Global burden of melioidosis, 2015: a systematic review and data synthesis

Emma Birnie, MD[1], Harjeet S. Virk, MD[1*], Jelmer Savelkoel, BSc[1], Rene Spijker, MsC[2] Eric Bertherat, MD[3], David A.B. Dance, Prof, FRCPath[4,5,6], Direk Limmathurotsakul, PhD[5,7], Brecht Devleesschauwer, PhD[8,9], Juanita A. Haagsma, PhD[10], W. Joost Wiersinga, Prof, PhD[1,11]*

*Authors contributed equally to the manuscript

[1] Center for Experimental and Molecular Medicine, Amsterdam UMC, location AMC, Amsterdam Infection & Immunity Institute, University of Amsterdam, Amsterdam, the Netherlands;

[2] Cochrane Netherlands, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, University Utrecht, the Netherlands and Amsterdam UMC, University of Amsterdam, Medical Library, Amsterdam Public Health, Amsterdam, the Netherlands;

[3] Department of Infectious Hazard Management, Health Emergency programme, World Health Organization, Geneva, Switzerland;

[4] Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit, Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao PDR;

[5] Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK;

[6] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK;

[7] Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand;

[8] Department of Epidemiology and Public Health, Sciensano, Brussels, Belgium;

[9] Department of Veterinary Public Health and Food Safety, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

[10] Department of Public Health, Erasmus MC University Medical Center, Rotterdam, the Netherlands;

[11] Division of Infectious Diseases, Amsterdam UMC, location Academic Medical Center, University of Amsterdam, , Amsterdam, the Netherlands .

Correspondence to: Emma Birnie, Amsterdam UMC, University of Amsterdam, Center for Experimental and Molecular Medicine, Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands; Phone number: +31205669111; Email: e.birnie@amc.uva.nl and/or w.j.wiersinga@amc.uva.nl

Word count abstract: 266; manuscript: 4061

SUMMARY

Background Melioidosis, caused by the environmental bacterium *Burkholderia pseudomallei*, is an often-fatal infectious disease with a high prevalence across tropical areas. Clinical presentation can vary from abscess formation to pneumonia and septicaemia. We assessed the global burden of melioidosis, expressed in disability-adjusted life years (DALYs), for the year 2015.

Methods A systematic review of the peer-reviewed literature for human melioidosis cases between 1990 and 2015 was performed. Using a broad search strategy, no language restrictions and combinations of search terms, *Burkholderia* spp. and disease names, all relevant articles were screened on title, abstract, and full text. Quantitative data from cases including mortality, age, sex, infectious and post-infectious sequelae, antibiotic treatment and symptom duration were extracted. This information was then combined with established disability weights and expert panel discussions to construct an incidence-based disease model. The disease model was integrated with established global incidence and mortality estimates to calculate global melioidosis DALYs.

Findings 2 888 articles were screened, of which 475 eligible studies containing quantitative information were retained. Sepsis/septic shock and pneumonia were the most common outcomes, occurring in 18.0% (1526/8469), 12.1% (1004/8298) and 35.7% (3633/10175) of patients respectively. The male to female ratio of infection was 2:1. We estimate that in 2015, the global burden of melioidosis was 4·6 million DALYs (UI 3·2-6·6) or 84·3 per 100 000 people (UI 57·5-120·0). Years of life lost (YLL) accounted for 98·9% (UI 97·7-99·5) of the total DALYs.

Interpretation Our estimates enable comparison with other tropical diseases which are already recognised as neglected and give policy makers the information necessary to reconsider melioidosis as a major neglected tropical disease.

Funding European Society of Clinical Microbiology and Infectious Diseases (ESCMID) Research Grant 2018; AMC PhD Scholarship; The Netherlands Organisation for Scientific Research (NWO); H2020 Marie Skłodowska-Curie Innovative Training Network (MC-ITN) European Sepsis Academy.

Key words Melioidosis, *Burkholderia pseudomallei*, global burden, DALY, diabetes, neglected tropical disease

RESEARCH IN CONTEXT

Evidence before this study

Previous studies have estimated incidence and mortality rates of melioidosis using regional cohorts. A recent study used epidemiological and environmental modelling to estimate the incidence and mortality of melioidosis. These global case numbers of incidence and deaths were based on modelling of a comprehensive database of 22 338 geographically located records of human and animal melioidosis, alongside the presence of environmental *B. pseudomallei* and are the only known prior global estimates. However, attempts to calculate disability-adjusted life years (DALYs) due to melioidosis are lacking, hampering comparisons with other neglected tropical diseases (NTDs). Our systematic review of the peer-reviewed literature for human melioidosis cases between 1990 and 2015, using a broad search strategy and combination of search terms, *Burkholderia* spp. and disease names, without language restrictions, returned 2 888 results. Screening abstracts and titles identified 698 reports. Full text screening eliminated 223 articles that did not meet the inclusion criteria. Therefore 475 studies were included in the data synthesis.

Added value of this study

To our knowledge, this study is the first to provide global estimates of melioidosis in terms of years of life lost, years lived with disability, and DALYs at country, regional, and global levels. As such, it is the most comprehensive assessment of the burden of melioidosis so far. Our estimates add important information to what is known about melioidosis and the related potential impact of the global diabetes epidemic. Our estimates enable comparison with other NTDs which are already recognised as neglected and give policy makers the information necessary to reconsider melioidosis in this perspective.

Implications of all the available evidence

Our results suggest that symptomatic melioidosis infections result in about 4·6 million DALYs annually. In comparison, estimates for Intestinal Nematode Infection and Dengue resulted in 4·6 million and 2·9 million DALYs respectively. This data has the potential not only to inform public health policy and priority setting to address a potentially preventable and debilitating disease, but should also lead to the official recognition of melioidosis as a major NTD.

INTRODUCTION

Burkholderia pseudomallei is the environmental Gram-negative bacillus that causes melioidosis; a disease characterized by sepsis, abscess formation and significant case-fatality (10-50%) even when appropriately treated.[1-3] First recognised in 1911,[3] melioidosis primarily affects individuals with altered immune function and those in regular contact with soil and ground water. Southeast Asia and northern-Australia are the major endemic regions, although melioidosis appears to be ubiquitous across the tropics.[4] Diagnosis can be difficult due to its diverse clinical manifestations and the inadequacy of conventional bacterial identification methods.[5] Additionally, a large proportion of cases may be missed due to paucity of diagnostic facilities.[6,7] A recent modelling study that mapped documented human and animal cases as well as the presence of environmental *B. pseudomallei* estimated the global incidence to be 165 000 (68 000-412 000) human melioidosis cases per year worldwide, of which 89 000 (36 000-227 000) people die,[4] most of whom are in low to middle-income countries (LMIC). Despite this, melioidosis is currently not included in the neglected tropical diseases (NTDs) listed by the World Health Organization (WHO).[3]

The disparity between the number of reported cases and estimated number of actual cases stems from under-recognition and under-reporting of melioidosis.[4] Symptomatic melioidosis infections are usually acute, but the broad range of clinical manifestations, from localised skin lesions to septic shock, hinders recogition.[8] Chronic melioidosis, defined as symptoms that last longer than two months, is present in approximately 11% of cases.[2] Unlike the incidence of some NTD,[9] the reported incidence of melioidosis is increasing, partly due to increasing awareness amongst physicians and researchers and the expansion of diagnostic services, although there may also be genuine increases in incidence.[10] Melioidosis often results in intensive care admission and requires prolonged antibiotic therapy (up to 6 months),[3] which also makes the treatment and consequences of this disease costly.

A metric that can be used to summarise morbidity, disability and mortality into a single index is the disability-adjusted life year (DALY). The DALY provides additional information to incidence/prevalence and mortality data, allowing for comparison of disease burden across populations and diseases.[11] DALYs of some NTDs have been estimated previously, which showed the relative importance of these diseases compared to other causes of ill health, although this has never been done for melioidosis.[9]

The aim of our study was to quantify for the first time the global burden of melioidosis in terms of DALYs. By combining the modelled estimates of the global incidence and mortality of melioidosis[4] with a systematic review of the published literature on its clinical impact, we calculated the global DALYs for melioidosis for the year 2015 by age, sex and country. In addition, we examined the relationship between melioidosis burden and the Socio-demographic Index (SDI),[12] a composite indicator based on income, education, and fertility. Furthermore, we analysed the relationship between Healthcare Access and Quality (HAQ) Index,[13] a score developed by the Global Burden of Disease (GBD) studies, which can be used as a robust method for tracking universal health access. By further elaborating the proportion of cases presenting with known risk factors (i.e., diabetes, chronic liver disease or alcohol abuse, chronic renal failure, and chronic lung disease), we provide crucial input into melioidosis control policies. Our estimation of the global burden of melioidosis is in accordance with the GATHER guidelines (webappendix pp 11-12).[14]

METHODS

Study design and procedures

We systematically searched Medline, Embase, WHO Global Health Library, and the database on melioidosis.info without language restriction, for reports of human melioidosis published between Jan 1, 1990 and Dec 31, 2015. A broad search strategy and combination of test searches and terms, *Burkholderia* spp. and disease names were used to capture a range of outcomes associated with melioidosis (webappendix pp 3-4). To foster data quality, we only included culture-confirmed cases of melioidosis. Two independent reviewers (JS, HV) screened titles and abstracts for relevance, and any disagreement about eligibility between reviewers was resolved by discussion and ultimately a third author (EB). The search of published works and data extraction was done by EB, HV and JS (webappendix pp 7-8). Due to the absence of data on post-infectious sequelae in the initial systematic review, an expert opinion-guided supplementary search was conducted (webappendix pp 3-4). We conducted the review according to guidance from the Cochrane handbook of interventions and reported the systematic review according to PRISMA guidelines where applicable (webappendix pp 9-10). This study was registered in PROSPERO (CRD42018106372).

Synthesis of global epidemiological data is used to quantify disease burden using the DALY metric, which is composed of time lost due to morbidity (YLD = years lived with disability) and time lost due to mortality (YLL = years of life lost). One DALY is equivalent to 1 year of healthy life lost.[11] An incidence-based disease model of melioidosis disease states (sequelae) and post-infectious sequelae, was developed to quantitatively assess the melioidosis disease burden (Figure 1).[15]

Disability weights (DWs), are weight factors reflecting severity of disease, ranging from 0 (perfect health) to 1 (equivalent to death). For this study, the DWs for health outcomes from the GBD study were adopted if possible,[20] otherwise a new DW for 'intensive care admission' was used from a European study involving 30,660 responses.[21] When exact matches were not available, proxy disease outcomes were identified based on best matching description and expert agreement (Table 1). See webappendix pp 13 for our analytical model flowchart for DALY calculation and melioidosis database development.

Based on a combination of literature, clinical expertise and consensus, we divided melioidosis into disease states (or sequelae) (Table 1): (1) septic shock, (2) sepsis, (3) pneumonia, (4) central nervous system infection (CNS), (5) intra-abdominal abscess, (6) musculoskeletal infection (MSK), (7) urinary tract infection (UTI), (8) parotitis (including lymphadenitis), (9) skin and soft tissue infection (SSTI), and (10) other (mainly pericarditis and mycotic aneurysms). Although we modelled individual outcomes/sequelae, overlap was allowed; thus implicitly, multifocal or disseminated cases of infection were also included. Oral antibiotic treatment was considered as an additional health state in non-fatal cases. Post-infectious sequelae data for melioidosis were also extracted from additional literature searches for sepsis and septic shock,[16] ongoing neurologic impairment,[17] and ongoing MSK problems,[18,19] which were validated against expert opinion. These models allowed quantification of global burden of melioidosis as expressed in DALYs. Due to the scarceness of good quality epidemiological data on melioidosis and to reduce duplication of effort, we extracted mortality and incidence estimates from a recent modelling study[4] and estimated DALYs based on the 2015 estimates of the UN World Population Prospects 2017 revision (https://population.un.org/wpp).

In addition, we established the age and sex distribution of melioidosis cases per WHO region based on the data resulting from our systematic review (Figure 2). We used the same age-sex distribution for all countries within the same region. The case definition of melioidosis was isolation of *B. pseudomallei* from any site, ensuring capture of all types of culture-positive melioidosis, including localised and disseminated forms. All included cases represented symptomatic infection. Relapse or recrudescence of infection were counted as separate cases.

YLDs were calculated for the main melioidosis symptoms (i.e., sepsis, pneumonia), as well as for antibiotic treatment and lifelong post-infectious sequelae among surviving cases. Our systematic review provided data on the health state durations and on the probabilities of developing the considered symptoms. All surviving patients were assumed to receive antibiotic treatment, while the probabilities of developing post-infectious sequelae among surviving cases were derived from the literature.[16-19] Disability weights were derived from the Global Burden of Disease study.[20] YLLs, YLDs and post-infectious sequelae were calculated using the WHO standard life expectancy table,[23] while the GBD standard life expectancy table[12] was used in a scenario analysis. The case data from our systematic review were used to derive an age and sex distribution of incident cases and deaths by WHO region. DALYs were calculated by country, and

subsequently aggregated at regional and global level. Based on our case data, we also calculated the proportion of patients who presented with known melioidosis risk factors, i.e., diabetes, chronic liver disease or alcohol abuse, chronic renal failure and chronic lung disease.

Parameter uncertainty was quantified and propagated using 10,000 Monte Carlo simulations (webappendix pp 18). The resulting uncertainty distributions were summarised by their mean and a 95% uncertainty interval (UI) defined as the distribution's $2{\cdot}5^{th}$ and $97{\cdot}5^{th}$ percentile. In subsequent analyses, we used linear regressions to analyse the associations between the country-specific log-transformed melioidosis DALYs and the countries' SDI scores[12] and HAQ indices[13] for 2015 (webappendix pp 15). We also quantified the association between global DALYs for melioidosis and other NTDs, and their respective levels of funding according to http://www.who.int/research-observatory.[24] All analyses were performed in R 3.5.1 (R Core Team, 2018).

Role of funding source

The study funders had no role in the study design, data collection, data analysis, data interpretation, or writing of the final report. The corresponding author had full access to all the data in the study and had final responsibility for decision to submit for publication.

RESULTS

Our systematic review identified 2 888 studies, of which 475 were included in the quantitative analyses (webappendix pp 6). In total, 11 767 cases from five of six WHO regions were available (webappendix pp 14). The incidence age and sex distribution is largely similar to the mortality age and sex distribution (Figure 2), and also to DALY age and sex distribution, given that the majority of patients die during the acute stage of their illness. However, regional differences were observed with respect to the median age of incidence, which was 36 years in the American region (AMR), compared to 50, 47, 49 and 60 years for the South-East Asian region (SEAR), Western-Pacific region (WPR), African region (AFR) and Eastern Mediterranean region (EMR) respectively (webappendix pp 19-21). Below the age of 14, the age-sex distribution of melioidosis incidence was similar across regions, whereas for 14 years and older the male to female incidence and mortality of melioidosis was 2:1 (Figure 2).

Of all melioidosis cases identified, 88·4% (4589/5194) were acute and 11·7% (605/5194) chronic. Sepsis, intra-abdominal abscess, and pneumonia were the most common outcomes, occurring in 18·0% (UI 17·2-18·9), 18·3% (UI 17·5-19·1) and 35·7% (UI 34·9-36·6) of patients respectively. In total, 12·6% (UI 12·0-13·3) presented with SSTI, 12·1% (UI 11·4-12·8) with septic shock, 8·2% (UI 7·7-8·7) with MSK infections, 6·7% (UI 6·2-7·2) developed UTI, 2·6% (UI 2·3-2·9) other infections such as pericarditis and mycotic aneurysms, 2·3% (UI 2·0-2·6) parotitis and 1·6% (UI 1·4-1·9) developed CNS infections (webappendix pp 22-23). Chronic post-infectious sequelae, most notably general malaise/weakness, cognitive impairment and readmissions predicted to occur in 16·7% (UI 0·5-52·1) of septic patients,[16] ongoing functional and cognitive impairment in 36·2% (UI 24·4-48·8) of CNS infection patients,[17] and ongoing arthritic symptoms and mobility problems in 40·7% (UI 34·1-47·5) of MSK infection patients (webappendix pp 22-23).[18,19] Septic shock had the shortest mean duration of symptoms prior to admission of 8·2 d (sd 8·4 d) and hospitalization of 14·5 d (sd 15·8 d). Pneumonia had a mean duration of symptoms prior to admission of 10·9 (sd 10·6) and hospitalization of 21·4 (sd 17·3) days. MSK and intra-abdominal abscess had the longest mean duration of symptoms prior to admission of 63·3 (sd 168·8) and 67·4 (sd 206·4) respectively which also coincides with longest mean number of days hospitalized, 33·9 (sd 56·2) and 32·9 (sd 60·2) days respectively. The mean duration of consolidation therapy was 129·5 days (sd 48·0).

Overall, by integrating the predicted incidence and mortality data with our disease model,[4] we estimated that melioidosis was responsible for 4 635 636 DALYS (UI 3 164 157-6 602 075) in 2015, corresponding to 84·3 DALYs (UI 57·5-120·0) per 100 000. YLLs accounted for 98·9% (UI 97·8-99·5) of the total DALYs. The highest total burden occurred in India, where melioidosis resulted in 1 596 733 DALYs (UI (503 727-3 320 277), while Cambodia had the highest DALY per 100 000 people (with 414·6 DALYs per 100 000; UI 111·9-919·4). In 2015, India, Bangladesh, Vietnam, Nigeria and Indonesia combined made up 70·5% (UI 57·7-80·9) of total melioidosis DALY burden (3 307 178 DALYs; UI 1 892 971-5 251 783). SEAR carried the highest burden of DALYs (158·1 per 100 000 people; UI 88·3-256·0), followed by AFR (84·1; UI 43·4-152·4) and then WPR (45·6; UI 27·7-69·5) (Figure 3; Table 2).

