management of antimicrobial resistance.[53] This approach would allow strengthening of care for melioidosis patients by using existing programmes and logistics already in place, thereby maximizing output.

Enhanced awareness among healthcare workers

Efforts to increase awareness should initially be focused on both front-line clinicians and staff in microbiology laboratories. There have recently been a number of initiatives aimed at doing just this, for example through specific training events on melioidosis in Laos and Cambodia.[54] Events have even been held outside regions that are well known to be melioidosis-endemic such as Southeast Asia, for example the first-ever African melioidosis workshop in Nigeria in 2019 and those in two countries in the Americas held in Colombia in 2018 and Mexico in 2019.[55,56] The International Melioidosis Network (IMN) plays an active role in creating melioidosis awareness by organizing (inter)national events and by fostering research collaborations.[57] Such events are especially important in regions where melioidosis has only rarely been recognised but is clearly an emerging infection.

Enhanced diagnosis

Although *B. pseudomallei* is commonly misidentified by untrained personnel, high technology facilities are not required to recognise *B. pseudomallei*. For example, a laboratory algorithm that included a three-antibiotic disc test proved to be 100% specific in identifying *B. pseudomallei* in clinical samples in Vietnam, and this could be rolled out more widely.[58] Another potentially useful approach is the direct detection of *B. pseudomallei* antigens in clinical samples, although the tests currently available lack an overall consistent sensitivity and specificity across various samples.[1,2,39,40]

Enhanced case management

The availability of adequate diagnostics and access to care is associated with better outcomes. For instance, a recent retrospective Thai study that included over 7,000 patients found an overall 30-day mortality of 39%.[43] In contrast, the Darwin Prospective Melioidosis Study reported a mortality rate of only 14% in 540 Australian melioidosis patients over a 20-year period, with further decreases to a mortality now around 5%.[51,52] One obstacle that will need to be overcome is the implementation of therapeutic algorithms that cover melioidosis once it is recognised as being present in a locality. Melioidosis requires an initial intensive phase of treatment with ceftazidime or a carbapenem followed by a prolonged eradication phase with trimethoprim-sulfamethoxazole, as *B. pseudomallei* is resistant to first- and second-generation cephalosporins and gentamicin amongst other agents.[1] Fortunately, the required antibiotics are already listed by the WHO as 'essential'.[59] In addition, screening tools and treatments for diabetes are also listed as essential by the WHO allowing a combined approach together with improved diabetes management (**Table 2**).[59,60] Comprehensive guidelines that give excellent results are available,[61] although local guidelines need to be developed to take into account local factors.

Prevention

The most important consideration is that "prevention is better than cure" and consequently we need to intensify preventive efforts. Preventive chemotherapy (one of the WHO approaches) has so far only found a very limited role in combatting melioidosis.[62-65] Several vaccine candidates are in development, of which one is planned to proceed to the first phase 1 clinical trial, and additional recognition and support might accelerate the development and licensure.[2,66] Should an effective vaccine targeted at high-risk individuals become available, it has been assessed as being a cost-effective approach in most melioidosis-endemic areas.[67] Until then, strategies to prevent melioidosis entail basic public health measures such as those recommended by the WHO to control other NTDs, namely intensifying case detection, improving case management and providing safe water, sanitation and hygiene.[50]

These measures have been used in a tailored approach to melioidosis prevention in northeast Thailand, which includes minimising contact with possibly contaminated soil (e.g. through the use of boots or waders) or water (e.g. drinking boiled water), and measures

that reduce the risk of acquiring, and improve management of, conditions that predispose to melioidosis, such as diabetes mellitus, chronic kidney disease or chronic respiratory disease (e.g. through healthy diet, avoiding smoking, etc.).[68] Awareness campaigns are undertaken annually in northern Australia, alongside chlorination of all domestic water supplies and specific projects aimed at increasing the use of protective footwear or reducing hazardous alcohol use, another known risk factor for melioidosis.[69,70] In Thailand, a trial of a multifaceted prevention programme in diabetic patients resulted in a lower hospital admission rate due to infectious diseases and reduced all-cause mortality, although the reduction in the incidence rate of culture-confirmed melioidosis did not achieve statistical significance.[71] Thus, prevention of melioidosis can be accomplished by increasing awareness of the disease amongst people at risk and the adoption of some simple measures, which has the additional benefit of reducing the risk of exposure to other infectious agents that are found in the environment. Altogether, national awareness campaigns directed towards the general public would ideally be a combined effort between researchers and government organizations, with efforts underpinned and driven by formal acknowledgement of the impact of this disease by WHO.

