Clinical Infection in Practice 7–8 (2020) 100051

Contents lists available at ScienceDirect

Clinical Infection in Practice

journal homepage: www.elsevier.com/locate/clinpr

Case Reports and Series

Imported melioidosis in the United Kingdom: Increasing incidence but continued under-reporting

Cavan O'Connor [a,b,*], Dervla Kenna [c], Amanda Walsh [c], Dania V. Zamarreño [c], David Dance [a,d,e]

[a] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, Keppel St, London WC1E 7HT, UK
[b] University College London Hospital, Microbiology Department, 5th Floor Central, 250 Euston Road, NW1 2BU, UK
[c] National Infection Service, Public Health England, 61 Colindale Avenue, London NW9 5EQ, UK
[d] Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit, Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao People's Democratic Republic
[e] Centre for Tropical Medicine and Global Health, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford OX3 7LG, UK

ARTICLE INFO

Article history:
Received 7 June 2020
Received in revised form 25 August 2020
Accepted 29 September 2020

Keywords:
Burkholderia infections
Burkholderia pseudomallei
Epidemiology
Melioidosis
Surveillance
Travel medicine
Tropical medicine

ABSTRACT

Introduction: Melioidosis, caused by the environmentally-acquired bacterium *Burkholderia pseudomallei*, is increasingly recognised as a globally significant public health problem, although difficult to diagnose and manage. We aimed to review all cases diagnosed in the UK since 2010, when notification became a legal requirement. This was compared with statutory reporting to assess completeness of surveillance.
Methods: A novel dataset was compiled comprising routinely collected clinical and demographic details for isolates of *B. pseudomallei* referred to Public Health England's reference laboratory. Isolates were cross-referenced with an existing database of mandatory reports of *B. pseudomallei* made under the Health Protection (Notification) Regulations 2010 to determine completeness of surveillance. The literature was also searched for missed non-referred or reported cases.
Results: Forty-six UK cases of melioidosis were identified from January 2010-July 2019. The majority of affected patients were male (65.2%); median age was 53. Four had cystic fibrosis. Other co-morbidities were poorly captured by current surveillance mechanisms. Respiratory disease, sepsis and abscess formation were the most common presenting features. Eighteen had acquired infection in Thailand; two cases were associated with travel to Nigeria. 40 UK cases were confirmed as *B. pseudomallei* by the reference laboratory. Nineteen of the identified cases were not found on the database of notified causative agents. Five patients had been notified with no confirmatory isolate received.
Discussion: Discordance between mandatory notification and isolate referral emphasises the challenges in routine epidemiological surveillance, even in a well-resourced, high-income country. The wide variety of presentations highlights the difficulties in clinical diagnosis. Cases identified following travel to Africa add further evidence that the disease is more widespread than previously thought. Sixteen patients required intensive care management, underlining challenges faced in resource limited settings. Individualised pre-travel counselling should be performed in travellers with high-risk comorbidities such as cystic fibrosis.

Introduction

Melioidosis is an environmentally-acquired infection caused by the organism *Burkholderia pseudomallei*, the clinical manifestations of which can vary extensively though most commonly include fever, pneumonia and abscess formation.[1–3] It is noteworthy for its high case fatality rate (10–50%). Whilst it is well known to be of public health importance in south-east Asia and northern Australia, it is increasingly being recognised in other tropical regions.[4] However it is grossly under-diagnosed and under-reported in many places due to its numerous clinical manifestations and the paucity of diagnostic facilities able to identify the causative organism.[5] Recent studies have suggested that melioidosis may have been responsible for as many as 4.6 million disability-adjusted life years (DALYs) and 89,000 deaths globally in 2015.[6] Furthermore, it is considered to have biothreat potential, resulting in the classification of *B. pseudomallei* as a Tier 1 Select Agent in the USA and schedule 5 pathogen in the UK. For these reasons melioidosis is considered to be a disease of high public health significance.