YLDs were responsible for 1·1% (50 541·7 UI 22 778·2-97 825·4) of the total melioidosis DALYs. With post-infectious sequelae contributing most to the YLDs (86·8%; UI 70·2-95·2), followed by symptoms 9·9% (UI 3·0-25·5) and oral antibiotic treatment 3·4% (UI 1·0-8·0). The proportion of patients with melioidosis also having underlying diabetes or newly diagnosed hyperglycaemia was 46·1% (UI 45·2-47·0), with chronic kidney disease, chronic liver disease or alcohol abuse, and chronic lung disease representing 9·3% (UI 8·8-9·8), 7·4% (UI 6·9-7·9) and 3·4% (UI 3·0-3·7) respectively (webappendix pp 22-23). As a proportion of DALYs, diabetes alone accounted for 2 137 433·3 (UI 1 459 182·0-3 046 177·1). Total DALYs per country showed a negative association with both SDI and HAQ Index (webappendix pp 28, Figure S6), reinforcing the known trend of improving outcomes with better access to healthcare and improved education. These associations also help to identify those countries with discrepancies in access to healthcare and high DALYs, such as Thailand and Singapore. Additionally, the Philippines, Indonesia and Thailand, despite having higher SDI, display a high burden of melioidosis (webappendix pp 28-31). For example, Thailand, despite having good access to healthcare (70·8 HAQ Index) and good socio-demographic development (0·705 SDI), still shows a high melioidosis DALY burden (212·6 per 100 000 people; UI 72·4-430·1). The scenario analysis using the GBD life expectancy tables resulted in 4 093 110 (UI 2 790 743-5 826 117) DALYs, 11·7% lower than the result using the WHO life expectancy table (webappendix pp 25-27, Table S6).

DISCUSSION

Our study, using a systematic review and data synthesis, is the first to provide estimates of the global burden of melioidosis in terms of DALYs. We estimated that in 2015 the global burden of melioidosis was 4·6 million DALYs (UI 3·2-6·6 million), corresponding to 84·3 DALYs (UI 57·5-120·0) per 100 000 people. YLLs accounted for 98·9% (UI 97·7%-99·5%) of the total DALYs.

Our study provides worldwide estimates, including regions of South Asia, South America, and Africa where the burden of melioidosis has been under-appreciated and possibly misallocated to other febrile illnesses such as malaria and tuberculosis.[6,7] Putting this into context, the global burden of melioidosis as expressed in DALYs (4·64 million) is higher than leptospirosis (2·90 million), dengue (2·86 million), schistosomiasis (2·63 million), lymphatic filariasis (1·24 million) and leishmaniasis (1·06 million) (webappendix pp 32-33). The burden per million DALYs of melioidosis compared to the estimates of officially recognized neglected and re-emerging tropical diseases estimated by the WHO and amount invested globally in research and development is showed in webappendix pp 32-33 (Figure S7). This shows that there is no clear association between DALY burden and level of global investment ($p = 0{\cdot}892$), which we feel should prompt re-evaluation of how resources are allocated for NTDs.

Our scenario analysis which represents differences between WHO and GBD life expectancy tables alone, resulted in 11·7% higher DALY estimates (webappendix pp 25-27). Additionally, an incidence-based approach was preferred as it has been shown to provide a more reliable metric for infectious diseases,[15,25] and we restricted our systematic review to culture confirmed cases only to limit bias.

The results of our systematic review also showed that incidence, mortality, and DALYs from melioidosis were about twice as high for men as for women, a finding similar to that in tuberculosis.[26] As with tuberculosis, several explanations have been given for the gender difference in melioidosis risk; including differential occupational exposures, differential access to health care, differential exposure to risk factors, and genetic variation.[3,26] This interplay of risk factors and age-sex distribution of melioidosis cases, deaths, and DALYs has strategic implications for melioidosis control programmes by allowing targeting of high risk groups.

The gold-standard for diagnosis of melioidosis is culture; therefore, we limited our case definition to only culture-proven melioidosis. Due to the low sensitivity and specificity of currently used serological tests,[3] we decided to take this more conservative approach. However, the estimated sensitivity of culture in melioidosis is only 60·2%.[3] This means that there is an opportunity for future studies using more robust serological tests than those that are currently available to provide even better estimates of the true burden of melioidosis that can be incorporated into DALY calculations.

Globally, in 2015, the top four risk factors for melioidosis (diabetes, chronic liver disease or alcohol abuse, chronic renal disease and chronic lung disease) were present in 46·1%, 7·4%, 9·3%, and 3·4% of melioidosis cases respectively (webappendix pp 24). Thus, efforts to prevent these risk factors or provide a cost-effective vaccine targeted 'at-risk' groups such as diabetic rice farmers, could have substantial collateral impact on the burden of melioidosis. Interestingly, in our analysis HIV, occurring in less than 1%, does not appear to be associated with acquiring melioidosis, which is consistent with evidence from previous smaller cohorts.[3,27] As many countries go through demographic and epidemiological transitions, particularly those in LMICs are poised to suffer the double burden of melioidosis and diabetes.[28] Global YLLs for diabetes have gone from rank 27 to rank 15 between 1990 and 2015, a 45·3% increase.[29] Indeed, diabetes alone carries a 12 times relative risk of acquiring melioidosis in endemic regions[3,10] and with the global diabetes pandemic, there is potential for catastrophic increase in melioidosis burden, with LMIC facing the brunt.

Our study has several limitations. First, globally reliable incidence and mortality data for calculating the global burden of melioidosis were scarce. Therefore, the global case numbers of incidence and deaths were based on modelling of a comprehensive database of 22 338 geographically located records of human and animal melioidosis, alongside the presence of environmental *B. pseudomallei.*[4] Given the imperfections in data sources, we believe our methodology of integrating existing information and knowledge through a systematic literature review and data synthesis provides a more robust assessment of melioidosis epidemiology than has been done so far. Second, we did not include all possible sequelae in our outcome tree designed to calculate DALYs, because of paucity of data particularly on the rarest sequelae. Specific DWs were not available for most of the disease outcomes (for example septic shock, sepsis, CNS infection, intra-abdominal abscess, MSK infection, UTI, parotitis, SSTI, and post-infectious sequelae amongst others) and proxy health states were decided based on the best matching descriptions

and expert opinion. Further studies generating DWs should include those disease outcomes in their future surveys. In particular, the lack of a DW for sepsis,[30] a critical illness with a high disability, is a significant handicap for such work and highlights the need for better DWs to be developed in future. We believe that it is insufficient to use the severe acute infectious disease disability weightDW[30] for sepsis given the mounting evidence of prolonged disability and involvement in organ dysfunction in sepsis (as per 3·0 guidelines definition).[31] Third, outcomes of post-melioidosis sequelae, such as those following sepsis/septic shock, CNS infection and MSK infection, had very limited data available, and were therefore extracted through review of additional literature.[16-19] These post-infectious sequelae were modelled on the remaining life expectancy of survivors and a shortened life expectancy was not accounted for. Although YLDs did not appear to have a significant contribution to overall DALYs in melioidosis, we only accounted for a limited number of post-infectious sequelae, and given that 86·8% (UI 70·2-95·2) of YLDs are due to the post-infectious sequelae component, this warrants further studies on long term disease outcomes. Since we made use of expert panel facilitation, careful interpretation of post-infection sequelae proportions may be required. Fourth, so far, we have included only regional age/sex distribution and country specific life expectancy values for post-infectious sequelae, but have been unable to include any regional differences in disease presentation and sequelae, which may be linked to virulence,[3] because of lack of data. Additionally, due to the lack of granularity we were unable to differentiate for transition between disease states and therefore we assumed to be similar across health-care systems globally. Fifth, as yet, reactivation of latent melioidosis does not seem to play a major role in the total burden of melioidosis, however, crucial data on this subject are missing and we are currently unable to determine exact figures. Sixth, we did not account for trends of increasing or decreasing melioidosis incidence that could have occurred across countries, because of the limited amount of data available. We found that extracting data from regional/national databases would not be representative, as exemplified by data validation in Thailand (webappendix pp 4).[32] Last, the nature of our study and modelling work only allowed us to generate estimates up to 2015. Extrapolation of estimates beyond this time point was considered, but this would have led to further widening of uncertainty intervals. Additionally, accurate populations estimates are only available up to 2015, hence reducing the ambiguity in modelling estimates of estimates. Moreover, in order to be consistent with the incidence and mortality rates for 2015 used, we only included data up to 2015 in our systematic review.[4] Despite these limitations, we believe the systematic methodological approach we have taken has yielded more robust estimates than would otherwise have been obtained using limited source data of countrywide health statistics/vital registration forms.

Access to healthcare and socio-demographic development are associated with the burden of melioidosis as assessed by DALYs. Previously it has been shown that below a SDI score of 0.25, communicable causes accounted for 30-45% of total disability, with NTDs playing a primary role.[33] Interestingly, the majority of melioidosis-endemic countries carry a higher SDI. This association between SDI and HAQ Index and DALYs allows one to benchmark those outliers showing a discrepant relationship for targeted improvement, at the same time providing insights into which public interventions contribute towards narrowing. Thus, efforts beyond reduction in income inequality, improved fertility or years of education (factors comprising SDI) will help catalyse additional gains in life expectancy and reduce disease burden (all-age YLDs), further emphasising the critical role of policy interventions beyond traditional health service delivery. For example, with increasing SDI, the proportion of workforce in agriculture would be expected to decrease, which is likely to have some effect on the burden of melioidosis as this group of population is at increased risk. It is important to note that the SDI instrument is still incomplete, because significant features of societal function are missing (including political stability, gender equity, urbanisation, technology penetration or infrastructure).[34] As melioidosis is caused by a saprophytic organism, climate change will also impact geographic spread and incidence. Further aims include characterizing knowledge gaps in respective epidemiological disease parameters. One such aspect would be to characterise DALYs according to seasonal changes given the close relationship between melioidosis incidence, the monsoon and severe weather events, which will help further target interventions.

Moreover, incidence data on melioidosis could vary depending on the surveillance system of the country (including whether it considers melioidosis a problem or not) and on the definition of case-based isolation of bacteria or detection by PCR or immunoassays test.[30] Strengthening melioidosis notification and vital registration systems is needed to improve the quality of data.[26] Until such systems are fully developed and integrated at national levels, it should be appreciated by users that variation in estimates is unavoidable. It is hoped from this work that endemic countries will be sensitised on the burden of the disease and the need to improve its surveillance in order to adapt control measures. Clearly, a key priority should be worldwide collaboration to fortify and develop basic microbiological diagnostic facilities (health technology) and capacity which forms the foundations of surveillance data, an area of importance also emphasised by the *Lancet* commission.[35] This in itself would have wider implications for other diseases/pathogens, not least better clinical management of patients.

Efforts against NTDs reached a watershed after the first Global Partners' Meeting convened by WHO in 2007. This landmark initiative resulted in a shared commitment to support WHO's strategies yielding significant gains for public health, including scale up of control and elimination programs and enhanced access to medicines. Subsequently, the first WHO report on NTDs demonstrated that the strategic approaches were technically feasible and the investment cost effective.[36] We feel it is time that these gains are also translated across to melioidosis as our estimates provide a clear motivation for considering melioidosis as a major NTD. It meets the proposed criteria for classifying a condition as an NTD, in that it *1) disproportionally affects populations living in poverty, causing important morbidity and mortality 2) primarily affects populations living in tropical and subtropical regions 3) is amenable to broad control, elimination or eradication strategies and 4) is relatively neglected by research funding allocation.*[37] Now that this precedent has been established, collaboration between member states and international partners, including organizations, foundations and donors is vital in order to increase international attention, prioritize national epidemiological surveillance, operational research and strengthen development of highly needed laboratory capacity, products and tools together with necessary public and health-care worker training. Due to the saprophytic nature of melioidosis and the fact that it can also affect a wide range of animal species, a One Health approach would be ideal.

Contributors

EB, HV, BD, JH, and WJW conceived the protocol. RS did the literature search. EB, HV, and JS collected the data. Expert panel consisted of DL, DD, BD, JH, and WJW. EB and HV synthesised the data. EB, HV, and BD performed the statistical analyses and prepared all tables and figures. BD, JH, and WJW supervised the whole process. EB, HV, BD, JH, and WJW prepared the first draft. All other authors provided critical feedback, provided guidance on methods and reviewed the report.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

EB received a Research Grant [2018] from the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and received the Academic Medical Center PhD scholarship award [grant number: 22162]; WJW received financial support through a VIDI-grant of The Netherlands Organisation for Scientific Research ([NOW; VIDI grant to W.J.W., grant number: 91716475]; WJW and HV are supported by the H2020 Marie Skłodowska-Curie Innovative Training Network (MC-ITN) European Sepsis Academy.

Table 1: Disability weights used for the calculation of the disability-adjusted life years due to melioidosis

Melioidosis disease states used in model	Most similar sequela from GBD 2015	Description	Disability Weight (95% CI)
Septic shock[a]	Intensive care unit admission [21]	Intensive care unit admission used as surrogate for septic shock.	0·655 (0·579-0·727)
Sepsis[a]	Infectious disease: acute episode (severe)	Has high fever and pain, and feels very weak, which causes great difficulty with daily activities.	0·133 (0·088-0·190)
Pneumonia[a]	Infectious disease: acute episode (severe) is equivalent to lower respiratory infections (severe)	Has high fever and pain, and feels very weak, which causes great difficulty with daily activities.	0·133 (0·088-0·190)
Central nerve system infection (brain or spinal)	Motor plus cognitive impairment (severe)	Cannot move around without help, and cannot lift or hold objects, get dressed or sit upright. The person also has very low intelligence, speaks few words, and needs constant supervision and help with all daily activities.	0·542 (0·374-0·702)
Intra-abdominal abscess (e.g. liver, spleen, pancreas)	Abdominal/Pelvic problems (moderate)	Has pain in the belly and feels nauseous. The person has difficulties with daily activities.	0·114 (0·078-0·159)
Musculoskeletal infection (osteomyelitis or septic arthritis)	Osteoarthritis (severe)	Musculoskeletal problems, lower limb has severe pain in the leg, which makes the person limp and causes a lot of difficulty walking, standing, lifting and carrying heavy things, getting up and down, and sleeping.	0·165 (0·112-0·232)
Urinary tract infection (e.g. prostatitis)	Epididymo-orchitis	Has swelling and tenderness in the testicles and pain during urination.	0·128 (0·086-0·180)
Parotitis (+lymphadenitis)	Infectious disease: acute episode (moderate)	Has a fever and aches, and feels weak, which causes some difficulty with daily activities.	0·051 (0·032-0·074)
Skin soft tissue infection	Mild cellulitis	Has a slight, visible physical deformity that is sometimes sore or itchy. Others notice the deformity, which causes some worry and discomfort. Has a low fever and mild discomfort, but no difficulty with daily activities.	0·027 (0·015-0·042)
Other (mainly pericarditis and mycotic aneurysms)	Infectious disease: acute episode (severe)	Has high fever and pain, and feels very weak, which causes great difficulty with daily activities.	0·133 (0·088-0·190)

Oral treatment	Generic uncomplicated disease: worry and daily medication	Has a chronic disease that requires medication every day and causes some worry but minimal interference with daily activities.	0·049 (0·031-0·072)
Post sepsis and septic shock sequelae	Infectious disease: Post-acute effects (fatigue, emotional lability, and insomnia)	Is always tired and easily upset. The person feels pain all over the body and is depressed.	0·217 (0·179 – 0·251)
Ongoing neurologic impairment	Infectious disease: Post-acute effects (fatigue, emotional lability, and insomnia)	Is always tired and easily upset. The person feels pain all over the body and is depressed.	0·217 (0·179 – 0·251)
Ongoing musculoskeletal problems	Osteoarthritis (severe)	Musculoskeletal problems, lower limb has severe pain in the leg, which makes the person limp and causes a lot of difficulty walking, standing, lifting and carrying heavy things, getting up and down, and sleeping.	0·165 (0·112 – 0·232)

Most recent version of already established DWs of most similar sequelae were selected from the GBD 2015 update.[20] For septic shock intensive care unit admission was used as a surrogate.[21] When exact matches were not available, proxy disease outcomes were identified based on the best matching description and expert opinion. We considered all pneumonia cases to be severe, because a priori evidence shows that primary pneumonia due to *B. pseudomallei* is acute in the majority of patients (>90%) and frequently rapidly progresses to sepsis and death.[22]

By definition, DWs range on a scale from 0 (perfect health) to 1 (death).

[a] Septic shock, sepsis, pneumonia, only acute cases were included

Abbreviations: CI = confidence interval, DW= disability weight and GBD= Global Burden Disease.

