Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis

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***Burkholderia pseudomallei*, a highly pathogenic bacterium that causes melioidosis, is commonly found in soil in Southeast Asia and Northern Australia[1,2]. Melioidosis can be difficult to diagnose due to its diverse clinical manifestations and the inadequacy of conventional bacterial identification methods[3]. The bacterium is intrinsically resistant to a wide range of antimicrobials, and treatment with ineffective antimicrobials may result in case fatality rates (CFRs) exceeding 70%[4,5]. The importation of infected animals has, in the past, spread melioidosis to non-endemic areas[6,7]. The global distribution of *B. pseudomallei* and the burden of melioidosis, however, remain poorly understood. Here, we map documented human and animal cases and the presence of environmental *B. pseudomallei* and combine this in a formal modelling framework[8-10] to estimate the global burden of melioidosis. We estimate there to be 165,000 (95% credible interval 68,000–412,000) human melioidosis cases per year worldwide, from which 89,000 (36,000–227,000) people die. Our estimates suggest that melioidosis is severely underreported in the 45 countries in which it is known to be endemic and that melioidosis is probably endemic in a further 34 countries that have never reported the disease. The large numbers of estimated cases and fatalities emphasize that the disease warrants renewed attention from public health officials and policy makers.**

Melioidosis is a disease of public health importance in areas of Southeast Asia and Australia, and is considered a potential emerging infectious disease in many tropical developing countries[11]. In northeast Thailand, there are around 2,000 culture-confirmed melioidosis cases per year, with a case fatality rate (CFR) of 40%[12]. In Singapore, 550 melioidosis cases have occurred during the last ten years, of which a fifth resulted in death[13]. Skin inoculation is considered the main route of infection in agricultural workers in developing countries[14]. Recent evidence also suggests that inhalation of *Burkholderia pseudomallei* during extreme weather events[15,16] and ingestion of *B. pseudomallei* contaminated water are also important routes of infection[17]. High-risk groups include patients with diabetes mellitus, chronic kidney disease and excessive alcohol intake[12,18]. Developed countries are also observing an emergence of melioidosis related to travelling and importation of cases[11]. No licensed vaccine for melioidosis is currently available. Strengthening of microbiological laboratories and research facilities often results in the discovery of *B. pseudomallei* in new areas, with recent national additions including India, southern China, Brazil and Malawi[11,19]. Given diagnostic limitations[3], it is likely that *B. pseudomallei* is present in many other tropical countries but has not yet been detected.

The importation of infected humans and animals could lead to the establishment of *B. pseudomallei* in previously unaffected areas because the organism can be released to and persist in the environment. Previous importation events to non-endemic regions include an outbreak of melioidosis in 1975 in Paris, resulting in the deaths of two humans and an unknown number of animals[6,7]. *B. pseudomallei* then persisted in the soil for up to six years[6]. A recent outbreak of melioidosis in a non-endemic area occurred at Tulane Primate Research Center, Louisiana, USA, in November 2014[20]. The results of a Center for Disease Control investigation concluded that the organism had spread from a building where mice were being infected experimentally to primates within the facility, possibly through contamination of the inner garments worn by staff[20]. It is, however, not yet known whether *B. pseudomallei* could have contaminated and persisted in the environment in Louisiana.

Knowledge about the global burden of melioidosis and its potential to become established in non-endemic areas is poor. Previous maps of melioidosis simply displayed countries that had reported melioidosis cases[11] and therefore provided no information on areas where melioidosis could be endemic but undiagnosed. In addition, earlier maps could not estimate the global morbidity and mortality of melioidosis[11], which are essential for policy makers to help determine the allocation of the limited resources available for public health. Finally, previous maps could not determine the level of risk of *B. pseudomallei* establishment in the event that the organism was released in non-endemic areas.