* Corresponding author at: University College London Hospital, Microbiology Department 5th Floor Central, 250 Euston Road, NW1 2BU, UK.
E-mail address: Cavan.O'Connor@nhs.net (C. O'Connor).

https://doi.org/10.1016/j.clinpr.2020.100051
2590-1702/

In addition to being endemic in tropical regions, melioidosis may also be imported into temperate countries, with fifteen cases known to have been confirmed in the UK between 1988–1998 and twenty-three between 1997 and 2007.[7,8] Many of these were not formally reported through the (then voluntary) laboratory-based surveillance system. The introduction of the Health Protection (Notification) Regulations 2010 represented the first time that laboratories were legally required to report the identification of certain agents, including *B. pseudomallei*, to Public Health England (PHE).[9] We undertook this review primarily in order to determine the completeness and accuracy of routine UK surveillance systems for melioidosis since notification by laboratories became a statutory requirement on 1st October 2010.

Methods

Three sources of data were used to identify cases of melioidosis in the UK occurring between 1st January 1010 and 31st July 2019 to undertake this review:

1. Notifications of *B. pseudomallei* made by laboratories under the Health Protection (Notification) Regulations 2010 extracted from the Notifications of Infectious Diseases (NOIDs) database.
2. Isolates referred to PHE's Antimicrobial Resistance and Healthcare Associated Infections (AMRHAI) Reference Unit for confirmation of *B. pseudomallei* identity were extracted from the 'MOLIS' laboratory information system (CompuGroup Medical, Wetteren, Belgium). Only those confirmed as *B. pseudomallei* were included in comparison with the NOIDs dataset. Referral of isolates is voluntary but, whilst a variety of techniques can be used to identify *B. pseudomallei* in diagnostic laboratories, species-specific PCR[10] confirmation for suspected *B. pseudomallei* isolates is only available in the UK at this reference laboratory.
3. A literature search was performed with a year restriction of 2010, finding 399 papers that were screened by title and, where relevant, abstract. Search terms of the Ovid database included Melioid* or *Burkholderia pseudomallei* or *Pseudomonas pseudomallei* or Whitmore* *AND* United Kingdom or UK or England or Wales or Scotland or Northern Ireland or Ireland or British or English or Welsh or Scottish or Irish or travel* or return* or import* or touris* or visit*.

Records were de-duplicated and manually reviewed including request forms and accompanying letters. Datasets were compared to identify patients who had isolates received at AMRHAI for confirmation that were not notified to NOIDs by the referring laboratory, as well as notifications to NOIDs for which isolates were not sent for confirmation.

We excluded cases of melioidosis diagnosed on the basis of serological tests for a variety of reasons, including interpretation of equivocal ELISA results and problems with the sensitivity and specificity of melioidosis serodiagnosis more generally.[11] Its use by PHE was discontinued in 2014.

Results

Completeness of notification

Initial searching of the MOLIS system yielded 97 samples tested by *B. pseudomallei* PCR. Of these, 10 were excluded as *B. pseudomallei* PCR was negative. A further six were excluded as they represented internal audit and quality control samples. This led to a final dataset of 81 isolates confirmed as *B. pseudomallei* over the period of this review. These isolates were received from a total of 46 individual patients.

Six patients were managed outside the UK, but with samples sent to AMRHAI for confirmatory testing – two from The Netherlands, two from the Republic of Ireland, one from Italy and one from Seychelles. Thus, confirmed *B. pseudomallei* isolates were received from 40 UK cases during the study period.

The literature search identified one additional published case of melioidosis imported into the UK for which an isolate had not been received at PHE and there was no NOIDs database notification. We thus initially identified 41 cases of imported melioidosis into the UK from these sources during the study period.

The NOIDs database yielded 132 distinct melioidosis notification events from local laboratories. These notifications related to 27 patients.

Twenty-two of these were included in both the NOIDs and MOLIS datasets, whilst five were not on the MOLIS system as no isolates had been received at AMRHAI for confirmation. Microbiological confirmation of the diagnosis in these patients was based on serology in one, culture from a corneal specimen in one, and culture from blood or sputum in three; methods used to confirm the identity of the organism in the reporting laboratories were not available.

Overall, 19 of the 46 patients (41.3%) with imported melioidosis were not notified to NOIDs despite this being mandated by the Health Protection (Notification) Regulations 2010. Fig. 1 summarises case identification from each dataset.

Clinical and epidemiological features

Of the 46 patients, 30 were male (65.2%). The median age was 53 years with a range of 17–71 years. Three patients were visiting the UK when they became unwell, one each from Borneo (country unspecified), India and Nigeria. As only basic demographic details were available for the five cases that were reported through NOIDs alone, these were excluded from subsequent analyses (clinical features, risk factors etc.), meaning that the data below are based on 41 patients (see Table 1).