Table 2 Melioidosis global disability-adjusted life years distribution with breakdown per country in 2015

Country	YLL (95% UI)	YLL per 100·000 (95% UI)	YLD (95% UI)	YLD per 100·000 (95% UI)	DALY (95% UI)	DALY per 100·000 (95% UI)
African Region	**769 448 (394 742-1 399 395)**	**83 (43-152)**	**5 817 (2 240-12 735)**	**0·631 (0·243-1·4)**	**775 266 (400 236-1 405 485)**	**84 (43-152)**
Angola	984 (61-3 199)	3·5 (0·218-11)	8·8 (0·590-31)	0·032 (0·002-0·111)	993 (68-3 206)	3·6 (0·246-12)
Benin	29 154 (6 264-69 760)	276 (59-660)	241 (44-671)	2·3 (0·419-6·3)	29 395 (6 510-69 975)	278 (62-662)
Burkina Faso	20 685 (2 802-56 695)	114 (15-313)	165 (20-509)	0·911 (0·112-2·8)	20 850 (2 948-56 834)	115 (16-314)
Cameroon	17 362 (2 608-46 249)	76 (11-203)	141 (20-420)	0·616 (0·087-1·8)	17 503 (2 738-46 378)	77 (12-203)
Central African Republic	4 479 (792-11 460)	99 (17-252)	33 (5·2-95)	0·725 (0·115-2·1)	4 512 (825-11 489)	99 (18-253)
Chad	13 457 (1 460-38 811)	96 (10-277)	103 (10-331)	0·738 (0·074-2·4)	13 561 (1 567-38 928)	97 (11-278)
Congo	8 295 (1 854-19 696)	166 (37-394)	68 (13-186)	1·4 (0·264-3·7)	8 363 (1 921-19 769)	167 (38-396)
Côte d'Ivoire	36 423 (7 354-89 402)	158 (32-387)	264 (44-756)	1·1 (0·192-3·3)	36 686 (7 599-89 665)	159 (33-388)
DRC	7 214 (769-20 814)	9·5 (1·0-27)	61 (6·2-197)	0·080 (0·008-0·258)	7 275 (830-20 871)	9·5 (1·1-27)
Equatorial Guinea	194 (39-477)	17 (3·3-41)	1·4 (0·251-4·0)	0·121 (0·021-0·342)	196 (41-478)	17 (3·4-41)
Eritrea	845 (59-2 675)	17 (1·2-55)	8·5 (0·686-29)	0·174 (0·014-0·589)	854 (68-2 683)	18 (1·4-55)
Ethiopia	8 399 (874-24 387)	8·4 (0·875-24)	76 (8·0-242)	0·076 (0·008-0·243)	8 475 (950-24 473)	8·5 (0·951-25)
Gabon	1 410 (323-3 323)	73 (17-172)	12 (2·2-33)	0·619 (0·112-1·7)	1 422 (335-3 335)	74 (17-173)
Gambia	255 (6·3-940)	13 (0·319-48)	2·8 (0·151-10)	0·140 (0·008-0·518)	257 (9·0-942)	13 (0·454-48)
Ghana	13 096 (1 335-38 275)	47 (4·8-139)	107 (9·7-352)	0·389 (0·035-1·3)	13 203 (1 443-38 382)	48 (5·2-139)
Guinea	42 961 (8 864-104 561)	355 (73-865)	333 (61-928)	2·8 (0·502-7·7)	43 294 (9 190-104 890)	358 (76-867)
Guinea-Bissau	3 315 (375-9 442)	187 (21-533)	26 (2·8-82)	1·5 (0·161-4·6)	3 341 (402-9 472)	189 (23-535)
Kenya	3 187 (413-8 852)	6·7 (0·875-19)	29 (3·5-90)	0·061 (0·007-0·190)	3 216 (442-8 879)	6·8 (0·935-19)
Liberia	14 131 (2 751-35 137)	314 (61-781)	111 (19-317)	2·5 (0·414-7·0)	14 242 (2 868-35 269)	317 (64-784)
Madagascar	27 359 (5 851-65 662)	113 (24-271)	235 (43-657)	0·972 (0·179-2·7)	27 594 (6 107-65 878)	114 (25-272)
Malawi	6 894 (1 242-17 539)	39 (7·1-100)	57 (9·4-163)	0·325 (0·054-0·929)	6 951 (1 303-17 587)	40 (7·4-100)
Mali	19 197 (2 763-51 629)	110 (16-296)	151 (20-459)	0·863 (0·112-2·6)	19 348 (2 913-51 768)	111 (17-296)
Mauritania	958 (74-2 977)	23 (1·8-71)	8·0 (0·572-28)	0·192 (0·014-0·661)	966 (82-2 987)	23 (2·0-71)
Mauritius	101 (9·1-302)	8·0 (0·720-24)	2·4 (0·212-8·0)	0·190 (0·017-0·633)	103 (11-304)	8·2 (0·887-24)
Mozambique	7 613 (966-21 195)	27 (3·4-76)	62 (7·7-192)	0·223 (0·028-0·686)	7 675 (1 026-21 253)	27 (3·7-76)
Niger	12 146 (1 034-36 906)	61 (5·2-185)	103 (8·5-349)	0·520 (0·043-1·8)	12 249 (1 130-37 026)	62 (5·7-186)
Nigeria	426 571 (89 803-1 031 369)	235 (50-569)	3 070 (551-8 590)	1·7 (0·304-4·7)	429 641 (92 865-1 034 804)	237 (51-571)
Senegal	2 097 (118-6 906)	14 (0·789-46)	18 (1·1-65)	0·123 (0·008-0·435)	2 115 (135-6 929)	14 (0·904-46)
Sierra Leone	19 140 (3 758-47 287)	264 (52-653)	132 (23-375)	1·8 (0·321-5·2)	19 272 (3 884-47 455)	266 (54-656)

South Africa	856 (64-2 678)	1·5 (0·116-4·8)	8·2 (0·696-27)	0·015 (0·001-0·049)	864 (72-2 686)	1·6 (0·130-4·9)
South Sudan	1 189 (120-3 492)	10 (1·0-29)	11 (1·2-35)	0·092 (0·010-0·292)	1 200 (131-3 504)	10 (1·1-29)
Tanzania	9 561 (1 272-26 347)	18 (2·4-49)	86 (11-264)	0·159 (0·019-0·490)	9 647 (1 354-26 437)	18 (2·5-49)
Togo	5 030 (748-13 431)	68 (10-181)	39 (5·1-119)	0·531 (0·069-1·6)	5 070 (783-13 474)	68 (11-182)
Uganda	1 026 (37-3 620)	2·6 (0·092-9·0)	9·7 (0·477-36)	0·024 (0·001-0·090)	1 036 (47-3 629)	2·6 (0·116-9·0)
Zambia	3 635 (424-10 318)	23 (2·6-64)	31 (3·6-96)	0·191 (0·022-0·595)	3 666 (454-10 350)	23 (2·8-64)
Zimbabwe	230 (15-733)	1·5 (0·098-4·6)	2·2 (0·158-7·4)	0·014 (<0·001-0·047)	232 (18-735)	1·5 (0·111-4·7)
American Region	**68 431 (36 003-118 711)**	**12 (6·3-21)**	**1 291 (460-2 892)**	**0·225 (0·080-0·504)**	**69 722 (37 135-120 070)**	**12 (6·5-21)**
Argentina	565 (37-1 801)	1·3 (0·085-4·1)	11 (0·652-41)	0·026 (0·002-0·093)	577 (47-1 815)	1·3 (0·108-4·2)
Bolivia	573 (49-1 735)	5·3 (0·458-16)	5·8 (0·479-19)	0·054 (0·004-0·182)	579 (55-1 741)	5·4 (0·509-16)
Brazil	26 116 (3 852-69 412)	13 (1·9-34)	517 (64-1 598)	0·251 (0·031-0·776)	26 632 (4 304-70 044)	13 (2·1-34)
Colombia	4 808 (725-12 722)	10·0 (1·5-26)	88 (12-267)	0·182 (0·024-0·554)	4 896 (806-12 817)	10 (1·7-27)
Costa Rica	391 (71-988)	8·1 (1·5-21)	11 (1·6-32)	0·225 (0·033-0·666)	402 (81-1 000)	8·4 (1·7-21)
Cuba	426 (21-1 428)	3·7 (0·181-12)	17 (0·791-62)	0·146 (0·007-0·542)	442 (34-1 444)	3·9 (0·296-13)
El Salvador	3 206 (769-7 411)	51 (12-117)	59 (12-160)	0·934 (0·184-2·5)	3 265 (827-7 470)	52 (13-118)
Guatemala	2 454 (443-6 205)	15 (2·7-38)	31 (4·7-90)	0·189 (0·029-0·553)	2 485 (474-6 234)	15 (2·9-38)
Guyana	449 (86-1 118)	58 (11-146)	4·7 (0·675-14)	0·606 (0·088-1·8)	453 (90-1 122)	59 (12-146)
Haiti	1 129 (89-3 472)	11 (0·835-32)	8·9 (0·804-29)	0·083 (0·008-0·274)	1 138 (98-3 481)	11 (0·918-32)
Honduras	2 894 (400-7 833)	32 (4·5-87)	45 (6·2-136)	0·503 (0·069-1·5)	2 939 (443-7 879)	33 (4·9-88)
Mexico	16 128 (2 711-41 615)	13 (2·2-33)	328 (45-987)	0·260 (0·036-0·784)	16 456 (3 012-41 937)	13 (2·4-33)
Nicaragua	2 205 (379-5 651)	36 (6·2-93)	33 (4·8-98)	0·546 (0·079-1·6)	2 238 (411-5 690)	37 (6·8-94)
Panama	1 995 (465-4 657)	50 (12-117)	38 (7·3-104)	0·954 (0·184-2·6)	2 033 (500-4 694)	51 (13-118)
Paraguay	455 (12-1 670)	6·9 (0·177-25)	8·6 (0·358-32)	0·129 (0·005-0·486)	464 (19-1 679)	7·0 (0·291-25)
Peru	1 227 (155-3 389)	3·9 (0·493-11)	22 (2·7-69)	0·070 (0·008-0·219)	1 249 (175-3 411)	4·0 (0·558-11)
Suriname	439 (94-1 052)	79 (17-190)	6·6 (1·1-19)	1·2 (0·200-3·4)	446 (100-1 059)	81 (18-191)
Venezuela	2 970 (533-7 511)	9·5 (1·7-24)	58 (8·6-170)	0·185 (0·028-0·546)	3 028 (590-7 569)	9·7 (1·9-24)
Eastern Mediterranean Region	**18 448 (6 357-42 250)**	**4·4 (1·5-10)**	**101 (31-252)**	**0·024 (0·007-0·060)**	**18 549 (6 460-42 347)**	**4·4 (1·5-10)**
Iran	279 (9·5-981)	0·351 (0·012-1·2)	3·0 (0·106-11)	0·004 (<0·001-0·014)	282 (12-983)	0·355 (0·016-1·2)
Iraq	562 (9·1-2 200)	1·6 (0·025-6·1)	3·4 (0·052-14)	0·010 (<0·001-0·040)	566 (12-2 204)	1·6 (0·034-6·1)
Oman	84 (20-194)	2·0 (0·468-4·6)	1·1 (0·162-3·2)	0·026 (0·004-0·077)	85 (21-195)	2·0 (0·493-4·7)
Pakistan	11 193 (848-34 627)	5·9 (0·448-18)	57 (4·3-190)	0·030 (0·002-0·100)	11 250 (900-34 705)	5·9 (0·475-18)
Saudi Arabia	675 (65-1 992)	2·1 (0·205-6·3)	10·0 (0·858-33)	0·032 (0·003-0·104)	685 (73-2 002)	2·2 (0·233-6·3)

Somalia	1 776 (166-5 271)	13 (1·2-38)	7·8 (0·726-25)	0·056 (0·005-0·181)	1 783 (174-5 280)	13 (1·3-38)
Sudan	1 555 (95-5 014)	4·0 (0·245-13)	7·9 (0·515-27)	0·020 (0·001-0·070)	1 563 (102-5 023)	4·0 (0·265-13)
Yemen	2 324 (398-5 934)	8·6 (1·5-22)	11 (1·6-31)	0·040 (0·006-0·115)	2 334 (408-5 945)	8·7 (1·5-22)
South-east Asian Region	**2 974 407 (1 649 716-4 835 486)**	**156 (87-254)**	**30 640 (12 500-62 865)**	**1·6 (0·658-3·3)**	**3 005 047 (1 678 472-4 866 872)**	**158 (88-256)**
Bangladesh	471 829 (162 015-944 388)	293 (101-586)	4 974 (1 366-11 993)	3·1 (0·848-7·4)	476 803 (166 451-949 640)	296 (103-589)
Bhutan	433 (87-1 052)	55 (11-134)	3·8 (0·552-11)	0·487 (0·070-1·4)	437 (91-1 055)	55 (12-134)
India	1 583 214 (490 572-3 306 747)	121 (37-253)	13 518 (3 390-33 836)	1·0 (0·259-2·6)	1 596 733 (503 727-3 320 277)	122 (38-254)
Indonesia	532 334 (132 919-1 210 328)	206 (51-469)	6 147 (1 297-16 220)	2·4 (0·503-6·3)	538 480 (138 880-1 216 825)	209 (54-471)
Myanmar	187 137 (52 103-407 584)	357 (99-778)	1 596 (372-4 086)	3·0 (0·710-7·8)	188 733 (53 729-409 251)	360 (103-781)
Nepal	25 799 (6 147-59 555)	90 (21-208)	259 (54-690)	0·903 (0·189-2·4)	26 057 (6 394-59 808)	91 (22-209)
Sri Lanka	30 677 (8 849-65 909)	148 (43-318)	834 (196-2 159)	4·0 (0·946-10)	31 511 (9 655-66 771)	152 (47-322)
Thailand	142 641 (46 506-291 800)	208 (68-425)	3 305 (848-8 261)	4·8 (1·2-12)	145 946 (49 726-295 285)	213 (72-430)
Timor-Leste	343 (40-964)	28 (3·2-78)	2·8 (0·307-8·7)	0·225 (0·025-0·703)	346 (43-967)	28 (3·5-78)
West-Pacific Region	**754 360 (454 818-1 157 728)**	**45 (27-69)**	**12 693 (5 185-26 073)**	**0·754 (0·308-1·5)**	**767 053 (466 874-1 170 486)**	**46 (28-70)**
Australia	1 963 (450-4 584)	8·2 (1·9-19)	99 (19-276)	0·417 (0·078-1·2)	2 062 (536-4 697)	8·7 (2·3-20)
Brunei Darussalam	481 (159-981)	115 (38-235)	15 (3·5-38)	3·6 (0·835-9·2)	496 (173-995)	119 (41-238)
Cambodia	63 674 (16 627-142 051)	410 (107-915)	654 (141-1 723)	4·2 (0·909-11)	64 328 (17 359-142 676)	415 (112-919)
China	136 733 (47 558-272 254)	9·8 (3·4-19)	3 226 (880-7 859)	0·231 (0·063-0·563)	139 958 (50 709-275 425)	10 (3·6-20)
Fiji	103 (13-283)	12 (1·5-32)	1·6 (0·163-5·1)	0·180 (0·018-0·574)	105 (15-285)	12 (1·7-32)
Laos	14 058 (3 998-30 345)	211 (60-455)	112 (25-291)	1·7 (0·382-4·4)	14 170 (4 110-30 455)	213 (62-457)
Malaysia	28 564 (7 665-63 033)	93 (25-205)	912 (195-2 431)	3·0 (0·635-7·9)	29 476 (8 435-64 088)	96 (27-209)
Papua New Guinea	4 311 (997-10 032)	54 (13-127)	33 (6·7-89)	0·421 (0·084-1·1)	4 344 (1 031-10 064)	55 (13-127)
Philippines	240 606 (95 218-453 084)	237 (94-445)	2 976 (934-6 893)	2·9 (0·918-6·8)	243 582 (98 035-456 063)	239 (96-448)
Singapore	2 808 (284-8 173)	51 (5·1-148)	202 (22-633)	3·6 (0·406-11)	3 010 (456-8 379)	54 (8·2-151)
Vietnam	261 059 (65 691-591 358)	279 (70-632)	4 462 (940-11 849)	4·8 (1·0-13)	265 521 (70 102-596 432)	284 (75-637)
GLOBAL	**4 585 094 (3 114 498-6 550 593)**	**83 (57-119)**	**50 542 (22 778-97 825)**	**0·919 (0·414-1·8)**	**4 635 636 (3 164 157-6 602 075)**	**84 (58-120)**

DALYs are presented per country in associated region from highest to lowest DALY. Abbreviations: DRC= Democratic Republic of Congo; UI=uncertainty interval; YLL= years life lost; YLD= years lived with disability and DALY= disability-adjusted life years.

FIGURE LEGENDS

Figure 1: Simplified disease model used to estimate the global burden of melioidosis

All surviving patients were considered to receive oral antibiotic treatment. Sequelae data on post-acute melioidosis consequences were also extracted from additional literature searches for sepsis and septic shock,[16] ongoing neurologic impairment,[17] and ongoing MSK problems.[18,19] Abbreviations: CNS= central nervous system; MSK= musculoskeletal; UTI= urinary tract infection; SSTI= skin soft tissue infection.