Conclusions and recommendations

The global health impact of melioidosis in resource-constrained countries warrants increased attention. In recent years, new evidence has underscored the fact that melioidosis is present across the tropics and causes a much higher disease burden than previously thought. Therefore, we argue for a combined approach of heightened melioidosis awareness, prevention and enhanced case management, together with improved prevention and management of diabetes as its most important risk factor, especially in the face of the growing prevalence of diabetes in the tropics. Commitment of governments in melioidosis-endemic countries to implementing awareness, prevention and management campaigns provides an opportunity to reduce the high mortality rates of melioidosis. Recognition of melioidosis as an NTD by WHO would undoubtedly help to improve awareness and mobilize funding for this serious and potentially fatal infectious disease. We urge member states to request WHO to revisit their list of NTDs and consider the inclusion of melioidosis. It is time to recognize this severely neglected tropical disease.

Acknowledgments

We would like to thank the whole melioidosis community, embodied in the International Melioidosis Network (IMN), for all the friendship, collegiality and continued support. Special thanks to Dr. Emma Birnie for carefully reading the manuscript. This work was supported by the Netherlands Organization for Scientific Research (VIDI grant number 91716475 to WJW). The work of DABD and DL on melioidosis was funded in part by the Wellcome Trust (Grant number 106698/Z/14/Z) and of BJC was supported by the Australian National Health and Medical Research Council grant numbers 1098337 and 1131932 (The HOT NORTH initiative). Biological Threat Reduction Program (BTRP) has supported the organization of a Melioidosis Threat Reduction Network (TRN) for melioidosis in Southeast Asia (grant no. HDTRA1-16-C-0017). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. For the purpose of open access, the author has applied a CC BY public copyright licence to any Author Accepted Manuscript version arising from this submission.

Contributors

JS, DABD, BJC, DL and WJW conceived the text and performed literature searches. JS and WJW prepared the first draft. DABD and WJW supervised the whole process. All authors gave critical feedback, provided guidance on methods, and reviewed the report.

Declaration of interests

DABD acts as a consultant to InBios International Inc. in relation to the development of rapid diagnostics for melioidosis. The other authors declare no competing interests.

Table 1. WHO criteria and arguments for classification of melioidosis as an NTD		
WHO criteria		Arguments for inclusion
Criterion 1	The condition disproportionately affects populations living in poverty; and causes important morbidity and mortality – including stigma and discrimination – in such populations, justifying a global response	- Worldwide estimated 165,000 annual cases and 89,000 deaths - >99% of deaths occur within low- and middle-income countries and predominantly amongst poor agricultural workers - Annual estimated disease burden of 4·64 million DALYs
Criterion 2	The condition primarily affects populations living in tropical and sub-tropical areas	- Melioidosis is only known to be endemic in the tropics and sub-tropics
Criterion 3	The condition is immediately amendable to broad control, elimination or eradication by applying one or more of the five public health strategies adopted by the Department for Control of NTDs, which include 1) preventive chemotherapy, 2) intensified case management, 3) vector control, 4) veterinary public health, and 5) safe water, sanitation and hygiene	*Preventative measures:* - Increased awareness amongst people of endemic countries - Avoiding possible exposure (e.g. use of protective footwear, boiled drinking water) - Diabetes prevention, detection and management *Intensified case management:* - Increased awareness amongst health care workers - Improvement of diagnostic facilities - Treatment according to melioidosis guidelines - Implementation of national surveillance systems
Criterion 4	The condition is relatively neglected by research – i.e., resource allocation is not commensurate with the magnitude of the problem – when it comes to developing new diagnostics, medicines and other control tools	- Global investment lags behind other NTDs, especially when considering estimated disease burden
The criteria for adoption of a disease as an NTD were derived from the WHO.[50] Abbreviations: DALY = Disability Adjusted Life Year, NTD = Neglected Tropical Disease, WHO = World Health Organization.		