Based on reported clinical details accompanying isolate referral requests, the most common presenting symptom was of fever, recorded in 34 patients (82.9%). Twenty-two patients were bacteraemic at presentation (53.7%). Other common findings were respiratory disease, skin and soft tissue abscess, and genito-urinary infection including prostatic abscess, which were seen in 36.6%, 31.7% and 14.6% of patients respectively.

Thirty-nine percent of patients were managed at some point on an intensive care or high dependency unit. Twelve percent of patients were managed as outpatients, either representing those with cystic fibrosis or bronchiectasis with chronic infection/colonisation, or uncomplicated skin and soft tissue infections.

Although treatment and outcome data are not recorded as part of routine surveillance, information available at PHE showed at least three of the patients for whom isolates were received had died.

Thailand was the most common country of acquisition of disease (43.9% of cases), followed by India and Nigeria, implicated in three and two cases respectively. Six patients had visited multiple countries, making it difficult to identify a single source of exposure. Countries visited by these six included Cambodia, China, India, Nepal, Sri Lanka, Thailand and Vietnam, all of which are known to be melioidosis-endemic apart from Nepal, where melioidosis is believed to exist but is as yet unconfirmed.[4] Travel history was unspecified for 17.1% of patients.

Of the 46 identified cases of melioidosis, nine of these had been published in the literature (19.6%) including one of the two cases

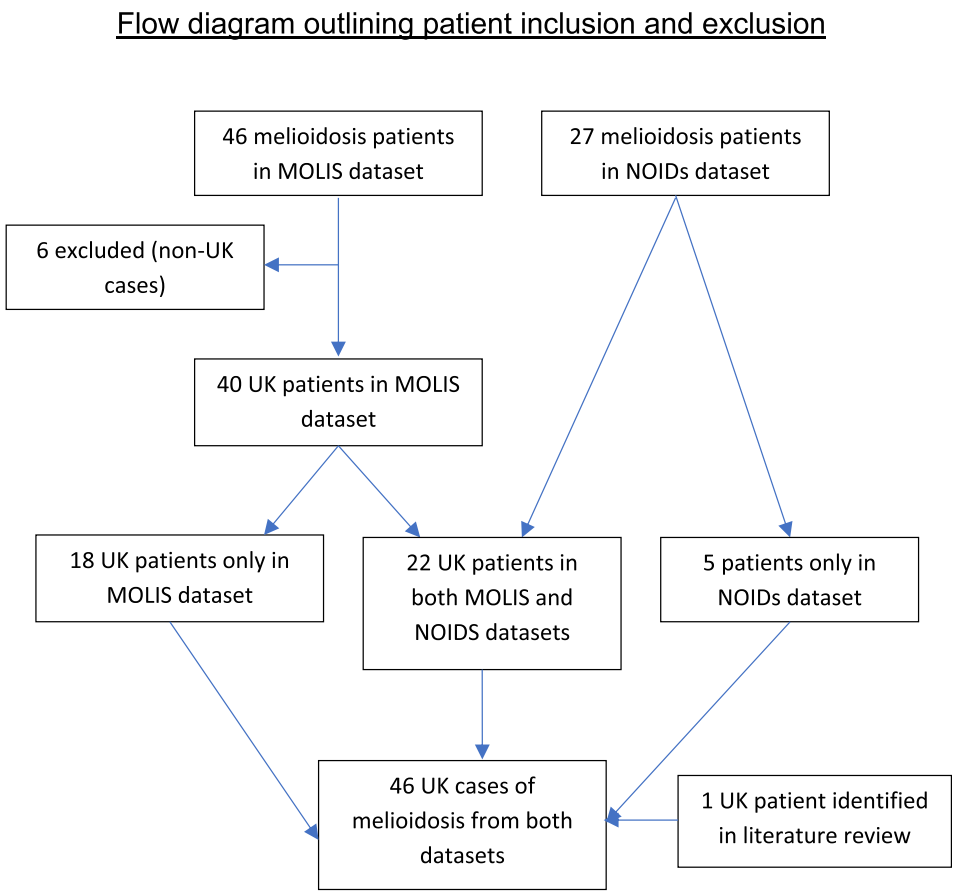

Fig. 1. Flow diagram of cases from each of the datasets contributing to the final total of 46 UK cases of melioidosis between 2010 and 2019.

associated with Nigeria. These can be found in supplementary material.