Figure 2: Age and sex distribution of melioidosis incident and fatal cases

Figure 3: Disability-adjusted life years per 100 000 people for melioidosis by country in 2015

REFERENCES

1. Wiersinga WJ, Currie BJ, Peacock SJ. Melioidosis. *N Engl J Med* 2012; **367**(11): 1035-44.
2. 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.
3. Wiersinga WJ, Virk HS, Torres AG, et al. Melioidosis. *Nat Rev Dis Primers* 2018; **4**: 17107.
4. Limmathurotsakul D, Golding N, Dance DA, et al. Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis. *Nat Microbiol* 2016; **1**(1).
5. Hoffmaster AR, AuCoin D, Baccam P, et al. Melioidosis diagnostic workshop, 2013. *Emerg Infect Dis* 2015; **21**(2).
6. Wiersinga WJ, Birnie E, Weehuizen TA, Alabi AS, Huson MA, Huis RA. Clinical, environmental, and serologic surveillance studies of melioidosis in Gabon, 2012–2013. *Emerg Infect Dis* 2015; **21**(1): 40.
7. Birnie E, Wiersinga WJ, Limmathurotsakul D, Grobusch MP. Melioidosis in Africa: should we be looking more closely? *Future Microbiol* 2015; **10**(2): 273-81.
8. Currie BJ. Melioidosis: evolving concepts in epidemiology, pathogenesis, and treatment. *Sem Respir Crit Care Med* 2015; **36**(1): 111-25.
9. Herricks JR, Hotez PJ, Wanga V, et al. The global burden of disease study 2013: What does it mean for the NTDs? *PLoS Negl Trop Dis* 2017; **11**(8): e0005424.
10. Limmathurotsakul D, Wongratanacheewin S, Teerawattanasook N, et al. Increasing incidence of human melioidosis in Northeast Thailand. *Am J Trop Med Hyg* 2010; **82**(6): 1113-7.
11. Murray CJ, Vos T, Lozano R, et al. Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2197-223.
12. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**(10053): 1459-544.
13. GBD 2015 Healthcare Access and Quality Collaborators. Healthcare Access and Quality Index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990-

2015: a novel analysis from the Global Burden of Disease Study 2015. *Lancet* 2017; **390**(10091): 231-66.

14. Stevens GA, Alkema L, Black RE, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *PLoS Med* 2016; **13**(6): e1002056.
15. Mangen MJ, Plass D, Havelaar AH, et al. The pathogen- and incidence-based DALY approach: an appropriate [corrected] methodology for estimating the burden of infectious diseases. *PloS One* 2013; **8**(11): e79740.
16. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. *JAMA* 2018; **319**(1): 62-75.
17. Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis. *Neurology* 2014; **82**(9): 806-13.
18. Lauper N, Davat M, Gjika E, et al. Native septic arthritis is not an immediate surgical emergency. *J Infect* 2018; **77**(1): 47-53.
19. Teparrukkul P, Nilsakul J, Dunachie S, Limmathurotsakul D. Clinical epidemiology of septic arthritis caused by *Burkholderia pseudomallei* and other bacterial pathogens in Northeast Thailand. *Am J Trop Med Hyg* 2017; **97**(6): 1695-701.
20. Salomon JA, Haagsma JA, Davis A, et al. Disability weights for the Global Burden of Disease 2013 study. *Lancet Glob Health* 2015; **3**(11): e712-23.
21. Haagsma JA, Maertens de Noordhout C, Polinder S, et al. Assessing disability weights based on the responses of 30,660 people from four European countries. *Pop Health Metr* 2015; **13**: 10.
22. Meumann EM, Cheng AC, Ward L, Currie BJ. Clinical features and epidemiology of melioidosis pneumonia: Results from a 21-year study and review of the literature. *Clin Infect Dis* 2012; **54**(3): 362-9.
23. World Health Organization. WHO methods and data sources for global burden of disease estimates 2000–2011. Geneva. Department of Health Statistics and Information Systems; 2013. Report No.: Global Health Estimates Technical Paper. WHO/HIS/HSI/GHE/2013.4. *http://www.who.int/healthinfo/statistics/GlobalDALYmethods_2000_2011.pdf?ua=1* (accessed January 2, 2018).
24. O'Sullivan BP, Torres B, Conidi G, et al. *Burkholderia pseudomallei* infection in a child with cystic fibrosis: acquisition in the Western Hemisphere. *Chest* 2011; **140**(1): 239-42.

25. Colzani E, Cassini A, Lewandowski D, et al. A software tool for estimation of burden of infectious diseases in Europe using incidence-based disability adjusted life years. *PloS One* 2017; **12**(1): e0170662.
26. GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. *Lancet Infect Dis* 2018; **18**(3): 261-84.
27. Chierakul W, Wuthiekanun V, Chaowagul W, et al. Short report: disease severity and outcome of melioidosis in HIV coinfected individuals. *Am J Trop Med Hyg* 2005; **73**(6): 1165-6.
28. 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**(6): 457-68.
29. McKee S. Rethinking Development and Health: Findings from the Global Burden of Disease Study. Seattle, Washington, USA: Institute for Health Metrics and Evaluation.
30. de Noordhout CM, Devleesschauwer B, Angulo FJ, et al. The global burden of listeriosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2014; **14**(11): 1073-82.
31. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016; **315**(8): 801-10.
32. Hinjoy S, Hantrakun V, Kongyu S, et al. Melioidosis in Thailand: Present and Future. *Trop Med Infect Dis* 2018; **3**(2): 38.
33. GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet* 2016; **388**(10053): 1545-602.
34. GBD 2016 Meningitis Collaborators. Global, regional, and national burden of meningitis, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol* 2018; **17**(12): 1061-82.
35. Howitt P, Darzi A, Yang GZ, et al. Technologies for global health. *Lancet* 2012; **380**(9840): 507-35.
36. World Health Organization. First WHO report on neglected tropical diseases: working to overcome the global impact of neglected tropical diseases. 2010. *https://apps.who.int/iris/bitstream/handle/10665/44440/9789241564090_eng.pdf?sequence=1* (accessed September 1, 2018).
37. The WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases (WHO STAG). Recommendations for the adoption of additional diseases as neglected tropical diseases.

https://www.who.int/neglected_diseases/diseases/Adoption_additional_NTDs.pdf (accessed December 1, 2018).

Supplementary webappendix

Global burden of melioidosis, 2015: a systematic review and data synthesis

Emma Birnie, MD[1], Harjeet S. Virk, MD[1*], Jelmer Savelkoel[1], Rene Spijker[2], Eric Bertherat, PhD[3], David A.B. Dance, PhD[4,5,6], Direk Limmathurotsakul, PhD[5,7], Brecht Devleesschauwer, PhD[8,9], Juanita A. Haagsma, PhD[10], W. Joost Wiersinga, PhD[1,11]*

*Authors contributed equally to the manuscript

[1] Amsterdam UMC, University of Amsterdam, Center for Experimental and Molecular Medicine, Infection and Immunity, Amsterdam, the Netherlands;

[2] Cochrane Netherlands, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, University Utrecht, Netherlands and Amsterdam UMC, University of Amsterdam, Medical Library, Amsterdam Public Health, Amsterdam, the Netherlands;

[3] Department of Pandemic and Epidemic Diseases, World Health Organization, Geneva, Switzerland;

[4] Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit, Microbiology Laboratory, Mahosot Hospital, Vientiane, Lao PDR;

[5] Centre for Tropical Medicine and Global Health, University of Oxford, Oxford, UK;

[6] Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, UK;

[7] Mahidol-Oxford Tropical Medicine Research Unit, Mahidol University, Bangkok, Thailand;

[8] Department of Epidemiology and Public Health, Sciensano, Brussels, Belgium;

[9] Department of Veterinary Public Health and Food Safety, Faculty of Veterinary Medicine, Ghent University, Merelbeke, Belgium

[10] Department of Public Health, Erasmus MC University Medical Center, Rotterdam, Netherlands;

[11] Amsterdam UMC, University of Amsterdam, Division of Infectious Diseases, Academic Medical Center, Amsterdam, the Netherlands.

Correspondence to: Emma Birnie, Amsterdam UMC, University of Amsterdam, Department Infection and Immunity, Center for Experimental and Molecular Medicine; Meibergdreef 9, 1105 AZ, Amsterdam, the Netherlands; Phone number: +31205669111; Email: e.birnie@amc.uva.nl

Appendix to the Global burden of melioidosis: a systematic review and data synthesis

This appendix provides details on the systematic review, modelling methodology, tables of GBD life expectancy estimates, risk factor contribution, and comparison to selected NTDs

Table of Contents:

Appendix A: Methods

A.1: Databases and Boolean operators (last search on 08 August 2018)

Table S1: Databases and Boolean operators (last search on 08 August 2018).

Databases	Melioidosis classification terms	Results
Medline	1: (Melioidosis or *Burkholderia pseudomallei* or *Pseudomonas pseudomallei* or *Bacillus pseudomallei or Bacterium whitmori* or "Whitmore* disease").ti,ab,kf. 2: exp Melioidosis/ 3. exp *Burkholderia pseudomallei* 4: 1 or 2 or 3 5: limit 4 to yr="1990-2015"	2394
Embase	1: exp melioidosis/ 2: *Burkholderia pseudomallei*/ 3: (Melioidosis or *Burkholderia pseudomallei* or *Pseudomonas pseudomallei* or *Bacillus pseudomallei* or *Bacterium whitmori* or "Whitmore* disease").ti,ab,kw. 4: 1 or 2 or 3 or 4 5: limit 4 to (conference abstract or conference paper or "conference review") 6: "review"/ 7: 5 or 6 8: 4 not 7 9 limit 8 to Embase 10: limit 9 to yr="1990-2015"	2067
WHO Global health library[a]	tw:(tw:((melioidosis OR "*Burkholderia pseudomallei*" OR "*Pseudomonas pseudomallei*" OR "*Bacillus pseudomallei*" OR "*Bacterium whitmori*" OR "Whitmore* disease")) AND (instance:"ghl") AND (db:("IMSEAR" OR "WPRIM" OR "LILACS" OR "WHOLIS" OR "IMEMR"))) AND (instance:"ghl") AND (year_cluster:("2009" OR "2011" OR "2012" OR "2015" OR "2005" OR "2013" OR "1991" OR "2006" OR "2008" OR "1996" OR "1997" OR "2007" OR "2001" OR "2004" OR "2010" OR "2003" OR "1995" OR "2000" OR "1993" OR "1998" OR "1992" OR "1994" OR "1999" OR "2002" OR "2014" OR "1990"))	257
Melioidosis.info[b]	http://www.melioidosis.info/info.aspx?pageID=107 No <1990 or > 2015	352

[a] The WHO Global Health library includes regional and other indexes such as AIM (AFRO), LILACS (AMRO/PAHO), IMEMR (EMRO), IMSEAR (SEARO), WPRIM (WPRO), MEDLINE, SciELO and WHO IRIS.
[b] Researchers, clinicians and public health officials can report all melioidosis cases on this website run by the Melioidosis Research Coordination Network.

Due to paucity of data available for post-infectious sequelae, particularly those related to melioidosis; we conducted a search with expert opinion facilitation and made use of large observational or systematic reviews regarding the specific post-infectious outcomes.

We identified national surveillance systems for example that in Thailand. This highly researched and melioidosis-endemic country sees more than 2000 culture-confirmed cases of melioidosis each year with a mortality rate of approximately 35%. Previously, only about 10 melioidosis deaths were formally reported to the National Notifiable Disease surveillance system (Report 506) each year. In 2015, the number of formally reported melioidosis deaths rose to 112 solely because Sunpasithiprasong Hospital, Ubon Ratchathani province, reported its own data (n=107) for the first time.[2] The discrepancy between the true numbers of melioidosis cases and deaths and those that are reported shows that it is likely the current national surveillance reports reflect only the tip of the iceberg. The fact that melioidosis is not officially listed as a reportable disease in most endemic countries shows that extracting data from regional/national databases is not yet the way to get an accurate picture of the burden of melioidosis.

Furthermore, we looked previously at the Eurosurveillance database (last search March 2017) and found 39 cases of melioidosis. Most of these were listed as 'probable' or 'suspected' melioidosis cases and the quality of the microbiological and clinical data was very limited. Additionally, a paper published in 2015 reviewed the literature on melioidosis in travellers and included 72 cases of which 50 were from Europe.[3] The number of cases in the Eurosurveillance database is thus lower than the number of cases reported in the literature. The cases in the literature are much better described and we have included those papers in our systematic review. Consequently, we decided not to include the Eurosurveillance database.

A.2: Inclusion, exclusion criteria

Inclusion criteria

Criteria for articles to be considered for TIAB inclusion:

- Human, culture positive *Burkholderia pseudomallei*

Criteria for inclusion based on full text analysis:

- Human, culture positive *B. pseudomallei*

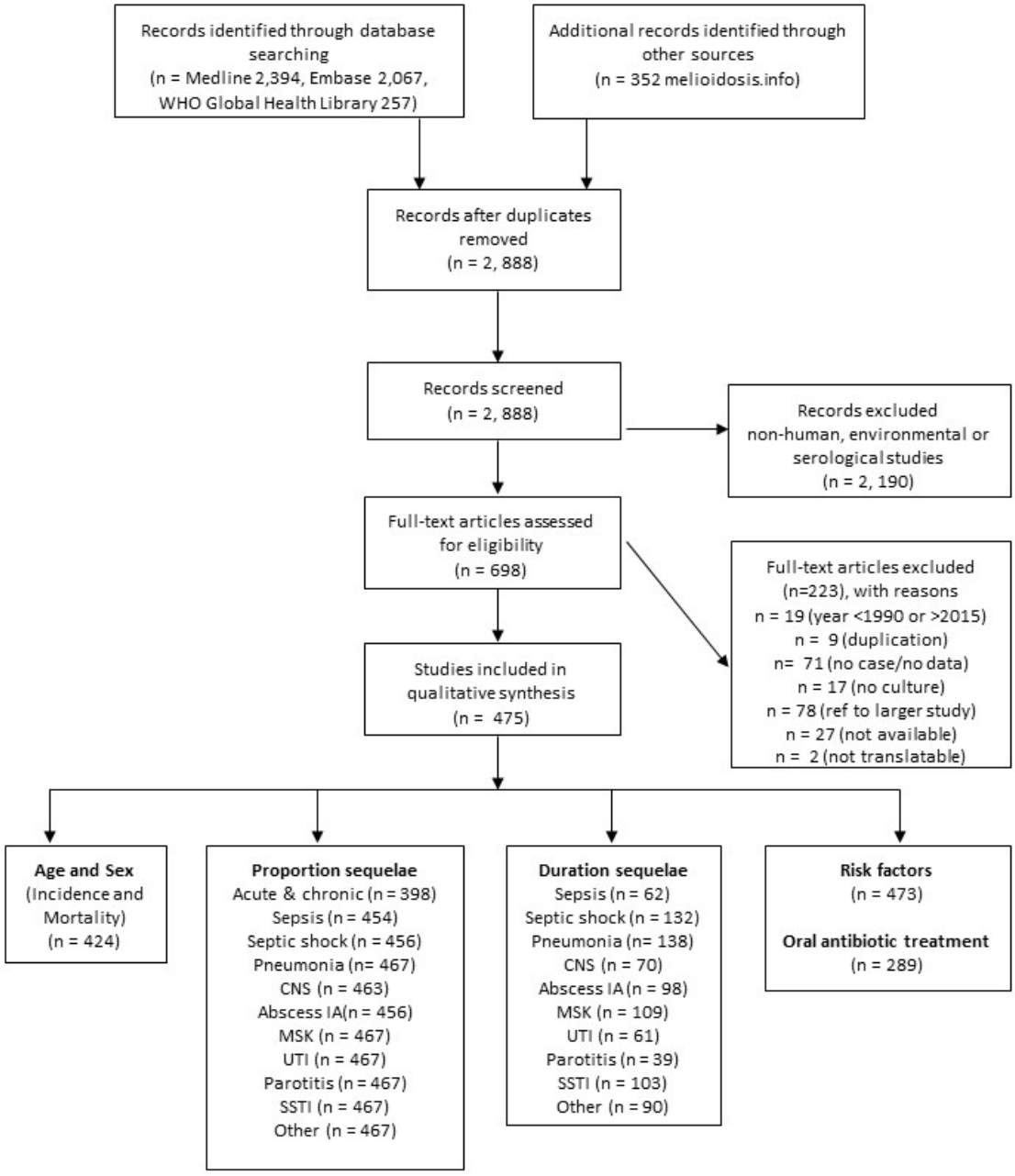
Exclusion criteria:

- Article does not pertain *B. pseudomallei* or melioidosis e.g.
- Article pertains solely to prevalence of *B. pseudomallei* in animals
- Article pertains solely to prevalence of *B. pseudomallei* in environment
- Article pertains solely laboratory methods for melioidosis diagnosis
- Article pertains solely the characterization of *B. pseudomallei* strains
- Article pertains solely diagnosis with serology
- Article pertains solely in to immunology or pathogenesis of melioidosis
- Article pertains solely to melioidosis as vaccine carrier
- Article published before 1990 or after 2015
- Diagnosis of the cases <1990 or after 2015
- Article without abstract, unclear abstract
- Article duplicated
- Article referred to a larger study
- Article not available
- Article not translatable

Cases occurring before 1990, after 2015, or diagnosed by serology were excluded from the analysis, unless included within culture-positive summary statistics. If only publication year was available or we were unable to separate out data overlapping with excluded time periods, we assumed it to meet our inclusion criteria.

A.3: Flow diagram

Figure S1: PRISMA flow diagram of study selection



References containing quantitative datasets for the estimation of the global burden of melioidosis are referenced in the link in webappendix pp 35.

Abbreviations: CNS= central nervous system; Abscess IA= Abscess intra-abdominal; MSK= musculoskeletal; UTI= urinary tract infection; SSTI= skin soft tissue infection.