Here, we present the first evidence-based predicted map of *B. pseudomallei* and estimate the total incidence and mortality due to melioidosis worldwide for 2015 (Supplementary Figs 1–3). A globally comprehensive database has been compiled, comprising 22,338 geo-located records of human and animal melioidosis, as well as the presence of environmental *B. pseudomallei* from reports published from 1910 to 2014 (Supplementary Fig. 4). We assessed the strength of evidence for melioidosis endemicity at a national level, ranging from complete consensus on absence to complete consensus on presence (Fig. 1 and Supplementary Methods). A boosted regression tree (BRT) statistical model was used to estimate

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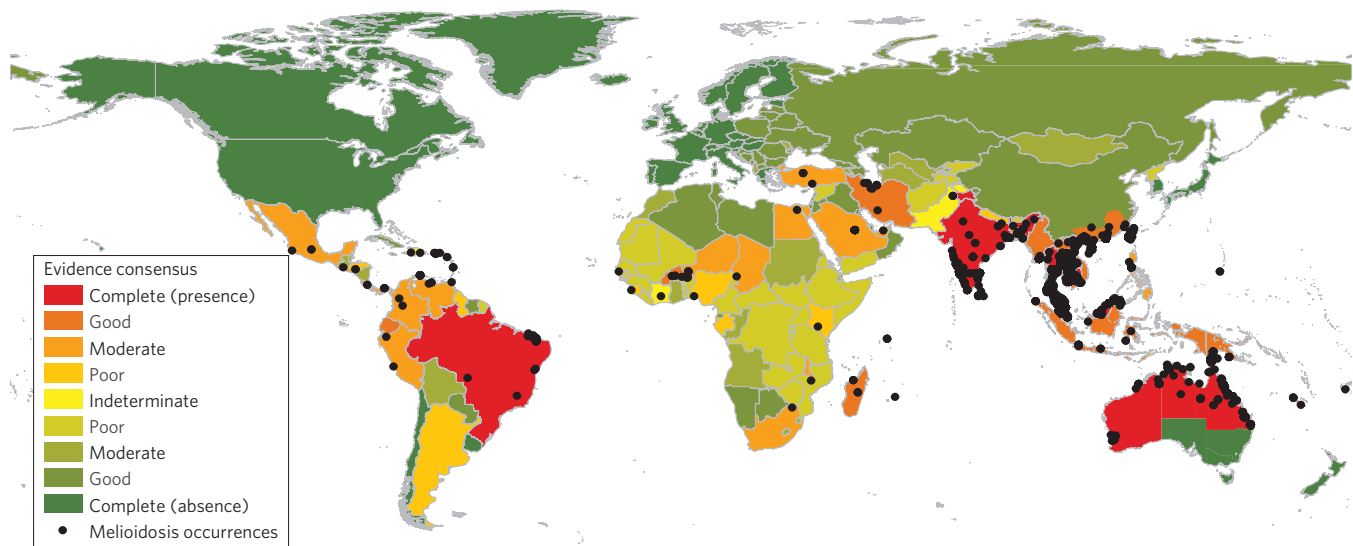
Figure 1 | Global evidence consensus and geographic locations of occurrence data from 1910 to 2014. Country colouring is based on evidence-based consensus, with green representing a complete consensus on absence of *B. pseudomallei* and red a complete consensus on presence of *B. pseudomallei*. Black dots represent geo-located records of melioidosis cases or presence of *B. pseudomallei*.

**Table 1 | Estimated burden of melioidosis in 2015, by continent.**

	Population at risk Millions (credible interval)	Melioidosis cases Thousands (credible interval)	Melioidosis deaths Thousands (credible interval)
South Asia	1,525 (1,402–1,595)	73 (31–171)	42 (18–101)
East Asia and Pacific	858 (795–920)	65 (28–161)	31 (13–77)
Sub-Saharan Africa	602 (482–695)	24 (8–72)	15 (6–45)
Latin America and Caribbean	246 (153–334)	2 (1–7)	1 (<1–3)
Middle East and North Africa	49 (29–80)	<1	<1
Europe and Central Asia	0	0	0
North America	0	0	0
Global	3,280 (2,862–3,624)	165 (68–412)	89 (36–227)

the environmental suitability for *B. pseudomallei* globally, with a resolution of 5×5 km^2, using a database of occurrence records and a set of gridded environmental covariates known, or hypothesized, to affect the presence of *B. pseudomallei*. We then used a multivariable negative binomial regression model to relate the environmental suitability values generated by the BRT model to geo-positioned incidence data to estimate the incidence of melioidosis cases in each 5×5 km^2 square. We similarly applied a logistic regression model to estimate the mortality in these cases. Using bootstrap resampling and Monte Carlo simulations we developed an ensemble model of 2,500 global realizations of these incidence and case fatality maps to derive spatial estimates of the numbers of cases and deaths caused by the disease in melioidosis-endemic areas, as well as the corresponding 95% credible intervals (CrI). We excluded countries in which there is complete consensus on *B. pseudomallei* absence from the estimation of global incidence and mortality of melioidosis, and finally evaluated the environmental suitability for *B. pseudomallei* in those areas to identify where imported cases may lead to subsequent *B. pseudomallei* establishment.