Table 2. Roadmap 2021-2030: required actions to combat the national and global burden of melioidosis		
	Melioidosis	**Diabetes***
Awareness	National awareness campaigns to establish basic knowledge on the disease and high-risk activities associated with possible exposure together with increased vigilance of physicians towards the condition	National awareness campaigns aimed to limit risk factors known to increase the chance of developing diabetes
Prevention	Use of protective equipment to minimize the risk of acquiring the disease together alongside support in vaccine development and implementation	Upscaling of lifestyle interventions and case-specific screening
Healthcare	Improved diagnostic facilities and trained personnel to enhance diagnosis and implementation of national treatment guidelines	Improved and intensified glycaemic management according to national guidelines
Surveillance	National disease surveillance to map the true incidence and understand the true burden of disease	National monitoring of efficacy of implemented approaches as mentioned above
Funding	Commitment of government and philanthropic organizations to allocate funds in implementing the approaches as mentioned above and to stimulate R&D	
* The actions to combat melioidosis include the improvement of care for diabetes as its most important risk factor.[30,31] Abbreviations: R&D = Research & Development.		

Figure 1. Disease burden and global investment of neglected tropical diseases

The percentage of DALYs per NTD for the year 2015 was calculated by dividing the individual DALYs per NTD by the summed DALYs of the 17 NTDs (i.e. a total of 27·98 million DALYs) as included in the analyses of the study on the global burden of melioidosis.[3] A similar approach was followed for the percentage of global investment per NTD in US$ for the year 2016 with a total global investment of 2983 million US$. Infectious diseases absent from the top 39 of investment in research and development were assigned less than 4 million US$, resembling the global investment of the last within the group of 39. Melioidosis and leptospirosis are not considered as an NTD by the WHO. Data was not available for Buruli ulcer, dracunculiasis (Guinea worm), mycetoma, scabies, snakebite, and yaws.

Abbreviations: DALY = Disability Adjusted Life Years, NTD = Neglected Tropical Diseases, US$ = United States Dollar, WHO = World Health Organization.