A.4: Data extracted from melioidosis database

Author - Date of publication - Journal - Title - PMID - Population size in year of data collection – Country of origin – Country infected– WHO region - Study area – Study design - Timeframe of the study - Study population - Case definition - Number of cases of melioidosis (overall) - Number of cases of melioidosis by age group - Number of cases by year - Mean number of cases by year - Proportion of cases by age group (%) - Mean [Median] age of cases (in years) - Standard deviation of mean [Range] (in years) - Number of septicemia caused by melioidosis – Proportion of septicemia caused by melioidosis (%) - Duration of symptoms prior admission septicemia (in days) - Duration of hospitalization septicemia (in days) - Number of septic shock caused by melioidosis- Proportion of septic shock caused by melioidosis (%) - Duration of symptoms prior admission septic shock (in days) - Duration of hospitalization septic shock (in days) - Number of pneumonia caused by melioidosis - Proportion of pneumonia (%) - Duration of symptoms prior admission pneumonia (in days) - Duration of hospitalization pneumonia (in days) - Number of central nervous system infections caused by melioidosis (CNS) - Proportion of CNS (%) - Duration of symptoms prior admission CNS (in days) - Duration of hospitalization CNS (in days) - Number of intra-abdominal abscesses caused by melioidosis - Proportion of intra-abdominal abscesses (%) - Duration of symptoms prior admission intra-abdominal abscesses (in days) - Duration of hospitalization intra-abdominal abscesses (in days) - Number of parotitis/lymphadenitis caused by melioidosis - Proportion parotitis/lymphadenitis (%) - Duration of symptoms prior admission parotitis/lymphadenitis (in days) - Duration of hospitalization parotitis/lymphadenitis (in days) - Number of urinary tract infection (UTI) caused by melioidosis - Proportion UTI (%) - Duration of symptoms prior admission UTI (in days) - Duration of hospitalization UTI (in days) - Number of skin soft tissue infection (SSTI) caused by melioidosis - Proportion SSTI (%) - Duration of symptoms prior admission SSTI (in days) - Duration of hospitalization SSTI (in days) - Number of other outcome - Proportion other outcome (%) - Duration of symptoms prior admission other outcome (in days) - Duration of hospitalization other outcome (in days) - Number of acute cases caused by melioidosis - Proportion of acute cases caused by melioidosis - Number of chronic cases caused by melioidosis – Proportion of chronic cases caused by melioidosis - Number of death - Duration of oral treatment (in days) - Number of Comorbidities (diabetes mellitus, liver cirrhosis, chronic kidney disease, chronic lung disease) - Proportion of comorbidities (diabetes mellitus, liver cirrhosis, chronic kidney disease, chronic lung disease) (%) - Comorbidities (diabetes mellitus, liver cirrhosis, chronic kidney disease, chronic lung disease) per disease outcome.

Abbreviations: PMID= PubMed identification number; WHO= World Health Organization and ICU= intense care unit.

The melioidosis DALY database contained a total of 11 767 patients across 5 WHO regions and 47 countries. Quantitative data was extracted by three authors, EB, HV and JS. EB and HV subsequently validated the database, removing duplication of data in published literature and ensured quality data extraction by cross-check validation of the whole database and subsequent random re-sampling. Additionally, some fields were standardized in that all patients on ICU were considered at least septic, all septic shock patients were also classified as septic and duration of intravenous antibiotics was used as a surrogate for hospitalization days. The term lymphadenitis mainly refers to head and neck region (i.e. cervical), however, cases of isolated lymphadenitis elsewhere (e.g. inguinal) were also included within this category. Other outcomes consisted of pericarditis and mycotic aneurysms predominantly.

We assumed that studies captured all culture-confirmed cases. We do not know enough about latent infection with *B. pseudomallei* or asymptomatic disease, although it certainly does exist.[4] Additionally, whilst milder disease might be detected by antigen (or possibly antibody) testing, we used culture confirmation in order to be more robust. So there are certainly cases that may have been excluded and which may have been of varying severity. See also our fifth limitation in the discussion.

For incidence rates, the modelling work aimed to estimate the incidence rates of culture-confirmed melioidosis cases. The work assumed that if incidence rates of culture-confirmed melioidosis (per 100,000 population/year) reported in or estimated from epidemiological studies with data for incidence rates (Limmathurotsakul *et al.*, supplementary figure 6) represent incidence rates of culture-confirmed melioidosis in each area, incidence rates of culture-confirmed melioidosis among people living in the other areas could be estimated based on the *B. pseudomallei* suitability and the prevalence of diabetes and aboriginal population.[5]

The model did not include symptomatic cases who did not have access to healthcare in epidemiological studies with data for incidence rates (Limmathurotsakul *et al,* supplementary figure 6) and who had no culture positivity for *B. pseudomallei*.[5]

A.5: PRISMA guidelines

Table S2: PRISMA Checklist for the Systematic Review and Meta-analysis to Estimate the Global Burden of Melioidosis circa 2015..[1]

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	SA 3-4 & Figure S1
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	SA 3-4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6 & SA 5
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-8 & SA 7-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	SA 3-5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-8 & SA 16-21
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-8 & SA 18
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	SA 16-21
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-8, 11 & SA 16-21

Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure S1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Figure S1 & SA 6, 34
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	NA
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	9-10 & SA 22-33
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	SA 22-33
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	9-10
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-12
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	12-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11 & 15
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	2

A.6: Statement of GATHER compliance

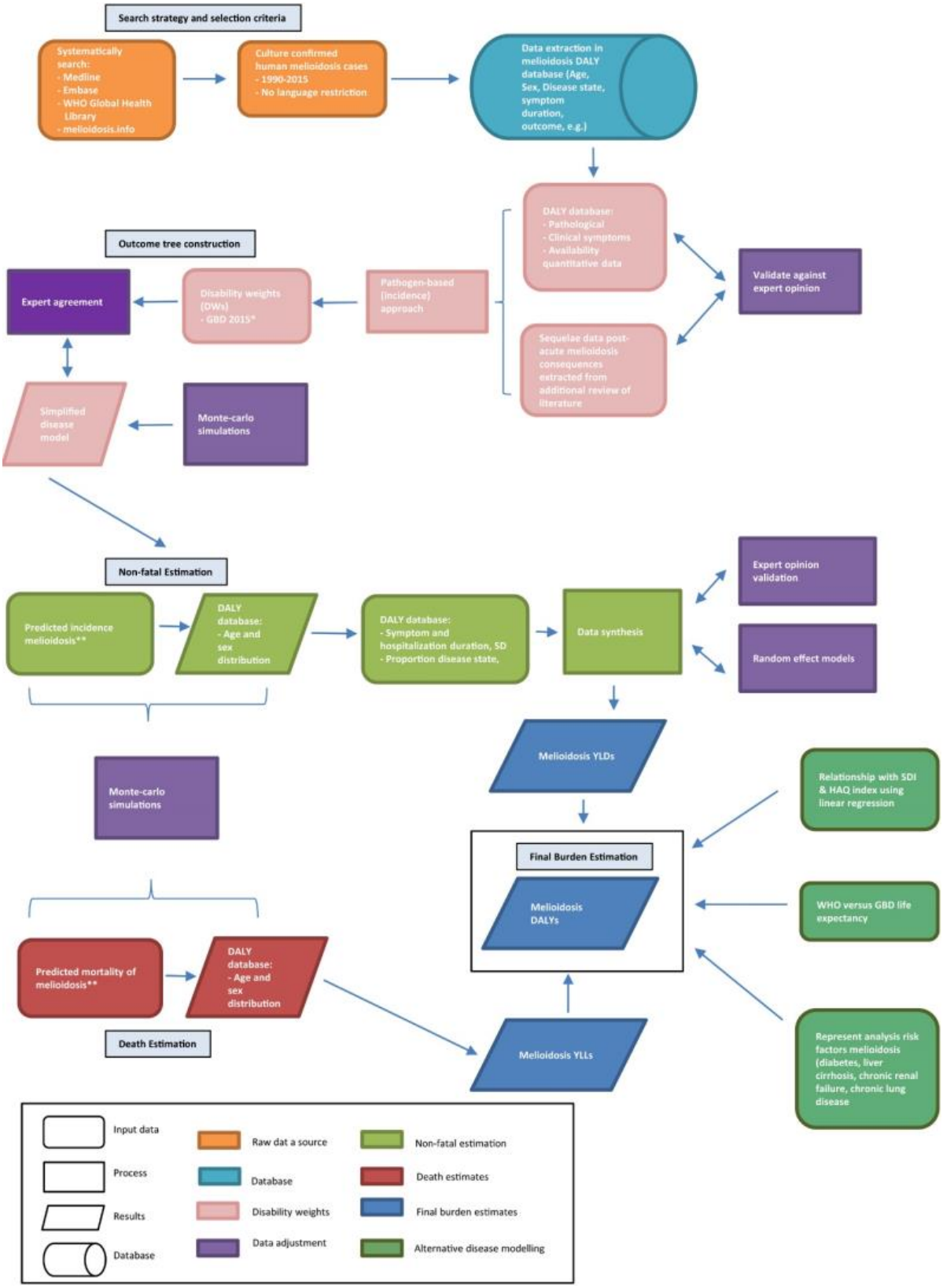
Table S3: GATHER checklist of information that should be included in reports of global health estimates, with description of compliance and location of information[6]

Item #	GATHER Checklist item	Description of compliance	Reported on page#
Objectives and funding			
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Narrative provided in paper describing indicators, definitions, time periods, and populations.	Main text (Introduction, Methods)
2	List the funding sources for the work.	Funding sources listed in paper.	Main text (Summary, Funding)
Data Inputs			
For all data inputs from multiple sources that are synthesized as part of the study:			
3	Describe how the data were identified and how the data were accessed.	All data seeking methodology referenced in main text.	Main text (Methods)
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	All inclusion and exclusion criteria by data type referenced i n main text and in appendix.	Main text (Methods) & SA pp 5
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Online data platform that provides references to studies included.	1. References of included studies are attached as necessary additional data (Will be live with publication on refworks.com) SA pp 36
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Post infectious sequelae were based on few publications, each with a small sample size. We addressed this in our uncertainty analysis, i.e., larger uncertainty because the smaller sample size. There are some methodological uncertainties, i.e. the DWs that had to be mapped to GBD health states because not all melioidosis health states have DWs; and the standard LE table, for which we used 2 versions (and thus addressed the uncertainty).	Main text (Methods) & SA 16-21
For data inputs that contribute to the analysis but were not synthesized as part of the study:			
7	Describe and give sources for any other data inputs.	All additional data inputs are included.	Main text and references
For all data inputs:			

8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Downloads of input data will be available through refworks.com. Input data not available in tools will be made available upon request.	1. References of included studies are attached as necessary additional data (Will be live with publication on refworks.com) SA pp 36
Data analysis			
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Flow diagrams of the overall methodological have been provided.	Main text (Methods) & SA pp 13
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Methodological write-up for the calculation of DALYs have been provided.	Main text (Methods) & SA 18
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Provided in the methodological write-up.	Main text (Methods) & SA
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Provided in the methodological write-ups and within appendix material.	Main text & SA pp 1-27
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Provided in the methodological write-ups and within appendix material.	Main text (Methods) & SA pp 16-21
14	State how analytic or statistical source code used to generate estimates can be accessed.	Access statement provided.	Git hub link for final submission, https://github.com/brechtdv/melioidosis
Results and Discussion			
15	Provide published estimates in a file format from which data can be efficiently extracted.	Estimates are provided in tables and will be made available on https://github.com/brechtdv/melioidosis	Main text (Results, tables) & SA pp 22-33
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Uncertainty intervals are provided with all results.	Main text (Results, tables) & SA 22-33
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Results are interpreted in light of existing evidence.	Main text (Discussion)
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Discussion of limitations provided in the narrative of the main paper.	Main text (Methods, Limitations)

A.7 Model flowchart

**Figure S2: Melioidosis DALY estimation flowchart. ***Most recent version of already established DWs of most similar sequelae were selected from the GBD 2015 update.[7] For septic shock intensive care unit admission was used as a surrogate.[8] **Predicted incidence and mortality of melioidosis was derived from literature.[9]



A.8 WHO regions included

Five of six World Health Organizations (WHO) regions are included.

AFR= African Region
Angola, Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Côte d'Ivoire, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mauritius, Mozambique, Niger, Nigeria, Senegal, Sierra Leone, South Africa, South Sudan, Tanzania, Togo, Uganda, Zambia, Zimbabwe.

AMR = Region of the Americas
Argentina, Bolivia, Brazil, Colombia, Costa Rica, Cuba, El Salvador, Guatemala, Guyana, Haiti, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Suriname, Venezuela

EMR = Eastern Mediterranean Region
Iran, Iraq, Oman, Pakistan, Saudi Arabia, Somalia, Sudan, Yemen.

SEAR = South-East Asia Region
Bangladesh, Bhutan, India, Indonesia, Myanmar, Nepal, Sri Lanka, Thailand, Timor-Leste.

WPR =Western Pacific Region
Australia, Brunei Darussalam, Cambodia, China, Fiji, Laos, Malaysia, Papua New Guinea, Philippines, Singapore, Vietnam

A.9 SDI and HAQ index

SDI is a composite indicator based on income, education, and fertility and was used as a summary measure of a geography's socio-demographic development.[10] It contains a scale from 0; lowest income per capita, lowest educational attainment and highest fertility, and 1 represents the highest income per capita, highest educational attainment and lowest fertility.[10]

HAQ index is a score developed by the GBD which can be used as a robust method for tracking universal health access.[11] This is a score between 0 to 100, estimated by a principle component analysis of three indicators from the GBD 2015 study (healthcare expenditure per capita, hospital beds per 1000, and the UHC tracer intervention index), a composite measure of 11 UHC tracer interventions (four childhood vaccinations, skilled birth attendance, coverage of at least one and four antenatal care visits, met need for family planning with modern contraception, tuberculosis case detection rates, insecticide-treated net coverage, and antiretroviral coverage for populations living with HIV); and three indicators from WHO (physicians, nurses, and midwives per 1000), the international Labour Organisation, and the World Bank (coverage index based on diphtheria-pertussis-tetanus vaccine coverage, coverage of at least four antenatal care visits, and proportion of children with diarrhoea receiving appropriate treatment).[11]

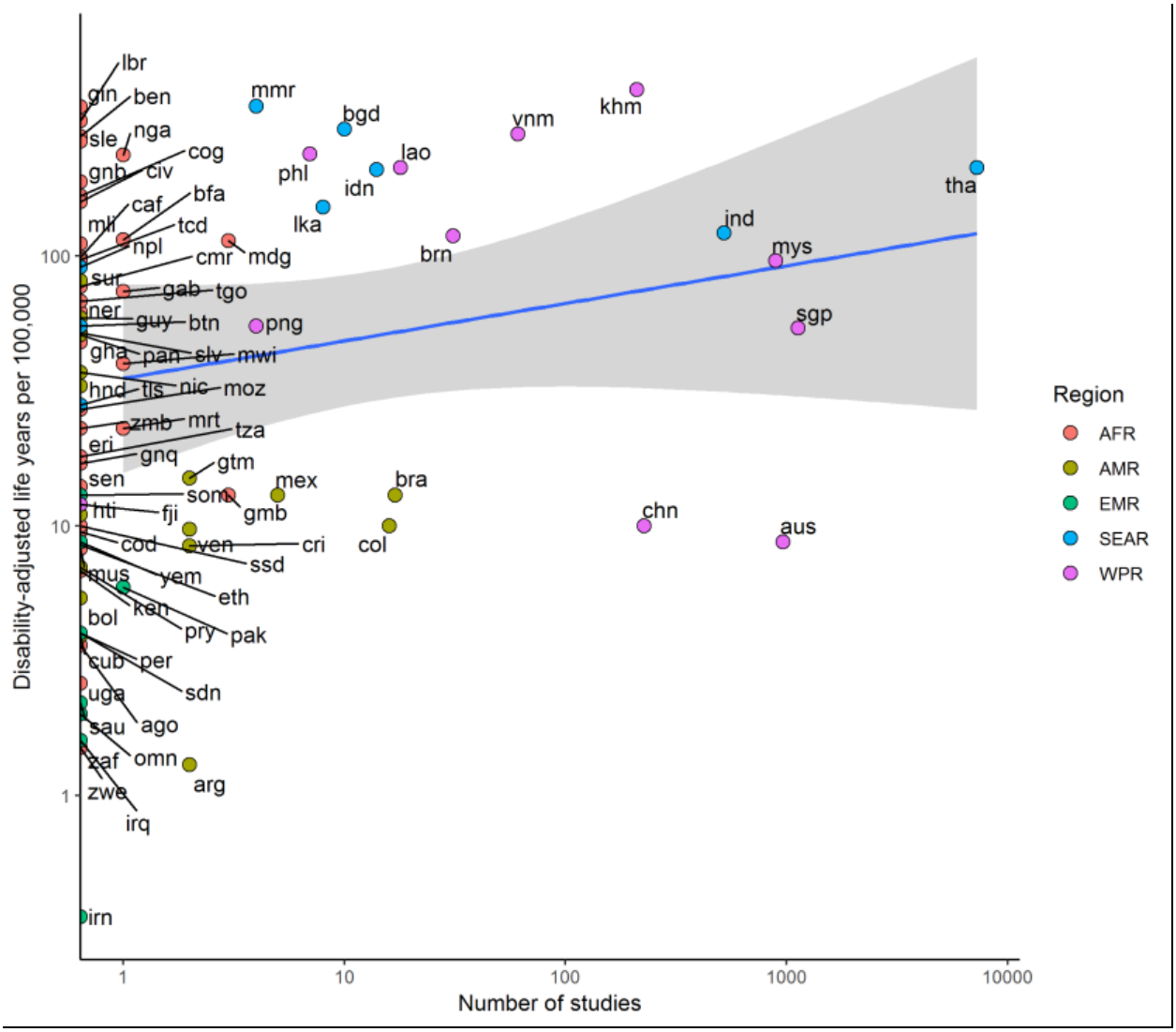
Abbreviations: SDI=Socio-demographic Index; HAQ= Healthcare Access and Quality, GBD= Global Burden Disease and WHO= World Health Organization

A.10 Handling of missing data

Systematic review and data synthesis

Supplementary Figure S3 shows the association between missing country level data (from systematic review) and reported DALYs. The systematic review results were aggregated at global or regional level. The association in Figure S3 (taking into account non-zero study counts only), is positive, but rather weak. There is a cluster of high-burden, zero-studies countries in the top left part of the graph – all of them are AFR countries. There is a cluster of low-burden, many-studies countries in the mid bottom part of the graph – all of them are AMR countries. The SEAR and WPR countries appeared to have consistent DALY-to-studies ratios (high DALY, high study count), and likewise for the EMR countries (low DALY, low study count).