We predict that *B. pseudomallei* is ubiquitous throughout the tropics (Fig. 2). The highest risk zones are in Southeast and South Asia, tropical Australia, Western sub-Saharan Africa and South America. Risk zones of varying sizes are also observed in Central America, Southern Africa and the Middle East. We found that high rainfall and temperature, and anthrosol and acrisol soil types, are strongly associated with the presence of *B. pseudomallei*. Anthrosol is a soil type that has been modified profoundly by human activities, particularly by irrigated agriculture, and acrisol

is clay-rich soil found in tropical climates[21]. We also found that high salinity and a high proportion of gravel are associated with the presence of *B. pseudomallei* (Supplementary Fig. 5). The association between the presence of *B. pseudomallei* and high soil salinity is consistent with previous laboratory studies[22]. Although our model did not find an association between the presence of *B. pseudomallei* and soil pH as reported in previous environmental studies[23], this could be because soil pH is generally associated with other soil factors, particularly soil salinity[21], reducing the capacity of our model to identify this as a geographic risk factor. Validation statistics indicated a high predictive performance of the BRT ensemble model with an area under the receiver operating characteristic curve of 0.81 (95% CrI, 0.76–0.86).

We estimate that there will be 165,000 melioidosis cases in 2015 among the three billion people living in the areas likely to contain *B. pseudomallei* (incidence rate of 5.0 per 100,000 people at risk per year) (Table 1). The reported incidence rate of melioidosis was positively associated with environmental suitability for *B. pseudomallei* predicted by BRT, adjusted by country income level[24] and the prevalence of diabetes mellitus[25] and indigenous ethnicity in Australia (Supplementary Figs 6 and 7). Country income level was included to take into account a trend showing lower incidence rates in high-income countries (adjusted incidence rate ratio [aIRR], 0.58; 95% CrI, 0.23–1.39), which could be due to comparatively lower exposure rates, better prevention in general, or other residual factors[14–17]. The prevalence of indigenous ethnicity was significantly associated with a higher incidence rate of melioidosis (aIRR, 1.23; 95% CrI, 1.09–1.38, for an increase of 10% prevalence
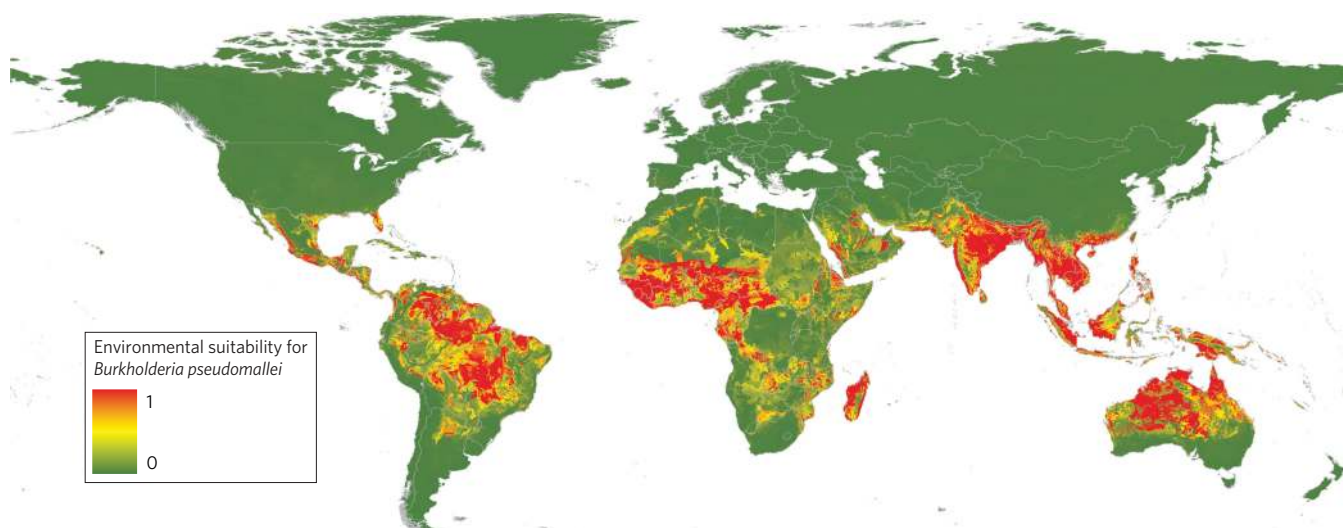
Figure 2 | Predicted environmental suitability for *B. pseudomallei* persistence at 5 × 5 km² spatial resolution. Areas of high environmental suitability are shown in red and areas of low suitability in green.
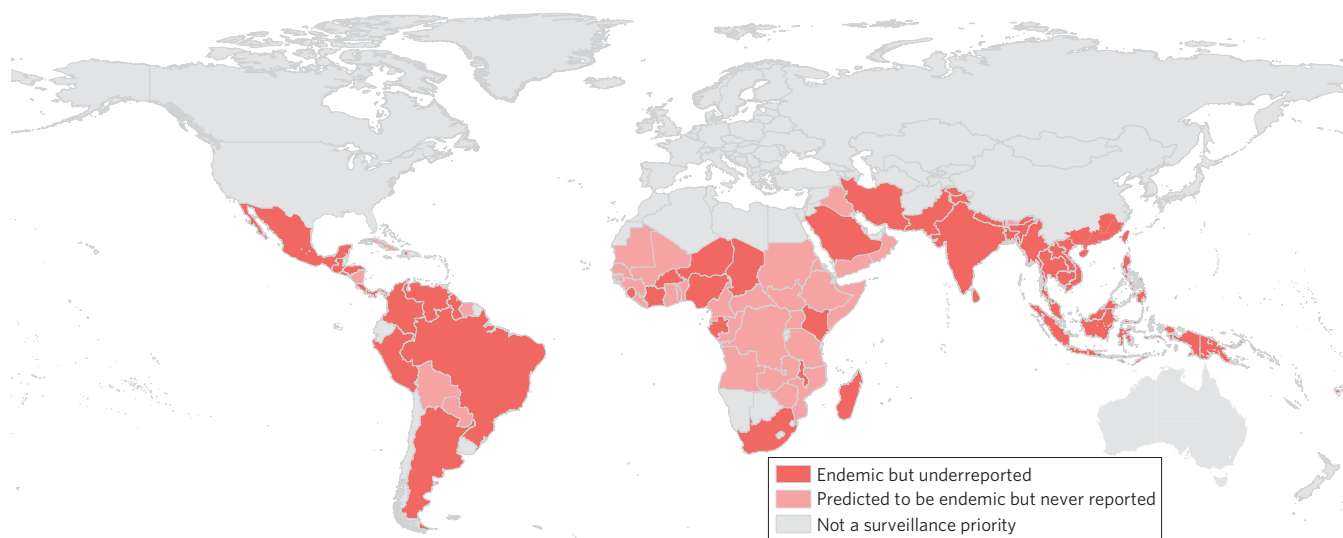
Figure 3 | Priority countries where microbiological diagnostic facilities and disease reporting systems for melioidosis should be strengthened. Countries where melioidosis is predicted to be endemic but is underreported or never reported are shown in red and pink, respectively.