Discussion

Melioidosis was first described in July 1912 by Alfred Whitmore and CS Krishnaswami amongst morphine injectors, prisoners and the malnourished, presenting with disseminated abscesses and sepsis in Rangoon.[12] Over the past 30 years it has become apparent that the disease is significantly under-diagnosed and is probably a more important cause of deaths worldwide than many tropical diseases which, unlike melioidosis, are officially regarded as 'neglected'.[6] With the rising prevalence of conditions that increase the risk of melioidosis, climate change and popularity of travel to melioidosis-endemic areas, it is likely that global melioidosis incidence will also increase.[13,14] In theory, surveillance should be close to complete in countries like the UK, where the disease is not endemic, diagnostic laboratories are widespread and well-equipped, and reporting of melioidosis by laboratories is now mandatory. This study confirmed a rising incidence of melioidosis imported into the UK in comparison with previous series[7,8] but has shown many cases are still not being formally notified and acts as a reminder that routinely collected 'official' data, even for rare diseases of public health concern such as melioidosis, may be unreliable.

The NOIDs database represents the official record of UK melioidosis cases since *B. pseudomallei* became a statutorily notifiable pathogen. This study found 41.3% of patients with melioidosis were not notified by diagnostic laboratories. The fact that a case was reported in the literature without either an isolate or a notification being sent to PHE suggests there may have been additional cases not captured in our three datasets. This represents a deficiency in routine reporting in the UK and suggests there is room for improvement in these systems. Possible mechanisms to improve this situation might rely on additional prompts, such as the inclusion of a reminder to the referring laboratory to notify causative agents on reference laboratory reports, or penalties for those which fail to report. Although there are potential financial penalties for laboratories that fail to notify pathogens, as far as we are aware these have never been imposed since the Health Protection (Notification) Regulations 2010 came into effect.

The degree of under-reporting seen in a well-resourced, high-income country with statutory notification legislation adds weight to the suggestion that under-reporting of melioidosis is a significant problem globally. Since allocation of resources and policies in lower- and middle-income settings are often driven by national surveillance data, underreporting of cases and fatalities may lead to a vicious cycle of inadequate surveillance, under-recognition and failure to develop and implement appropriate disease control programmes. Recent work in Thailand suggests completeness of national surveillance data for melioidosis could be successfully enhanced simply by integrating data from readily available datasets.[15]

Not all notifying laboratories sent an isolate to PHE for confirmation. Whilst not mandatory, the potential for misidentification by local MALDI-TOF or other identification methods must be remembered.[16,17] There is also potential risk to laboratory staff working with *B. pseudomallei*.[18] From a public health perspective, if more isolates are received at the reference laboratory there can be more accurate epidemiological monitoring of imported melioi-

Table 1
Patient demographics and clinical details.

	Variable	Number of patients (%)
Demographics	Male sex	30 (65.2)
	Median age [range]	53 [17–71]
	Age < 25	6 (13.0)
	Age 25–40	10 (21.7)
	Age 41–55	14 (30.4)
	Age > 55	16 (34.7)
Co-morbidities	Cystic fibrosis	4 (9.8)
	End-stage renal failure	2 (4.9)
	Type 2 diabetes	2 (4.9)
	Bronchiectasis	1 (2.4)
Clinical features	Fever	34 (82.9)
	Bacteraemia	22 (53.7)
	Respiratory disease	15 (36.6)
	Sepsis	13 (31.7)
	Abscess	13 (31.7)
	Genito-urinary	6 (14.6)
	Gastrointestinal	4 (9.8)
	Osteomyelitis & septic arthritis	4 (9.8)
	Cardiovascular	3 (7.3)
	Skin lesion or ulcer	2 (4.9)
	Neurological	2 (4.9)
Care setting	Intensive care/high dependency	16 (39.0)
	General ward	15 (36.6)
	Outpatient	5 (12.2)
	Unspecified	10 (24.4)
Country implicated in acquisition	Thailand	18 (43.9)
	India	3 (7.3)
	Nigeria	2 (4.9)
	Bangladesh	1 (2.4)
	Borneo (country unspecified)	1 (2.4)
	Cambodia	1 (2.4)
	Singapore	1 (2.4)
	Vietnam	1 (2.4)
	Multiple countries visited	6 (14.6)
	Not specified	7 (17.1)