Figure S3: Missing country level data and reported DALYs



Abbreviations: SEAR=South-east Asian Region; AFR=African Region; AMR=American Region; EMR Eastern Mediterranean Region; WPR=West-Pacific Region

Incidence and mortality

Additionally, previously published modelling work (Limmathurotsakul *et al.*) used a negative binomial model to estimate the incidence of melioidosis cases (per 100,000 population) based on the *B. pseudomallei* suitability and the prevalence of risk factors such as diabetes and aboriginal population. The *B. pseudomallei* suitability at a resolution of 5 km × 5 km was estimated using a boosted regression tree (BRT) statistical model and a database of occurrence records and a set of gridded environmental covariates known, or hypothesised, to affect the presence of *B. pseudomallei*. The occurrence records of melioidosis were based on 22,338 geo-located records from reports published from 1910 to 2014. For all countries, including countries with little published data on melioidosis, the strength of evidence for melioidosis endemicity at a national level, ranging from complete consensus on absence to complete consensus on presence, was defined. The strength of evidence was used in the formal modelling framework of the boosted regression tree statistical model as previously described and used for many other diseases.

For incidence rates, the modelling work aimed to estimate the incidence rates of culture-confirmed melioidosis cases. The work assumed that if incidence rates of culture-confirmed melioidosis (per 100,000 population/year) reported in or estimated from epidemiological studies with data for incidence rates (Limmaturotsakul *et al*., supplementary figure 6) represent incidence rates of culture-confirmed melioidosis in each area, incidence rates of culture-confirmed melioidosis among people living in the other areas could be estimated based on the *B. pseudomallei* suitability and the prevalence of diabetes and aboriginal population.[5]

For mortality, the modelling work aimed to estimate the outcomes of culture-confirmed melioidosis cases. The work assumed that if case fatality rates of culture-confirmed melioidosis reported in epidemiological studies with data for case fatality rate (CFR) (Limmaturotsakul *et al*., supplementary figure 6) represent CFR of culture-confirmed melioidosis in those countries, CFR of culture-confirmed melioidosis in the other countries could be estimated based on the log10 transformed national-level under-5 mortality rate (U5MR) of that country.[5]

A.11 Uncertainty analysis

Parameter uncertainty was quantified and propagated using 10,000 Monte Carlo simulations. The resulting uncertainty distributions were summarised by their mean and a 95% uncertainty interval (UI) defined as the distribution's 2·5th and 97·5th percentile.

Uncertainty in the country-specific incidence and mortality estimates[9] was represented by Gamma distributions fitted using one-dimensional optimization to the estimated medians and 95% confidence intervals. Uncertainty in durations was represented by Gamma distributions fitted using the method of moments to the mean and standard deviation derived from the systematic review's case data. Uncertainty in the probabilities of developing specific symptoms or post-infectious sequelae was represented by Beta distributions defined by numerators and denominators derived from the systematic review's case data. Uncertainty in disability weights was represented by Beta distributions fitted using one-dimensional optimization to the disability weights' means and 95% confidence intervals.

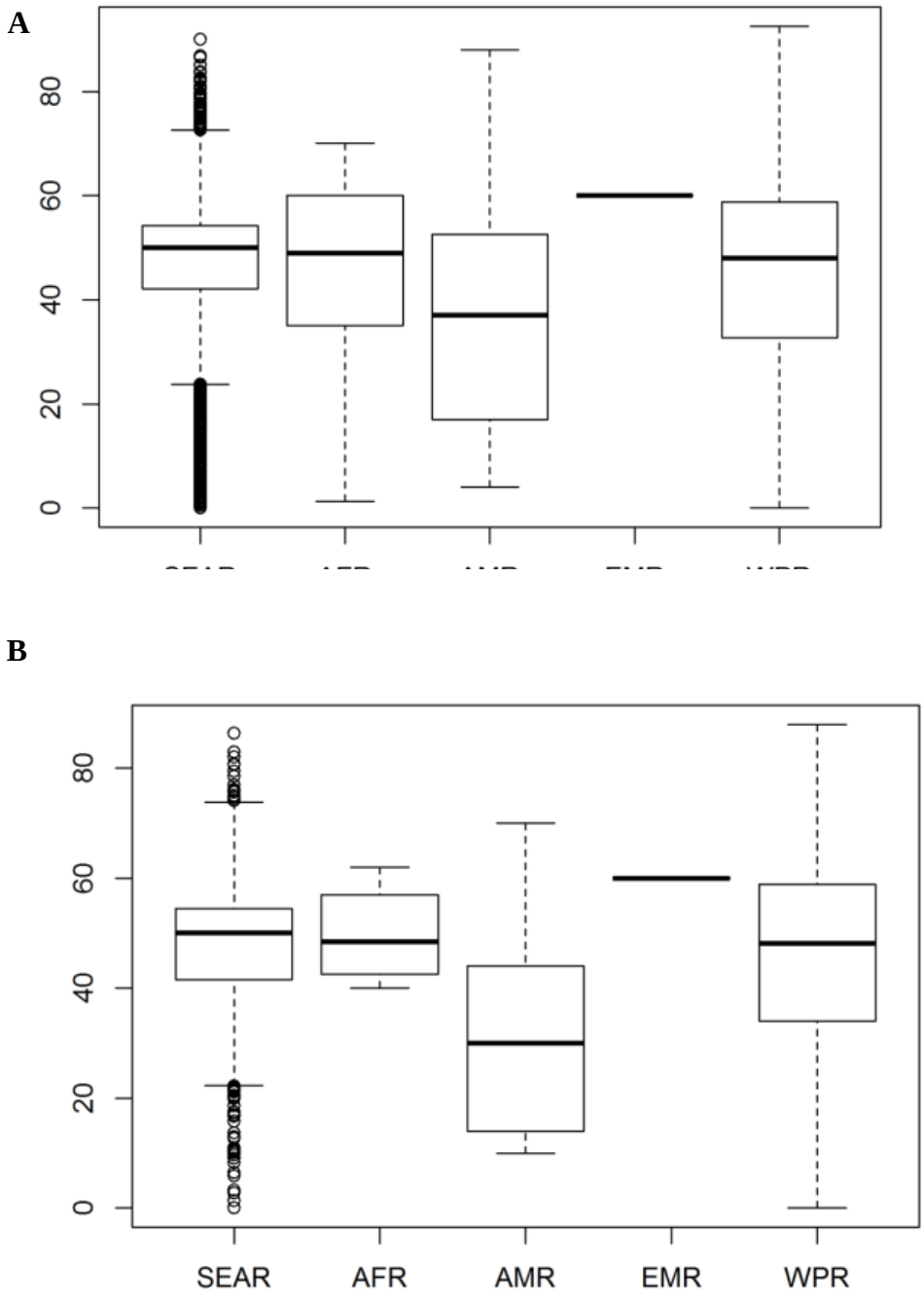
The age and sex distribution of incident cases and deaths by WHO region was derived by pooling the cases from our systematic review. When individual data were not available, we simulated the age and sex distribution of the cases based on the available data. For the redistribution of age, we used PERT distributions if a minimum, maximum and point estimate were available; and uniform distributions if only a minimum and maximum age were available. If only a point estimate was available, the age was assigned to each case. For sex, a binomial distribution was used to divide patients per study into males/females according to the percentage of males. This approach was performed separately for all cases and for deaths, and results were pooled per WHO region.

The uncertainty interval for our overall DALY estimate approximately spans +/- 50% the point estimate, which is quite wide but not uncommon for global burden estimates. As the DALY estimates were mainly driven by the years of life lost (YLL), the overall uncertainty was mainly a result of the uncertainty in the YLL estimates. For YLLs, we combined available mortality estimates by country with regional age distributions obtained through our systematic review.

The relative uncertainty in these elements was lower than in the elements defining the years lived with disability (YLD), hence the overall low uncertainty.

A.12 Incidence and Mortality age distribution

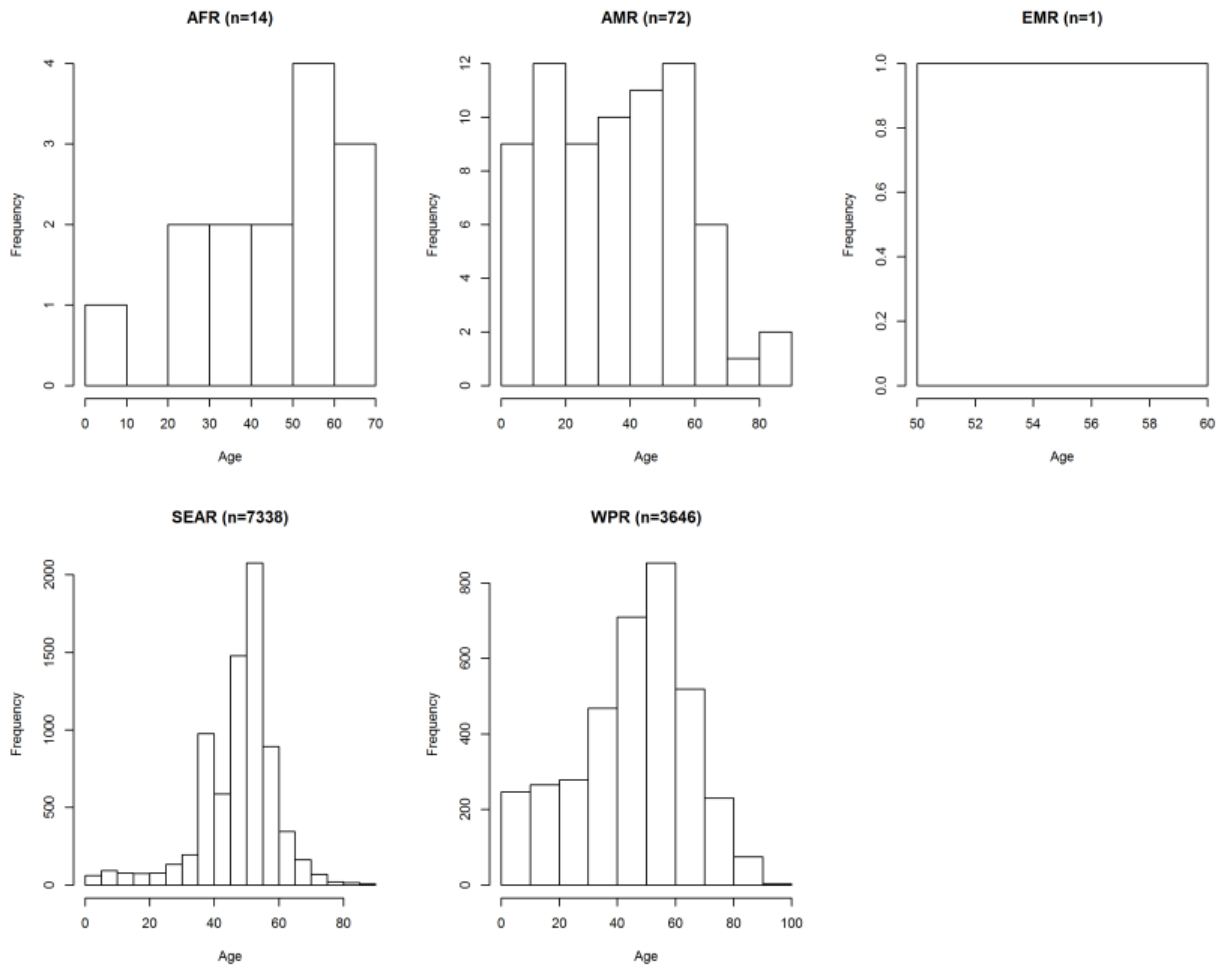
Figure S4. Regional age distribution for incidence (A) and mortality (B)



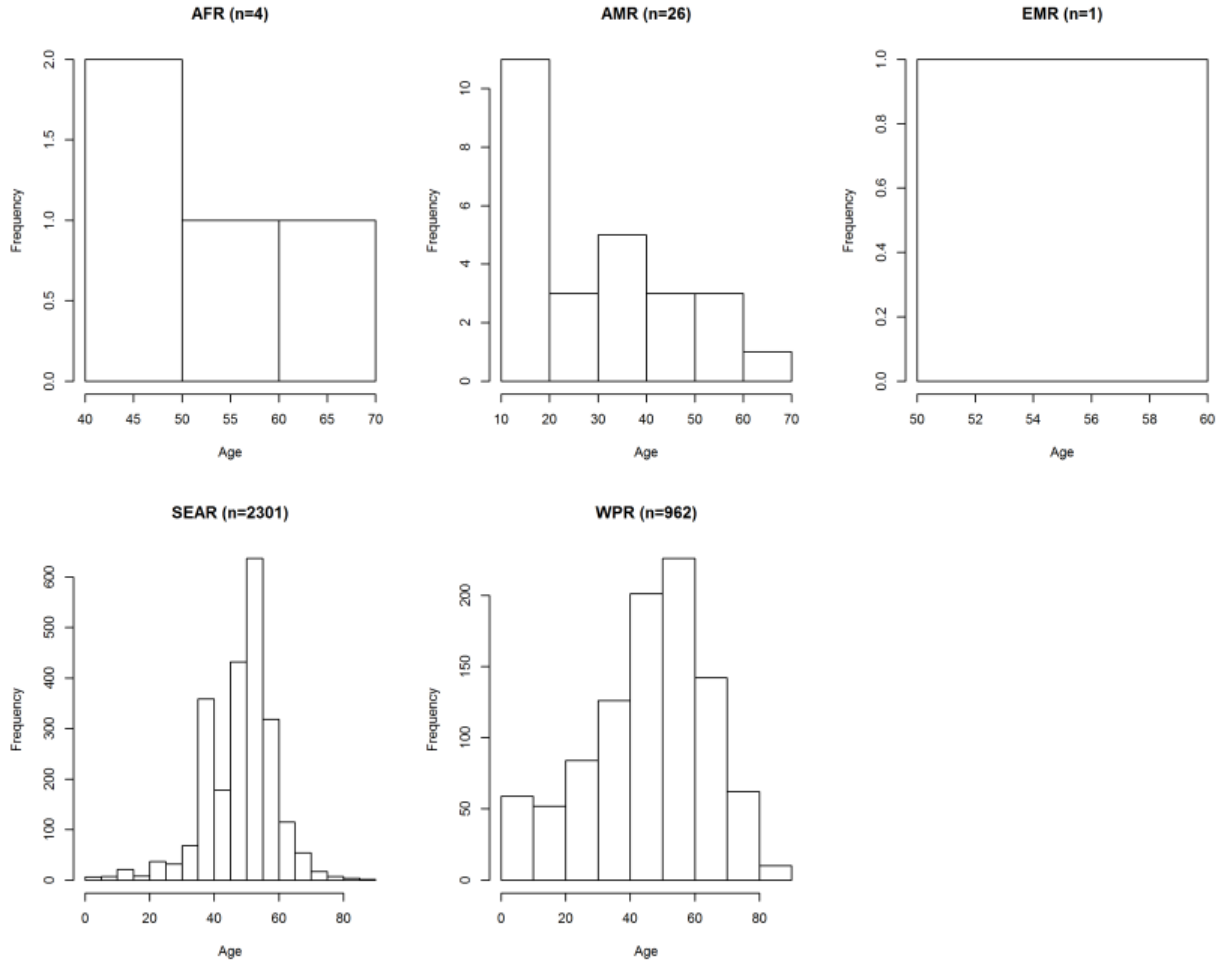
Abbreviations: SEAR=South-east Asian Region; AFR=African Region; AMR=American Region; EMR Eastern Mediterranean Region; WPR=West-Pacific Region

Figure S5 Data points regional age distribution for incidence (A) and mortality (B)

A



B



Abbreviations: SEAR=South-east Asian Region; AFR=African Region; AMR=American Region; EMR Eastern Mediterranean Region; WPR=West-Pacific Region

Appendix B: Infectious and post-infectious sequelae (disease states)

Table S4: Overall proportion, symptom duration prior admission and hospitalization numbers used for the

Melioidosis disease states used in model	Overall Proportion	Average duration of symptoms prior to admission (sd)	Average duration of hospitalization (sd)
Septic shock	1004/8298 12·10% (UI 11·4-12·8)	8·20 (8·43)	14·45 (15·75)
Sepsis	1526/8469 18·02% (UI 17·2-18·8)	9·26 (8·84)	18·86 (15·80)
Pneumonia	3633/10175 35·71% (UI 34·8-36·6)	10·85 (10·61)	21·42 (17·26)
Central nervous infection (brain or spinal)	158/9827 1·61% (UI 1·4-1·9)	19·21 (27·64)	38·8 (66·44)
Abscess intra-abdominal (e.g. liver, spleen, pancreas)	1619/8830 18·32% (UI 17·5-19·1)	67·35 (206·37)	32·93 (60·18)
Musculoskeletal infection (osteomyelitis or septic arthritis)	805/9833 8·19% (UI 7.7-8.7)	63·30 (168·81)	33·92 (56·15)
Urinary tract infection (e·g. prostatitis)	654/9833 6·65% (UI 6·2-7·2)	29·64 (40·87)	24·07 (18·83)
Parotitis (+lymphadenitis)	225/9833 2·29% (UI 2·0-2·6)	43·59 (61·33)	18·57 (16·09)
Skin soft tissue infection	1240/9833 12·61% (UI 12·0-13·3)	51·04 (117·47)	17.64 (12·88)
Other (mainly pericarditis and mycotic aneurysms)	256/9832 2·60% (UI 2·3-2·9)	26·97 (36·84)	24·82 (16·02)
Post-sepsis and septic shock	1/6[12] 16·67% (UI 0·5-52·1)	Post-infectious sequelae durations were modelled on the remaining life expectancy.	
Ongoing neurologic impairment	21/58[13] 36·20% (UI 24·4-48·8)		
Ongoing musculoskeletal impairment	83/204[14,15] 40·69% (UI 34·1-47·5)		

All proportions, symptom duration prior admission and hospitalization numbers were calculated with the melioidosis DALY database, except post sepsis and septic shock,[12] ongoing neurologic impairment,[13] and ongoing musculoskeletal impairment [14,15] which were calculated with additional literature searches. Since melioidosis is mostly prevalent in LMIC, we made the assumption that intravenous antibiotic therapy was solely administered in-hospital and where hospital duration was missing intravenous antibiotic therapy duration could be used as a surrogate minimum time period.