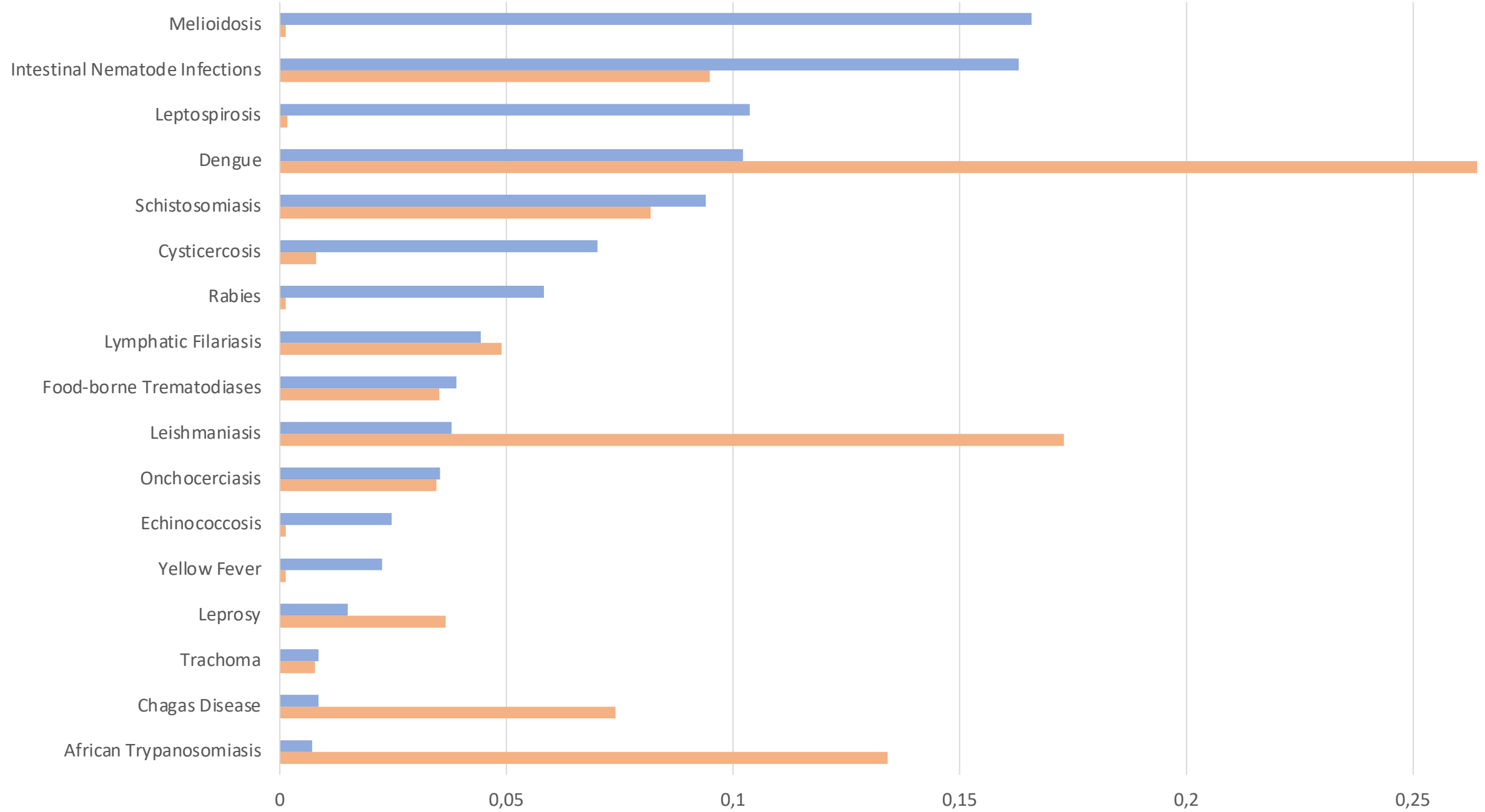
References

1. Wiersinga WJ, Virk HS, Torres AG, et al. Melioidosis. *Nat Rev Dis Primers* 2018; **4:** 17107.
2. Virk HS, Mukhopadhyay C, Wiersinga WJ. Melioidosis: A Neglected Cause of Community-Acquired Pneumonia. *Semin Respir Crit Care Med* 2020; **41:** 496–508.
3. Birnie E, Virk HS, Savelkoel J, et al. Global burden of melioidosis in 2015: a systematic review and data synthesis. *Lancet Infect Dis* 2019; **19:** 892–902.
4. Limmathurotsakul D, Golding N, Dance DA, et al. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. *Nat Microbiol* 2016; **1:** 15008.
5. CDC. Select Agents and Toxins List. https://www.selectagents.gov/sat/list.htm (accessed February 15 2021).
6. WHO. Neglected tropical diseases. https://www.who.int/neglected_diseases/diseases/en/ (accessed October 2 2020).
7. Hotez PJ, Aksoy S, Brindley PJ, Kamhawi S. What constitutes a neglected tropical disease? *PLoS Negl Trop Dis* 2020; **14:** e0008001.
8. Molyneux DH, Asamoa-Bah A, Fenwick A, Savioli L, Hotez P. The history of the neglected tropical disease movement. *Trans R Soc Trop Med Hyg* 2021; **115:** 169–75.
9. WHO. Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030. https://apps.who.int/iris/bitstream/handle/10665/332094/WHO-UCN-NTD-2020.01-eng.pdf?ua=1 (accessed February 7 2021).
10. Dance DA, Limmathurotsakul D. Global Burden and Challenges of Melioidosis. *Trop Med Infect Dis* 2018; **3:** 13.
11. Wiersinga WJ. Melioidosis: time to recognize a deadly but neglected tropical disease. https://naturemicrobiologycommunity.nature.com/posts/37031-melioidosis-time-to-recognize-a-deadly-but-neglected-tropical-disease (accessed February 7 2021).
12. Gibney KB, Cheng AC. Reducing the melioidosis burden: public health, chronic disease prevention, or improved case management? *Lancet Infect Dis* 2019; **19:** 800–2.
13. Wiersinga WJ, Birnie E, Weehuizen TA, et al. Clinical, environmental, and serologic surveillance studies of melioidosis in Gabon, 2012-2013. *Emerg Infect Dis* 2015; **21:** 40–7.
14. Dance DAB, Knappik M, Dittrich S, et al. Evaluation of consensus method for the culture of Burkholderia pseudomallei in soil samples from Laos. *Wellcome Open Res* 2018; **3:** 132.
15. Sanchez-Villamil JI, Torres AG. Melioidosis in Mexico, Central America, and the Caribbean. *Trop Med Infect Dis* 2018; **3:** 24.
16. Rolim DB, Lima RXR, Ribeiro AKC, et al. Melioidosis in South America. *Trop Med Infect Dis* 2018; **3:** 60.
17. Steinmetz I, Wagner GE, Kanyala E, et al. Melioidosis in Africa: Time to Uncover the True Disease Load. *Trop Med Infect Dis* 2018; **3:** 62.
18. Zheng X, Xia Q, Xia L, Li W. Endemic Melioidosis in Southern China: Past and Present. *Trop Med Infect Dis* 2019; **4:** 39.
19. Mukhopadhyay C, Shaw T, Varghese GM, Dance DAB. Melioidosis in South Asia (India, Nepal, Pakistan, Bhutan and Afghanistan). *Trop Med Infect Dis* 2018; **3:** 51.
20. Birnie E, Wiersinga WJ, Limmathurotsakul D, Grobusch MP. Melioidosis in Africa: should we be looking more closely? *Future Microbiol* 2015; **10:** 273–81.
21. Almog Y, Yagel Y, Geffen Y, Yagupsky P. A Burkholderia pseudomallei Infection Imported from Eritrea to Israel. *Am J Trop Med Hyg* 2016; **95:** 997–8.