Baseline demographic characteristics, documented co-morbidities, clinical presentation and travel history of 46 patients. Note for clinical features patients may have contributed to more than one category depending on their presentation. Respiratory disease includes pneumonia, cough, breathlessness and cystic fibrosis. Five cases solely reported to NOIDs only contributed to demographics.

dosis, detection of potential clusters through Multilocus Sequence Typing (MLST) / Variable Number Tandem Repeat (VNTR) analysis, and confirmation of antimicrobial susceptibility. Furthermore, the true number of cases in the UK may well be higher if some patients are presumptively treated in the absence of culture confirmation, especially given the limitations of sensitivity of culture particularly where selective media are not used, though the need for long periods of treatment to avoid relapses means that standard antibiotic regimes may well not eradicate the infection.[19,20]

Although we have attempted to summarise the clinical and epidemiological features of the patients in this study, the data highlight the shortcomings of using routinely collected surveillance data for this purpose. For example only 4.9% of the cases in this series were known to be diabetic, whereas in other series this is the commonest predisposing risk factor for melioidosis, present in more than 50% of patients.[21,22] Conversely, the proportion of patients with cystic fibrosis and bronchiectasis in this series (12.1%) is higher than that from melioidosis-endemic areas. The Cystic Fibrosis Trust in the UK has produced specific guidance about melioidosis for patients with the condition planning to travel to melioidosis-endemic areas.[23] Thailand was the most common country implicated in acquisition, reflecting both high endemicity and frequency of travel.[4,13] The occurrence of two cases associated with Nigeria is worthy of note.

Conclusion

The under-recognition and under-reporting of melioidosis globally remains a challenge. As both non-communicable diseases and international travel become more prevalent, clinicians everywhere need to be mindful of the potential for imported infections such as melioidosis and the provision of individualised pre-travel counselling for high risk patients such as those with cystic fibrosis. The extent of under-reporting of melioidosis in a well-resourced setting such as the UK not only highlights the difficulties faced by developing endemic countries in assessing their own disease burden and allocating appropriate priority to melioidosis, but also acts as a warning to treat all surveillance data with a degree of caution. In high-income settings these challenges should be amenable to an IT solution, but in many melioidosis-endemic areas, better and locally appropriate diagnostic techniques are an even more urgent priority.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics statement

Ethical approval was received from the London School for Hygiene and Tropical Medicine MSc Research Ethics Committee.

CRediT authorship contribution statement

Cavan O'Connor: Conceptualization, Methodology, Data curation, Visualization, Writing - original draft. **Dervla Kenna:** Data curation, Resources. **Amanda Walsh:** Data curation, Resources. **Dania V. Zamarreño:** Resources. **David Dance:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1 Wiersinga WJ, Virk HS, Torres AG, Currie BJ, Peacock SJ, Dance DAB, et al. Melioidosis. Nat Rev Dis Prim; 2018. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6456913/pdf/nihms-1021577.pdf.
2 Wiersinga JW, Currie JB, Peacock JS. Melioidosis. N Engl J Med 2012;367(11):1035–44.
3 Currie BJ. Melioidosis: evolving concepts in epidemiology, pathogenesis, and treatment. Semin Respir Crit Care Med 2015;36(01):111–25.
4 Limmathurotsakul D, Golding N, Dance DAB, Messina JP, Pigott DM, Moyes CL, et al. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. Nat Microbiol 2016;1(Jan):15008. https://doi.org/10.1038/nmicrobiol.2015.8.
5 Dance DA. Melioidosis: the tip of the iceberg? Available from Clin Microbiol Rev 1991;4(1):52–60. https://pubmed.ncbi.nlm.nih.gov/2004347.
6 Birnie E, Virk HS, Savelkoel J, Spijker R, Bertherat E, Dance DAB, et al. Global burden of melioidosis in 2015: a systematic review and data synthesis. Lancet Infect Dis 2019;19(8):892–902. https://doi.org/10.1016/S1473-3099(19)30157-4.
7 Dance DAB, Smith MD, Aucken HM, Pitt TL. Imported melioidosis in England and Wales. Lancet 1999;353(9148):208. https://doi.org/10.1016/S0140-6736(05)77217-2.
8 Malnick H, Englender HA, Dance DAB, Smith MD, Simpson AJH, Pitt TL. A decade of experience of the United Kingdom's melioidosis diagnostic service. 5th World Melioidosis Congress, Khon Kaen; 2007.
9 Legislation. The Health Protection (Notification) Regulations 2010 [Internet]. UK Statutory Instruments; 2010. p. 659. Available from: http://www.legislation.gov.uk/uksi/2010/659/contents/made.
10 Novak RT, Glass MB, Gee JE, Gal D, Mayo MJ, Currie BJ, et al. Development and evaluation of a real-time PCR assay targeting the type III secretion system of