Uncertainty intervals for average durations were calculated using gamma distribution fitted to the mean and standard deviation, except for post infectious sequelae which were fitted to the remaining life expectancy. Whereas, for proportions, a beta-distribution was used based on number of cases and sample size.

Abbreviations: DALY= disability-adjusted life years, sd= standard deviation and UI= uncertainty interval.

Appendix C: Risk factor contribution to melioidosis

Table S5 Proportion of melioidosis cases with underlying co-morbidities.

Comorbidity	Proportion (95% UI)	YLD (95% UI)	YLD per 100.000 (95% UI)	DALY (95% UI)	DALY per 100.000 (95% UI)
Diabetes	46·1% (45·2-47·0)	23 304 (10 490-45 111)	0·42 (0·191-0·820)	2 137 433 (1 459 182-3 046 177)	38·9 (26·5-55·4)
Chronic liver disease or alcohol abuse	7·4% (6·9-7·9)	3 755 (1 688-7 284)	0·068 (0·031-0·132)	344 449 (233 462-493 074)	6·3 (4·2-9·0)
Chronic kidney disease	9·3% (8·8-9·8)	4 696 (2 107-9 112)	0·085 (0·038-0·166)	430 712 (292 249-615 674)	7·8 (5·3-11·2)
Chronic lung disease	3·4% (3·0-3·7)	1 697 (760-3 303)	0·031 (0·014-0·060)	155 677 (104 688-224 390)	2·8 (1·9-4·1)

Uncertainty intervals for comorbidity proportions were calculated using beta-distribution, based on the number presenting with comorbidity and sample size.
Abbreviations: YLD=years lived with disability; DALY=disability-adjusted life years, sd=standard deviation, and UI=uncertainty interval.

Appendix D: GBD life expectancy estimates

Table S6 Global disability-adjusted life years distribution with breakdown per country in 2015 using Global Burden Disease life expectancy

Country	YLL (95% UI)	YLL per 100·000 (95% UI)	YLD (95% UI)	YLD per 100·000 (95% UI)	DALY (95% UI)	DALY per 100·000 (95% UI)
African Region	**675 169 (343 268-1 236 755)**	**73 (37-134)**	**5 817 (2 240-12 735)**	**0·631 (0·243-1·4)**	**680 986 (348 716-1 242 627)**	**74 (38-135)**
Angola	864 (52-2 816)	3·1 (0·188-10)	8·8 (0·590-31)	0·032 (0·002-0·111)	873 (61-2 826)	3·1 (0·219-10)
Benin	25 580 (5 509-61 703)	242 (52-583)	241 (44-671)	2·3 (0·419-6·3)	25 820 (5 744-61 885)	244 (54-585)
Burkina Faso	18 149 (2 422-49 711)	100 (13-274)	165 (20-509)	0·911 (0·112-2·8)	18 314 (2 583-49 834)	101 (14-275)
Cameroon	15 229 (2 276-40 566)	67 (10·0-178)	141 (20-420)	0·616 (0·087-1·8)	15 370 (2 412-40 718)	67 (11-178)
Central African Republic	3 928 (697-10 043)	86 (15-221)	33 (5·2-95)	0·725 (0·115-2·1)	3 961 (730-10 077)	87 (16-222)
Chad	11 811 (1 275-33 978)	84 (9·1-243)	103 (10-331)	0·738 (0·074-2·4)	11 914 (1 380-34 097)	85 (9·8-243)
Congo	7 278 (1 619-17 322)	146 (32-347)	68 (13-186)	1·4 (0·264-3·7)	7 345 (1 685-17 397)	147 (34-348)
Côte d'Ivoire	31 979 (6 431-78 844)	138 (28-341)	264 (44-756)	1·1 (0·192-3·3)	32 243 (6 704-79 141)	140 (29-342)
DRC	6 331 (673-18 312)	8·3 (0·883-24)	61 (6·2-197)	0·080 (0·008-0·258)	6 392 (733-18 388)	8·4 (0·962-24)
Equatorial Guinea	170 (34-418)	14 (2·9-36)	1·4 (0·251-4·0)	0·121 (0·021-0·342)	172 (36-420)	15 (3·0-36)
Eritrea	742 (52-2 354)	15 (1·1-49)	8·5 (0·686-29)	0·174 (0·014-0·589)	750 (60-2 365)	15 (1·2-49)
Ethiopia	7 375 (767-21 525)	7·4 (0·768-22)	76 (8·0-242)	0·076 (0·008-0·243)	7 451 (837-21 615)	7·5 (0·838-22)
Gabon	1 237 (281-2 926)	64 (15-152)	12 (2·2-33)	0·619 (0·112-1·7)	1 249 (293-2 941)	65 (15-152)
Gambia	224 (5·5-828)	11 (0·278-42)	2·8 (0·151-10)	0·140 (0·008-0·518)	226 (8·1-831)	11 (0·412-42)
Ghana	11 490 (1 165-33 607)	42 (4·2-122)	107 (9·7-352)	0·389 (0·035-1·3)	11 598 (1 271-33 742)	42 (4·6-122)
Guinea	37 706 (7 736-92 247)	312 (64-763)	333 (61-928)	2·8 (0·502-7·7)	38 039 (8 067-92 570)	315 (67-766)
Guinea-Bissau	2 908 (328-8 338)	164 (19-471)	26 (2·8-82)	1·5 (0·161-4·6)	2 935 (354-8 363)	166 (20-472)
Kenya	2 795 (361-7 731)	5·9 (0·765-16)	29 (3·5-90)	0·061 (0·007-0·190)	2 824 (390-7 755)	6·0 (0·825-16)
Liberia	12 397 (2 393-31 019)	276 (53-689)	111 (19-317)	2·5 (0·414-7·0)	12 507 (2 506-31 105)	278 (56-691)
Madagascar	24 013 (5 117-57 931)	99 (21-239)	235 (43-657)	0·972 (0·179-2·7)	24 248 (5 339-58 180)	100 (22-240)
Malawi	6 050 (1 085-15 471)	34 (6·2-88)	57 (9·4-163)	0·325 (0·054-0·929)	6 107 (1 142-15 533)	35 (6·5-88)
Mali	16 849 (2 419-45 529)	96 (14-261)	151 (20-459)	0·863 (0·112-2·6)	16 999 (2 568-45 666)	97 (15-261)
Mauritania	841 (65-2 623)	20 (1·6-63)	8·0 (0·572-28)	0·192 (0·014-0·661)	849 (73-2 631)	20 (1·7-63)
Mauritius	88 (7·9-267)	7·0 (0·626-21)	2·4 (0·212-8·0)	0·190 (0·017-0·633)	91 (10-270)	7·2 (0·798-21)
Mozambique	6 680 (845-18 564)	24 (3·0-66)	62 (7·7-192)	0·223 (0·028-0·686)	6 742 (910-18 622)	24 (3·2-66)
Niger	10 656 (903-32 503)	54 (4·5-163)	103 (8·5-349)	0·520 (0·043-1·8)	10 759 (1 005-32 576)	54 (5·0-164)
Nigeria	374 282 (78 458-909 318)	207 (43-502)	3 070 (551-8 590)	1·7 (0·304-4·7)	377 352 (81 303-912 324)	208 (45-504)
Senegal	1 840 (103-6 077)	12 (0·689-41)	18 (1·1-65)	0·123 (0·008-0·435)	1 858 (121-6 101)	12 (0·807-41)
Sierra Leone	16 790 (3 312-41 626)	232 (46-575)	132 (23-375)	1·8 (0·321-5·2)	16 922 (3 439-41 746)	234 (48-577)
South Africa	751 (56-2 342)	1·4 (0·102-4·2)	8·2 (0·696-27)	0·015 (0·001-0·049)	759 (64-2 352)	1·4 (0·115-4·3)

South Sudan	1 044 (105-3 054)	8·8 (0·884-26)	11 (1·2-35)	0·092 (0·010-0·292)	1 055 (116-3 064)	8·9 (0·974-26)
Tanzania	8 389 (1 105-23 046)	16 (2·1-43)	86 (11-264)	0·159 (0·019-0·490)	8 475 (1 195-23 150)	16 (2·2-43)
Togo	4 414 (652-11 830)	60 (8·8-160)	39 (5·1-119)	0·531 (0·069-1·6)	4 453 (693-11 868)	60 (9·3-160)
Uganda	901 (32-3 167)	2·2 (0·081-7·9)	9·7 (0·477-36)	0·024 (0·001-0·090)	911 (42-3 177)	2·3 (0·104-7·9)
Zambia	3 190 (369-9 084)	20 (2·3-56)	31 (3·6-96)	0·191 (0·022-0·595)	3 220 (399-9 115)	20 (2·5-57)
Zimbabwe	202 (13-645)	1·3 (0·085-4·1)	2·2 (0·158-7·4)	0·014 (<0·001-0·047)	204 (15-647)	1·3 (0·098-4·1)
American Region	**62 317 (32 648-108 711)**	**11 (5·7-19)**	**1 291 (460-2 892)**	**0·225 (0·080-0·504)**	**63 608 (33 820-110 132)**	**11 (5·9-19)**
Argentina	515 (34-1 643)	1·2 (0·078-3·8)	11 (0·652-41)	0·026 (0·002-0·093)	526 (44-1 657)	1·2 (0·100-3·8)
Bolivia	522 (45-1 574)	4·9 (0·416-15)	5·8 (0·479-19)	0·054 (0·004-0·182)	528 (50-1 579)	4·9 (0·466-15)
Brazil	23 786 (3 520-63 372)	12 (1·7-31)	517 (64-1 598)	0·251 (0·031-0·776)	24 303 (3 965-63 987)	12 (1·9-31)
Colombia	4 379 (661-11 614)	9·1 (1·4-24)	88 (12-267)	0·182 (0·024-0·554)	4 467 (745-11 710)	9·3 (1·5-24)
Costa Rica	356 (64-901)	7·4 (1·3-19)	11 (1·6-32)	0·225 (0·033-0·666)	367 (74-913)	7·6 (1·5-19)
Cuba	387 (19-1 298)	3·4 (0·165-11)	17 (0·791-62)	0·146 (0·007-0·542)	404 (32-1 315)	3·5 (0·278-11)
El Salvador	2 918 (702-6 734)	46 (11-107)	59 (12-160)	0·934 (0·184-2·5)	2 977 (760-6 795)	47 (12-108)
Guatemala	2 235 (404-5 642)	14 (2·5-35)	31 (4·7-90)	0·189 (0·029-0·553)	2 265 (436-5 674)	14 (2·7-35)
Guyana	409 (78-1 017)	53 (10-132)	4·7 (0·675-14)	0·606 (0·088-1·8)	413 (83-1 022)	54 (11-133)
Haiti	1 028 (81-3 170)	9·6 (0·758-30)	8·9 (0·804-29)	0·083 (0·008-0·274)	1 037 (90-3 179)	9·7 (0·841-30)
Honduras	2 635 (362-7 149)	29 (4·0-80)	45 (6·2-136)	0·503 (0·069-1·5)	2 680 (406-7 197)	30 (4·5-80)
Mexico	14 688 (2 467-37 874)	12 (2·0-30)	328 (45-987)	0·260 (0·036-0·784)	15 015 (2 762-38 244)	12 (2·2-30)
Nicaragua	2 008 (346-5 135)	33 (5·7-84)	33 (4·8-98)	0·546 (0·079-1·6)	2 041 (378-5 175)	34 (6·2-85)
Panama	1 816 (420-4 241)	46 (11-107)	38 (7·3-104)	0·954 (0·184-2·6)	1 854 (456-4 277)	47 (12-108)
Paraguay	415 (11-1 521)	6·2 (0·161-23)	8·6 (0·358-32)	0·129 (0·005-0·486)	423 (18-1 529)	6·4 (0·273-23)
Peru	1 117 (141-3 087)	3·6 (0·449-9·8)	22 (2·7-69)	0·070 (0·008-0·219)	1 139 (161-3 112)	3·6 (0·514-9·9)
Suriname	400 (85-958)	72 (15-173)	6·6 (1·1-19)	1·2 (0·200-3·4)	406 (91-965)	73 (17-174)
Venezuela	2 704 (487-6 841)	8·7 (1·6-22)	58 (8·6-170)	0·185 (0·028-0·546)	2 762 (542-6 902)	8·9 (1·7-22)
Eastern Mediterranean Region	**15 713 (5 414-35 987)**	**3·7 (1·3-8·6)**	**101 (31-252)**	**0·024 (0·007-0·060)**	**15 814 (5 518-36 082)**	**3·8 (1·3-8·6)**
Iran	237 (8·1-835)	0·299 (0·010-1·1)	3·0 (0·106-11)	0·004 (<0·001-0·014)	240 (11-838)	0·303 (0·014-1·1)
Iraq	479 (7·8-1 874)	1·3 (0·021-5·2)	3·4 (0·052-14)	0·010 (<0·001-0·040)	482 (11-1 878)	1·3 (0·031-5·2)
Oman	71 (17-165)	1·7 (0·399-3·9)	1·1 (0·162-3·2)	0·026 (0·004-0·077)	72 (18-167)	1·7 (0·424-4·0)
Pakistan	9 534 (722-29 494)	5·0 (0·381-16)	57 (4·3-190)	0·030 (0·002-0·100)	9 591 (775-29 572)	5·1 (0·409-16)
Saudi Arabia	575 (55-1 696)	1·8 (0·175-5·4)	10·0 (0·858-33)	0·032 (0·003-0·104)	585 (64-1 708)	1·9 (0·202-5·4)
Somalia	1 512 (142-4 490)	11 (1·0-32)	7·8 (0·726-25)	0·056 (0·005-0·181)	1 520 (149-4 499)	11 (1·1-32)
Sudan	1 325 (81-4 271)	3·4 (0·209-11)	7·9 (0·515-27)	0·020 (0·001-0·070)	1 333 (88-4 279)	3·4 (0·228-11)
Yemen	1 979 (339-5 054)	7·4 (1·3-19)	11 (1·6-31)	0·040 (0·006-0·115)	1 990 (350-5 065)	7·4 (1·3-19)
South-east Asian Region	**2 618 321 (1 451 689-4 256 437)**	**138 (76-224)**	**30 640 (12 500-62 865)**	**1·6 (0·658-3·3)**	**2 648 960 (1 480 429-4 286 603)**	**139 (78-226)**
Bangladesh	415 343 (142 696-831 078)	258 (89-516)	4 974 (1 366-11 993)	3·1 (0·848-7·4)	420 317 (147 071-836 268)	261 (91-519)
Bhutan	381 (77-926)	48 (9·7-118)	3·8 (0·552-11)	0·487 (0·070-1·4)	385 (80-930)	49 (10-118)