of indigenous ethnicity). Indigenous ethnicity is likely to be a proxy of other risk factors such as excessive alcohol intake and chronic kidney disease and higher exposure rates[18]. The development of high-resolution geographic data for these risk factors and additional epidemiological studies outside Southeast Asia and Australia would probably improve the model further.

We predict that only 40% of all melioidosis cases occur in the East Asia and Pacific region, where melioidosis is considered highly endemic. By contrast, South Asia is predicted to bear 44% of the overall burden, because large populations live in areas contaminated with *B. pseudomallei*. Only Australia, Brunei Darussalam and Singapore have national surveillance data for melioidosis that are comparable to our estimates. Our estimates for other countries where melioidosis is known to be endemic were higher than reported (Supplementary Table 1), supporting the suggestion that the burden of melioidosis in many tropical developing countries is hidden and masked by under-development of microbiological facilities, lack of relevant clinical and laboratory expertise[3], and poor reporting systems.

We estimate that 89,000 people globally will die from melioidosis in 2015. We found that the mortality of melioidosis is strongly associated with the under-five mortality rate (odds ratio (OR), 1.88; 95% CrI, 1.73–2.07, for a ten times increase in infant deaths per 1,000 live births)[24] and used this to estimate the CFR for all predicted melioidosis cases. We predict that >99% of all deaths due to melioidosis occur in low- and middle-income countries, and <1% occur in high-income countries including Australia, Brunei Darussalam and Singapore (Supplementary Fig. 8).