22. Canales R, Sanchez-Okrucky R, Bustamante L, Vences M, Dennis MM. Melioidosis in a bottlenose dolphin (*Tursiops truncatus*) after a hurricane in the Caribbean islands. *J Zoo Wildl Med* 2020; **51:** 443–7.
23. Nolen LD, Lirow E, Gee JE, et al. Differentiating New from Newly Detected: Melioidosis in Yap, Federated States of Micronesia. *Am J Trop Med Hyg* 2019; **101:** 323–7.
24. Hogan C, Wilmer A, Badawi M, et al. Melioidosis in Trinidad and Tobago. *Emerg Infect Dis* 2015; **21:** 902–4.
25. Martin de Frémont G, Gominet M, Bousquet A, Gervaise A, Andriamanantena D, Ficko C. Burkholderia pseudomallei: prostatic abscesses in an AIDS patient back from Cameroon. *Aids* 2019; **33:** 1403–4.
26. Shrestha N, Adhikari M, Pant V, et al. Melioidosis: misdiagnosed in Nepal. *BMC Infect Dis* 2019; **19:** 176.
27. Cossaboom CM, Marinova-Petkova A, Strysko J, et al. Melioidosis in a Resident of Texas with No Recent Travel History, United States. *Emerg Infect Dis* 2020; **26:** 1295–9.
28. Gee JE, Gulvik CA, Elrod MG, et al. Phylogeography of Burkholderia pseudomallei Isolates, Western Hemisphere. *Emerg Infect Dis* 2017; **23:** 1133–8.
29. Kaestli M, Grist EPM, Ward L, Hill A, Mayo M, Currie BJ. The association of melioidosis with climatic factors in Darwin, Australia: A 23-year time-series analysis. *J Infect* 2016; **72:** 687–97.
30. van Crevel R, van de Vijver S, Moore DAJ. The global diabetes epidemic: what does it mean for infectious diseases in tropical countries? *Lancet Diabetes Endocrinol* 2017; **5:** 457–68.
31. Dunachie S, Chamnan P. The double burden of diabetes and global infection in low and middle-income countries. *Trans R Soc Trop Med Hyg* 2019; **113:** 56–64.
32. Koh GC, Peacock SJ, van der Poll T, Wiersinga WJ. The impact of diabetes on the pathogenesis of sepsis. *Eur J Clin Microbiol Infect Dis* 2012; **31:** 379–88.
33. World Bank. Poverty. https://www.worldbank.org/en/topic/poverty/overview (accessed October 2 2020).
34. Tang RY, Lim SH, Lam JE, Nurasykin S, Eileen T, Chan YW. A 5-year retrospective study of melioidosis cases treated in a district specialist hospital. *Med J Malaysia* 2019; **74:** 472–6.
35. Wilson ML, Fleming KA, Kuti MA, Looi LM, Lago N, Ru K. Access to pathology and laboratory medicine services: a crucial gap. *Lancet* 2018; **391:** 1927–38.
36. Hoffmaster AR, AuCoin D, Baccam P, et al. Melioidosis diagnostic workshop, 2013. *Emerg Infect Dis* 2015; **21:** e141045.
37. Rodríguez JY, Morales-López SE, Rodríguez GJ, et al. Case Series Study of Melioidosis, Colombia. *Emerg Infect Dis* 2019; **25:** 1531–4.
38. Greer RC, Wangrangsimakul T, Amornchai P, et al. Misidentification of Burkholderia pseudomallei as Acinetobacter species in northern Thailand. *Trans R Soc Trop Med Hyg* 2019; **113:** 48–51.
39. Robertson G, Sorenson A, Govan B, et al. Rapid diagnostics for melioidosis: a comparative study of a novel lateral flow antigen detection assay. *J Med Microbiol* 2015; **64:** 845–8.
40. Woods KL, Boutthasavong L, NicFhogartaigh C, et al. Evaluation of a Rapid Diagnostic Test for Detection of Burkholderia pseudomallei in the Lao People's Democratic Republic. *J Clin Microbiol* 2018; **56:** e02002–17.