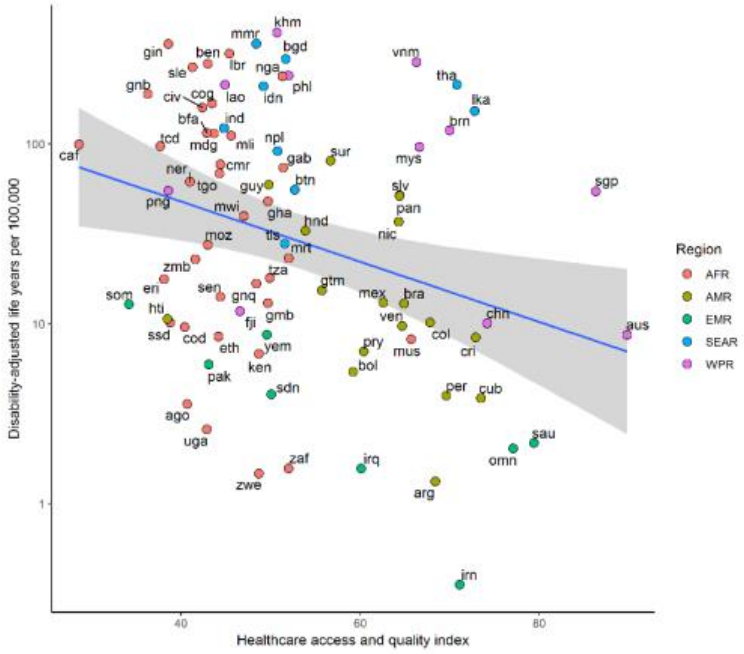
India	1 393 679 (432 258-2 912 344)	106 (33-222)	13 518 (3 390-33 836)	1·0 (0·259-2·6)	1 407 197 (445 480-2 925 456)	107 (34-223)
Indonesia	468 604 (117 143-1 064 654)	182 (45-412)	6 147 (1 297-16 220)	2·4 (0·503-6·3)	474 751 (122 945-1 070 956)	184 (48-415)
Myanmar	164 733 (45 906-358 681)	314 (88-684)	1 596 (372-4 086)	3·0 (0·710-7·8)	166 329 (47 382-360 422)	317 (90-688)
Nepal	22 710 (5 408-52 402)	79 (19-183)	259 (54-690)	0·903 (0·189-2·4)	22 968 (5 668-52 666)	80 (20-184)
Sri Lanka	27 004 (7 796-58 001)	130 (38-280)	834 (196-2 159)	4·0 (0·946-10)	27 839 (8 589-58 923)	134 (41-284)
Thailand	125 564 (40 893-257 155)	183 (60-375)	3 305 (848-8 261)	4·8 (1·2-12)	128 870 (44 116-260 432)	188 (64-379)
Timor-Leste	302 (35-849)	24 (2·9-68)	2·8 (0·307-8·7)	0·225 (0·025-0·703)	305 (38-852)	25 (3·1-69)
West-Pacific Region	**671 048 (404 144-1 029 387)**	**40 (24-61)**	**12 693 (5 185-26 073)**	**0·754 (0·308-1·5)**	**683 741 (416 769-1 042 312)**	**41 (25-62)**
Australia	1 746 (400-4 083)	7·3 (1·7-17)	99 (19-276)	0·417 (0·078-1·2)	1 846 (486-4 195)	7·8 (2·0-18)
Brunei Darussalam	428 (141-872)	102 (34-209)	15 (3·5-38)	3·6 (0·835-9·2)	443 (156-888)	106 (37-213)
Cambodia	56 637 (14 794-126 210)	365 (95-813)	654 (141-1 723)	4·2 (0·909-11)	57 291 (15 475-126 878)	369 (100-818)
China	121 635 (42 238-242 450)	8·7 (3·0-17)	3 226 (880-7 859)	0·231 (0·063-0·563)	124 861 (45 453-245 661)	8·9 (3·3-18)
Fiji	92 (12-252)	10 (1·3-28)	1·6 (0·163-5·1)	0·180 (0·018-0·574)	93 (13-254)	10 (1·5-28)
Laos	12 505 (3 560-27 011)	188 (53-405)	112 (25-291)	1·7 (0·382-4·4)	12 617 (3 669-27 117)	189 (55-407)
Malaysia	25 409 (6 814-56 128)	83 (22-183)	912 (195-2 431)	3·0 (0·635-7·9)	26 321 (7 584-57 130)	86 (25-186)
Papua New Guinea	3 834 (888-8 934)	48 (11-113)	33 (6·7-89)	0·421 (0·084-1·1)	3 868 (920-8 961)	49 (12-113)
Philippines	214 037 (84 580-402 442)	210 (83-396)	2 976 (934-6 893)	2·9 (0·918-6·8)	217 012 (87 539-405 440)	213 (86-399)
Singapore	2 498 (253-7 265)	45 (4·6-131)	202 (22-633)	3·6 (0·406-11)	2 700 (420-7 477)	49 (7·6-135)
Vietnam	232 227 (58 497-526 753)	248 (63-563)	4 462 (940-11 849)	4·8 (1·0-13)	236 689 (62 704-531 692)	253 (67-568)
GLOBAL	**4 042 568 (2 740 388-5 775 291)**	**74 (50-105)**	**50 542 (22 778-97 825)**	**0·919 (0·414-1·8)**	**4 093 110 (2 790 743-5 826 117)**	**74 (51-106)**

Abbreviations: DRC= Democratic Republic of Congo; UI= uncertainty interval; YLL= years life lost; YLD= years lived with disability and DALY= disability-adjusted life years·

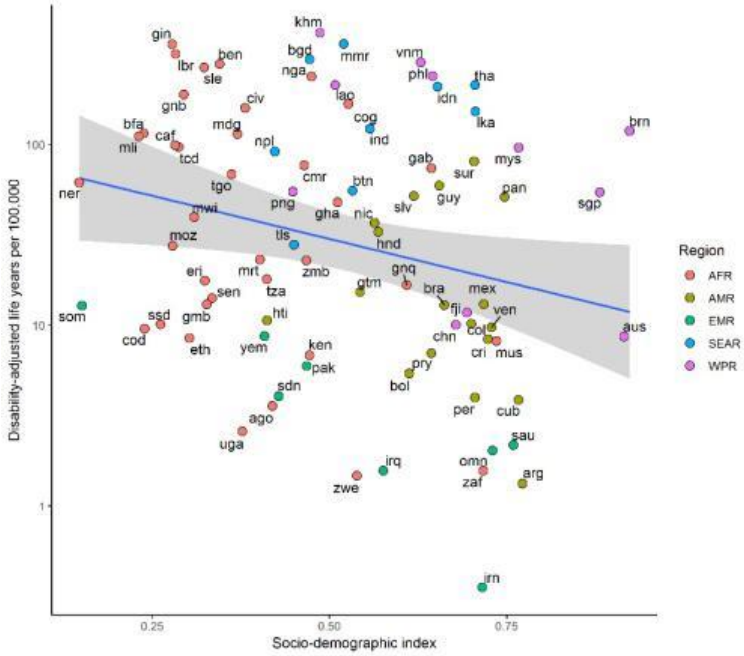
Appendix E: SDI and HAQ results

Figure S6: Healthcare Access and Quality Index (A) and Socio-demographic Index (B) per country versus disability-adjusted life years

A



B



Abbreviations: AFR= African region; AMR= American region; EMR= Eastern Mediterranean region, SEAR= South-east Asian region, WPR= West-Pacific region; and DALYs= disability-adjusted life years.

Table S7 Healthcare Access and Quality Index and Socio-demographic Index per country

Country	HAQ	SDI
African Region		
Angola	40·7	0·419
Benin	43·0	0·345
Burkina Faso	42·9	0·237
Cameroon	44·4	0·464
Central African Republic	28·6	0·282
Chad	37·7	0·287
Congo	43·5	0·527
Côte d'Ivoire	42·4	0·381
DRC	40·4	0·239
Equatorial Guinea	48·4	0·609
Eritrea	38·1	0·324
Ethiopia	44·2	0·302
Gabon	51·4	0·644
Gambia	49·7	0·327
Ghana	49·7	0·511
Guinea	38·6	0·278
Guinea-Bissau	36·3	0·294
Kenya	48·7	0·472
Liberia	45·4	0·283
Madagascar	43·7	0·370
Malawi	47·0	0·309
Mali	45·6	0·231
Mauritania	52·0	0·401
Mauritius	65·7	0·735
Mozambique	43·0	0·278
Niger	41·0	0·146
Nigeria	51·3	0·474
Senegal	44·4	0·334
Sierra Leone	41·3	0·323
South Africa	52·0	0·716
South Sudan	38·8	0·262
Tanzania	49·9	0·411
Togo	44·3	0·362
Uganda	42·9	0·377
Zambia	41·6	0·467
Zimbabwe	48·7	0·538
American Region		

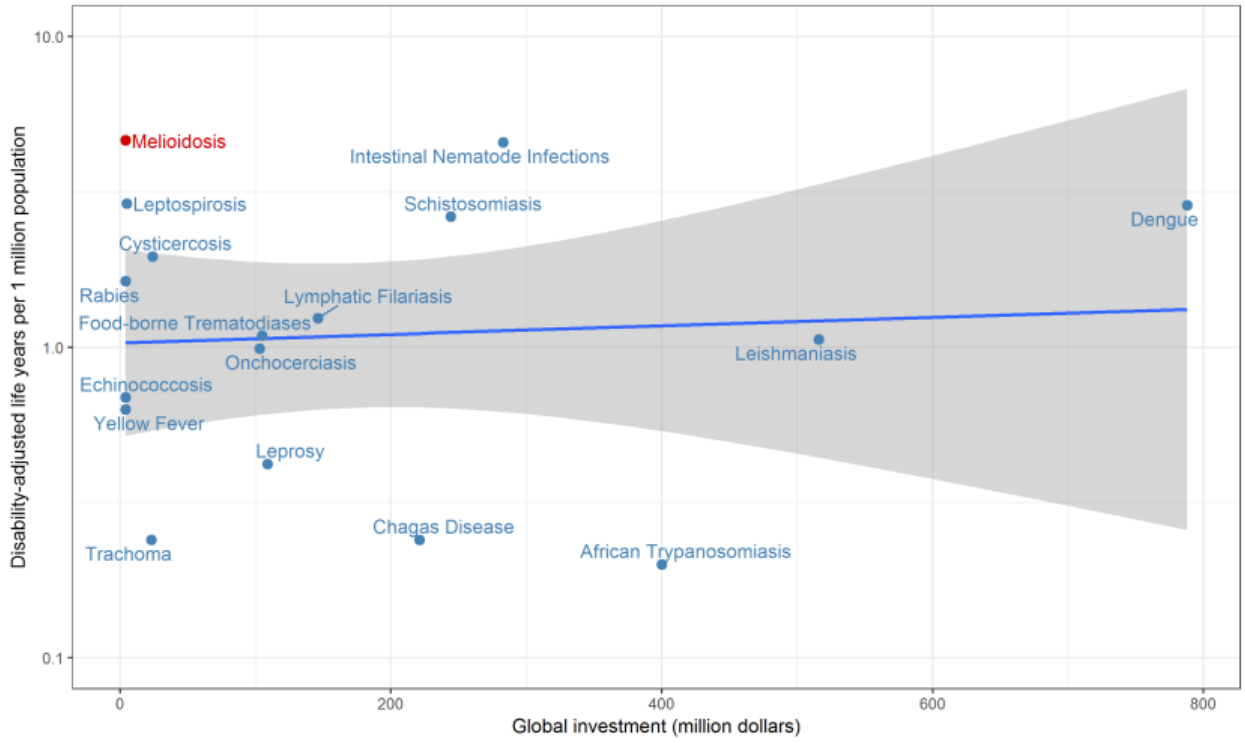
Argentina	68·4	0·772
Bolivia	59·2	0·612
Brazil	64·9	0·662
Colombia	67·8	0·700
Costa Rica	72·9	0·723
Cuba	73·5	0·766
El Salvador	64·4	0·619
Guatemala	55·7	0·543
Guyana	49·8	0·655
Haiti	38·5	0·412
Honduras	53·9	0·568
Mexico	62·6	0·718
Nicaragua	64·3	0·563
Panama	64·4	0·747
Paraguay	60·4	0·644
Peru	69·6	0·705
Suriname	56·7	0·704
Venezuela	64·7	0·728
Eastern Mediterranean Region		
Iran	71·1	0·715
Iraq	60·1	0·576
Oman	77·1	0·730
Pakistan	43·1	0·468
Saudi Arabia	79·4	0·759
Somalia	34·2	0·151
Sudan	50·1	0·428
Yemen	49·6	0·408
South-east Asian Region		
Bangladesh	51·7	0·472
Bhutan	52·7	0·532
India	44·8	0·556
Indonesia	49·2	0·652
Myanmar	48·4	0·520
Nepal	50·8	0·423
Sri Lanka	72·8	0·705
Thailand	70·8	0·705
Timor-Leste	51·6	0·450
West-Pacific Region		
Australia	89·8	0·915
Brunei Darussalam	70·0	0·923
Cambodia	50·7	0·486

China	74·2	0·678
Fiji	46·6	0·693
Lao	44·9	0·508
Malaysia	66·6	0·767
Papua New Guinea	38·6	0·448
Philippines	52·0	0·645
Singapore	86·3	0·881
Vietnam	66·3	0·628

Abbreviations: DRC= Democratic Republic of Congo; DALYs= disability-adjusted life years; SDI=Socio-demographic Index; HAQ= Healthcare Access and Quality.

Appendix F: Global burden of a select neglected and emerging/re-emerging tropical diseases and corresponding investments in research and development

Figure S7: Global burden of a selection of neglected and emerging/re-emerging tropical diseases and corresponding investments in research and development



Leptospirosis is not officially recognized as a neglected tropical disease. Recognized neglected tropical diseases (by WHO) and leptospirosis are depicted in blue and melioidosis in red.
Abbreviations: DALYs= disability-adjusted life years and WHO= World Health Organization.

Table S8: Global burden of melioidosis and selected neglected tropical diseases.

Neglected tropical diseases	WHO DALY in million (2015)	Global Investment by disease in million $ (2016)
Intestinal Nematode Infections	4·56	283 M
Leishmaniasis	1·06	516M
Schistosomiasis	2·63	244M
Lymphatic Filariasis	1·24	146M
Food-borne Trematodiases	1·09	105M
Rabies	1·63	<4M
Dengue	2·86	788M
African Trypanosomiasis	0·20	400M
Chagas Disease	0·24	221M
Cysticercosis	1·96	24M
Onchocerciasis	0·99	103M
Trachoma	0·24	23M
Echinococcosis	0·69	<4M
Yellow Fever	0·63	<4M
Leprosy	0·42	109M
Leptospirosis[a]	2·90	5M
Melioidosis[a]	4·64	<4M

All investments by disease in millions of $ are from the WHO.[16] All WHO DALY estimates are from the WHO[16] except leptospirosis from Torgerson et al.[17] Infectious diseases not represented in the top 39 in terms of research and development, were assigned <4M, corresponding to the global investment of the last of the 39. Abbreviations: WHO= World Health Organization and DALY = disability-adjusted life years.

Appendix G: Bibliographic details of references containing information for estimation of the global burden of melioidosis

*****References of included studies are attached as necessary additional data (word document). Will be live with publication on refworks.com.

Appendix H: R code

All code and results are now available on github: https://github.com/brechtdv/melioidosis

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS medicine* 2009; **6**(7): e1000097.
2. Hinjoy S, Hantrakun V, Kongyu S, et al. Melioidosis in Thailand: Present and Future. *Trop Med Infect Dis* 2018; **3**(2): 38.
3. Dan M. Melioidosis in Travelers: Review of the Literature. *Journal of Travel Medicine* 2015; **22**(6): 410-4.
4. Wiersinga WJ, Virk HS, Torres AG, et al. Melioidosis. *Nature reviews Disease primers* 2018; **4**: 17107.
5. Limmathurotsakul D, Golding N, Dance DA, et al. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. *Nature microbiology* 2016; **1**(1): 15008.
6. Stevens GA, Alkema L, Black RE, et al. Guidelines for Accurate and Transparent Health Estimates Reporting: the GATHER statement. *Lancet (London, England)* 2016; **388**(10062): e19-e23.
7. Haagsma JA, Maertens de Noordhout C, Polinder S, et al. Assessing disability weights based on the responses of 30,660 people from four European countries. *Population health metrics* 2015; **13**: 10.
8. Salomon JA, Haagsma JA, Davis A, et al. Disability weights for the Global Burden of Disease 2013 study. *The Lancet Global health* 2015; **3**(11): e712-23.
9. Limmathurotsakul D, Golding N, Dance DA, et al. Predicted global distribution of Burkholderia pseudomallei and burden of melioidosis. *Nature microbiology* 2016; **1**(1).
10. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet (London, England)* 2016; **388**(10053): 1459-544.
11. Healthcare Access and Quality Index based on mortality from causes amenable to personal health care in 195 countries and territories, 1990-2015: a novel analysis from the Global Burden of Disease Study 2015. *Lancet (London, England)* 2017; **390**(10091): 231-66.
12. Prescott HC, Angus DC. Enhancing Recovery From Sepsis: A Review. *Jama* 2018; **319**(1): 62-75.
13. Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess: systematic review and meta-analysis. *Neurology* 2014; **82**(9): 806-13.
14. Lauper N, Davat M, Gjika E, et al. Native septic arthritis is not an immediate surgical emergency. *The Journal of infection* 2018; **77**(1): 47-53.
15. Teparrukkul P, Nilsakul J, Dunachie S, Limmathurotsakul D. Clinical Epidemiology of Septic Arthritis Caused by Burkholderia pseudomallei and Other Bacterial Pathogens in Northeast Thailand. *Am J Trop Med Hyg* 2017; **97**(6): 1695-701.
16. Organization WH. WHO methods and data sources for global burden of disease estimates 2000–2011. Global Health Estimates Technical Paper. . Geneve, 2013.
17. Torgerson PR, Hagan JE, Costa F, et al. Global Burden of Leptospirosis: Estimated in Terms of Disability Adjusted Life Years. *PLoS neglected tropical diseases* 2015; **9**(10): e0004122.