Burkholderia pseudomallei Available from. J Clin Microbiol [Internet] 2006;44 (1):85–90. https://www.ncbi.nlm.nih.gov/pubmed/16390953.
11 Cheng AC, Brien MO, Freeman K, Lum G, Currie BJ. Indirect hemagglutination assay in patients with melioidosis in northern Australia. 2006;74(2): 330–4.
12 Whitmore A, Krishnaswami C. An account of the discovery of a hitherto undescribed infectious disease occurring among the population of Rangoon Available from. Ind Med Gaz 1912;47:262–7. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5168169/pdf/indmedgaz71624-0010.pdf.
13 The World Bank. International tourism, number of arrivals [Internet]; 2020 [cited 2020 Apr 7]. Available from: https://data.worldbank.org/indicator/ST.INT.ARVL?end=2017&name_desc=false&start=1995&view=chart.
14 Vos T, Abajobir AA, Abbafati C, Abbas KM, Abate KH, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016 Available from. Lancet 2017;390 (10100):1211–59. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2817%2932154-2.
15 Hantrakun V, Kongyu S, Klaytong P, Rongsumlee S, Day NPJ, Peacock SJ, et al. Clinical epidemiology of 7,126 melioidosis patients in Thailand and the implications for a national notifiable diseases surveillance system. Open Forum Infect Dis 2019.
16 Pomerleau-Normandin D, Heisz M, Su M. Misidentification of risk group 3/ security sensitive biological agents by MALDI-TOF MS in Canada: november 2015-October 2017. Canada Commun Dis Rep 2018;44(5):110–5. , https://pubmed.ncbi.nlm.nih.gov/31007621.
17 Greer RC, Wangrangsimakul T, Amornchai P, Wuthiekanun V, Laongnualpanich A, Dance DAB, et al. Misidentification of Burkholderia pseudomallei as Acinetobacter species in northern Thailand. Trans R Soc Trop Med Hyg 2019;113(1):48–51. , https://pubmed.ncbi.nlm.nih.gov/30295891.
18 Peacock SJ, Schweizer HP, Dance DAB, Smith TL, Gee JE, Wuthiekanun V, et al. Management of accidental laboratory exposure to Burkholderia pseudomallei and B. mallei. Emerg Infect Dis 2008;14(7):e2. , https://pubmed.ncbi.nlm.nih.gov/18598617.
19 Limmathurotsakul D, Jamsen K, Arayawichanont A, Simpson JA, White LJ, Lee SJ, et al. Defining the true sensitivity of culture for the diagnosis of melioidosis using Bayesian latent class models. PLoS One 2010;5(8):e12485. , https://www.ncbi.nlm.nih.gov/pubmed/20830194.
20 Dance DAB, Sihalath S, Rith K, Sengdouangphachanh A, Luangraj M, Vongsouvath M, et al. The cost-effectiveness of the use of selective media for the diagnosis of melioidosis in different settings. PLoS Negl Trop Dis 2019;13(7): e0007598.
21 Suputtamongkol Y, Chaowagul W, Chetchotisakd P, Lertpatanasuwun N, Intaranongpai S, Ruchutrakool T, et al. Risk factors for melioidosis and bacteremic melioidosis. Clin Infect Dis 1999;29(2):408–13. https://doi.org/10.1086/520223.
22 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(11):e900. , https://www.ncbi.nlm.nih.gov/pubmed/21152057.
23 Pitt T, Jones A, Kenna D, Simpson A, Denton M. Melioidosis and world-wide travel [Internet]; 2016. Available from: https://www.cysticfibrosis.org.uk/the-work-we-do/support-available/travel.