41. Dance DAB, Luangraj M, Rattanavong S, et al. Melioidosis in the Lao People's Democratic Republic. *Trop Med Infect Dis* 2018; **3:** 21.
42. Hinjoy S, Hantrakun V, Kongyu S, et al. Melioidosis in Thailand: Present and Future. *Trop Med Infect Dis* 2018; **3:** 38.
43. Hantrakun V, Kongyu S, Klaytong P, 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:** ofz498.
44. O'Connor C, Kenna D, Walsh A, Zamarreño DV, Dance D. Imported melioidosis in the United Kingdom: Increasing incidence but continued under-reporting. *Clin Infect Pract* 2020; **7–8:** 100051.
45. Laws TR, Taylor AW, Russell P, Williamson D. The treatment of melioidosis: is there a role for repurposed drugs? A proposal and review. *Expert Rev Anti Infect Ther* 2019; **17:** 957–67.
46. Aldhous P. Tropical medicine: melioidosis? Never heard of it. *Nature* 2005; **434:** 692–3.
47. Birnie E, Savelkoel J, Reubsaet F, et al. Melioidosis in travelers: An analysis of Dutch melioidosis registry data 1985-2018. *Travel Med Infect Dis* 2019; **32:** 101461.
48. Le Tohic S, Montana M, Koch L, Curti C, Vanelle P. A review of melioidosis cases imported into Europe. *Eur J Clin Microbiol Infect Dis* 2019; **38:** 1395–408.
49. Currie BJ. Melioidosis: evolving concepts in epidemiology, pathogenesis, and treatment. *Semin Respir Crit Care Med* 2015; **36:** 111–25.
50. WHO. Recommendations for the adoption of additional diseases as neglected tropical diseases. https://www.who.int/neglected_diseases/diseases/Adoption_additional_NTDs.pdf?ua=1 (accessed February 7 2021).
51. Currie BJ, Ward L, Cheng AC. The epidemiology and clinical spectrum of melioidosis: 540 cases from the 20 year Darwin prospective study. *PLoS Negl Trop Dis* 2010; **4:** e900.
52. Currie BJ, Mayo M, Ward LM, et al. *Lancet Infect Dis* 2021: in press.
53. The Fleming Fund. https://www.flemingfund.org (accessed February 7 2021).
54. Bory S, Daily F, Khim G, et al. A Report from the Cambodia Training Event for Awareness of Melioidosis (C-TEAM), October 2017. *Trop Med Infect Dis* 2018; **3:** 23.
55. Torres AG, Montufar FE, Gee JE, et al. Melioidosis is in the Americas: A Call to Action for Diagnosing and Treating the Disease. *Am J Trop Med Hyg* 2018; **99:** 563–4.
56. Alvarez-Hernandez G, Torres AG. Melioidosis in Mexico: a Coordinated Effort to Educate the Medical Specialists and the Community About an Unknown Disease Endemic in the Country. *Curr Trop Med Rep* 2019; **6:** 116–9.
57. International Melioidosis Network. https://groups.google.com/forum/#!forum/melioidosis (accessed May 3 2021).
58. Trinh TT, Hoang TS, Tran DA, et al. A simple laboratory algorithm for diagnosis of melioidosis in resource-constrained areas: a study from north-central Vietnam. *Clin Microbiol Infect* 2018; **24:** 84.e1–e4.
59. WHO. World Health Organization Model List of Essential Medicines. https://apps.who.int/iris/bitstream/handle/10665/325771/WHO-MVP-EMP-IAU-2019.06-eng.pdf?ua=1 (accessed February 7 2021).
60. WHO. Second WHO Model List of Essential In Vitro Diagnostics. https://www.who.int/medical_devices/publications/Standalone_document_v8.pdf?ua=1 (accessed February 7 2021).