We developed a list of priority countries where microbiological diagnostic facilities and disease reporting systems should be strengthened urgently, so that accurate diagnosis[3] can be provided and the burden of melioidosis can then be defined. Appropriate prevention campaigns[14] and treatment guidelines[5] could then be implemented to reduce disease mortality rates. The list of priority countries includes 45 countries where melioidosis is known to be endemic but is underreported, and a further 34 countries where melioidosis is probably endemic but has never been reported (Fig. 3).

We also predict that two (USA and Japan) of the 44 countries where *B. pseudomallei* is considered currently absent have areas that would be suitable for *B. pseudomallei* establishment. These include a geographically contiguous area covering southern parts of Florida, Louisiana and Texas in the USA, and Okinawa and Kagoshima prefectures in Japan. These areas share similar environmental values to the Caribbean islands and Taiwan where melioidosis is known to be endemic (Fig. 1). Following the recent outbreak at Tulane Primate Research Center, we evaluated the *B. pseudomallei* suitability level in Louisiana in more detail. The *B. pseudomallei* suitability level is very low at the Center (suitability level 0.02) and is moderately high in New Orleans, 35 miles south of the Center (suitability level 0.55). The suitability level of 0.55 is comparable to other known endemic areas such as Saravane in Laos[26] (suitability level 0.54), suggesting that it would be possible for *B. pseudomallei* to become established in Louisiana if the bacterium were to be released widely. It is also possible that *B. pseudomallei* is already present in the environment in the USA and Japan but has never been detected.

We have striven to be exhaustive in the assembly of contemporary data on melioidosis and have applied new modelling approaches to maximize the predictive power of these analyses. Our estimate of global mortality due to melioidosis (89,000 per year) is comparable to measles (95,600 per year)[27] and higher than for leptospirosis (50,000 per year)[28] and dengue infection (9,100–12,500 per year)[27,29], diseases that are considered to be of high priority by many international health organizations[27]. The global burden of melioidosis is likely to be substantial and increasing due to population and pathogen movements increasing the likelihood of establishment in new areas, fuelled by an increase in anthrosol[30] and the marked rise in the prevalence of diabetes mellitus globally[27]. This wide and potentially increasing geographical distribution and burden, combined with the high CFR, particularly when melioidosis patients are undiagnosed and treated with ineffective antimicrobials[4,5], highlight the need for public health officials and policy makers to raise the priority of this disease.

Methods

The occurrence database. The occurrence data set comprised geo-located records of human cases, animal cases and the presence of *B. pseudomallei* in the environment derived from (1) peer-reviewed literature and (2) case reports (Supplementary Fig. 1a). For peer-reviewed literature we searched PubMed, GenBank database (http://www.ncbi.nlm.nih.gov/genbank), MLST database (http://bpseudomallei.mlst.net) and Eurosurveillance database (http://eurosurveillance.org) for studies describing human cases, animal cases or the presence of *B. pseudomallei* in the environment between 1 January 1920 and 31 December 2014 using the MeSH terms 'melioidosis' or '*pseudomallei*'. No language restrictions were placed on these searches, but only those citations with a full title and abstract were retrieved. We searched bibliographies from selected studies for secondary references. For case reports we searched ProMED (http://www.promedmail.org) and Ministry of Health websites for each country. We also searched Google News archives (http://news.google.co.uk/archivesearch) using the same search terms and country name for news and reports of melioidosis at a country level.

An occurrence was defined as the reporting of a case of melioidosis infection or an identification of *B. pseudomallei* at an environmental sampling point. After processing, a total of 22,338 geo-located occurrences spanning a period from 1910 to 2014 were included. A summary of the data management procedure, beginning with the raw inputs and showing the proportion of data lost through the stages of quality control before reaching the final occurrence database, is provided in Supplementary Fig. 2. The final occurrence database with geo-positioned data points and the data dictionary are publicly available online (http://dx.doi.org/10.6084/m9.figshare.1447097).

Evidence for the presence of melioidosis was obtained from three types of source: health reporting organizations, peer-reviewed articles and case reports (Supplementary Fig. 1b). We then used a weighted scoring system to quantify evidence consensus (Supplementary Methods and Supplementary Fig. 3).