61. Sullivan RP, Marshall CS, Anstey NM, Ward L, Currie BJ. 2020 Review and revision of the 2015 Darwin melioidosis treatment guideline; paradigm drift not shift. *PLoS Negl Trop Dis* 2020; **14:** e0008659.
62. Lipsitz R, Garges S, Aurigemma R, et al. Workshop on treatment of and postexposure prophylaxis for Burkholderia pseudomallei and B. mallei Infection, 2010. *Emerg Infect Dis* 2012; **18:** e2.
63. Yew KL. Antimicrobial prophylaxis for melioidosis and leptospirosis for at risk rescue workers. *Med J Malaysia* 2013; **68:** 88.
64. Majoni SW, Hughes JT, Heron B, Currie BJ. Trimethoprim+Sulfamethoxazole Reduces Rates of Melioidosis in High-Risk Hemodialysis Patients. *Kidney Int Rep* 2018; **3:** 160–7.
65. Chau KWT, Smith S, Kang K, Dheda S, Hanson J. Antibiotic Prophylaxis for Melioidosis in Patients Receiving Hemodialysis in the Tropics? One Size Does Not Fit All. *Am J Trop Med Hyg* 2018; **99:** 597–600.
66. National Institute for Health Research. Developing a vaccine to prevent death from melioidosis in people with type 2 diabetes mellitus in low and middle income countries. https://www.nihr.ac.uk/documents/current-nihr-research-professors/21758 (accessed May 3 2021).
67. Luangasanatip N, Flasche S, Dance DAB, et al. The global impact and cost-effectiveness of a melioidosis vaccine. *BMC Med* 2019; **17:** 129.
68. Limmathurotsakul D, Kanoksil M, Wuthiekanun V, et al. Activities of daily living associated with acquisition of melioidosis in northeast Thailand: a matched case-control study. *PLoS Negl Trop Dis* 2013; **7:** e2072.
69. Boyd R, McGuinness S, Draper A, Neilson M, Krause V. Melioidosis awareness campaign. Don't get melioidosis. *North Territ Dis Control Bull* 2016; **23:** 1–4.
70. Neilson M, Tinoco N, Boyd R. Shoe project to raise awareness about melioidosis and its prevention. *North Territ Dis Control Bull* 2017; **24:** 7–9.
71. Suntornsut P, Teparrukkul P, Wongsuvan G, et al. Effectiveness of a multifaceted prevention programme for melioidosis in diabetics (PREMEL): a stepped-wedge cluster-randomised controlled trial. *medRxiv* 2020: 2020.12.18.20248448.


Melioidosis
Intestinal Nematode Infections
Leptospirosis
Dengue
Schistosomiasis
Cysticercosis
Rabies
Lymphatic Filariasis
Food-borne Trematodiases
Leishmaniasis
Onchocerciasis
Echinococcosis
Yellow Fever
Leprosy
Trachoma
Chagas Disease
African Trypanosomiasis
0
0,05
0,1
0,15
0,2
0,25