Explanatory covariates. We assembled gridded (5×5 km^2 pixel) global data for a suite of explanatory covariates of soil characteristics, climatic conditions and other covariates. These were chosen based on factors known or hypothesized to contribute to the presence of *B. pseudomallei* in soil. Covariates included (1) soil characteristics from the Harmonized World Soil Database (HWSD) (http://www.iiasa.ac.at)[21], (2) precipitation and land surface temperature variables from the WorldClim

database (www.worldclim.org) and (3) a vegetation/moisture index from the Advanced Very High Resolution Radiometer (AVHRR) database of the National Oceanic and Atmospheric Administration (www.noaa.gov). HWSD and WorldClim are freely available sets of global soil and climate data, respectively, at 1×1 km^2 spatial resolution. All grids were resampled to the same 5×5 km^2 grid to ensure uniformity of land/water boundaries and spatial resolution.

Predicting environmental suitability for *B. pseudomallei*. We used a BRT approach[31] to establish a multivariable empirical relationship between the distribution of occurrence records of *B. pseudomallei* and the environmental conditions at each location, as has been previously applied to mapping dengue[8], avian influenza[9] and Ebola[10] (Supplementary Fig. 1c). Model accuracy was assessed by calculating the mean cross-validated area under the curve (AUC) statistic[32].

Estimation of populations at risk. People living in each 5×5 km^2 pixel with a predicted environmental suitability for *B. pseudomallei* greater than the value of the fifth percentile of the positive occurrence records were considered at risk of acquiring melioidosis in each submodel. The population density map was derived from the Global Rural–Urban Mapping Project (GRUMP) 2010 (http://sedac.ciesin.org/data/collection/grump-v1) and levelled to match national and global population projections for 2015 from the UN World Population Prospects (http://esa.un.org/wpp/). World regions were categorized according to the World Bank[24].

Estimation of incidence of melioidosis. Published literature reporting the annual incidence rates of melioidosis from the literature search described above were used to make a spatial prediction of incidence rates (Supplementary Fig. 1d). Inclusion criteria were restricted to the literature reporting annual incidence rates (per 100,000 population) of culture-confirmed melioidosis or equivalent in a defined area. We then used a negative binomial model to estimate the incidence of melioidosis cases based on the *B. pseudomallei* suitability and the prevalence of diabetes and aboriginal population. The fitted negative binomial model was then applied to the 2015 human population surface, *B. pseudomallei* suitability, the prevalence of diabetes[25] and the prevalence of indigenous Australians to provide a mapped estimate of incidence.

Estimation of mortality of melioidosis. Published literature reporting CFRs of melioidosis from the literature search described above was used to make a spatial prediction of CFRs. Inclusion criteria were restricted to the literature reporting CFRs (%) of culture-confirmed melioidosis in a defined area. We evaluated the association of reported CFRs with national-level healthcare expenditure (HE) per capita, $\log_{10}$ transformed HE per capita, the national-level under-five mortality rate (U5MR)[24] and $\log_{10}$ transformed U5MR by constructing multivariable logistic regression models and assessing their goodness of fit to the data. Reported HE and U5MR were expected to be a proxy for the capacity of medical services in the countries and associated with the CFRs of melioidosis. The optimal logistic regression model contained only $\log_{10}$ transformed U5MR. This model was then used to predict the number of deaths due to melioidosis by applying it to national-level $\log_{10}$ transformed U5MR and multiplying this by the gridded predictions of melioidosis incidence.

Development of priority country list. Priority countries included countries where melioidosis is known to be endemic but underreported and countries where melioidosis is probably endemic but is never reported. Countries where melioidosis is known to be endemic were defined as countries with a national level of evidence from 'complete presence' to 'poor presence' and having the lower limit of 95% CrI of predicted incidence of human melioidosis as more than or equal to one case per year. Countries where melioidosis is probably endemic were defined as countries with a national level of evidence from 'indeterminate' to 'good absence' and having the lower limit of 95% CrI of predicted incidence of human melioidosis as more than or equal to one case per year. Countries with a level of evidence equal to 'complete absence' were considered not endemic for melioidosis, and the level of risk of *B. pseudomallei* establishment was evaluated in the countries within this category.

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Author contributions

D.L., D.D., E.B., N.P.J.D., S.J.P. and S.I.H. conceived the research. D.L. and S.I.H. drafted the manuscript. D.L. and D.D. reviewed all the occurrence data. D.L. and N.G. carried out the modelling and analysis with advice from S.I.H. D.L., N.G., J.M. and D.P. created the maps and figures. All authors discussed the results and contributed to the revision of the final manuscript.

Additional information

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Competing interests

The authors declare no competing financial interests.