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

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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.

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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.

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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.

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Keywords

Melioidosis; *Burkholderia pseudomallei*; global burden; DALY; diabetes; neglected tropical disease

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 2·5th and 97·5th 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 ($p = 0·892$), 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

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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,

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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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

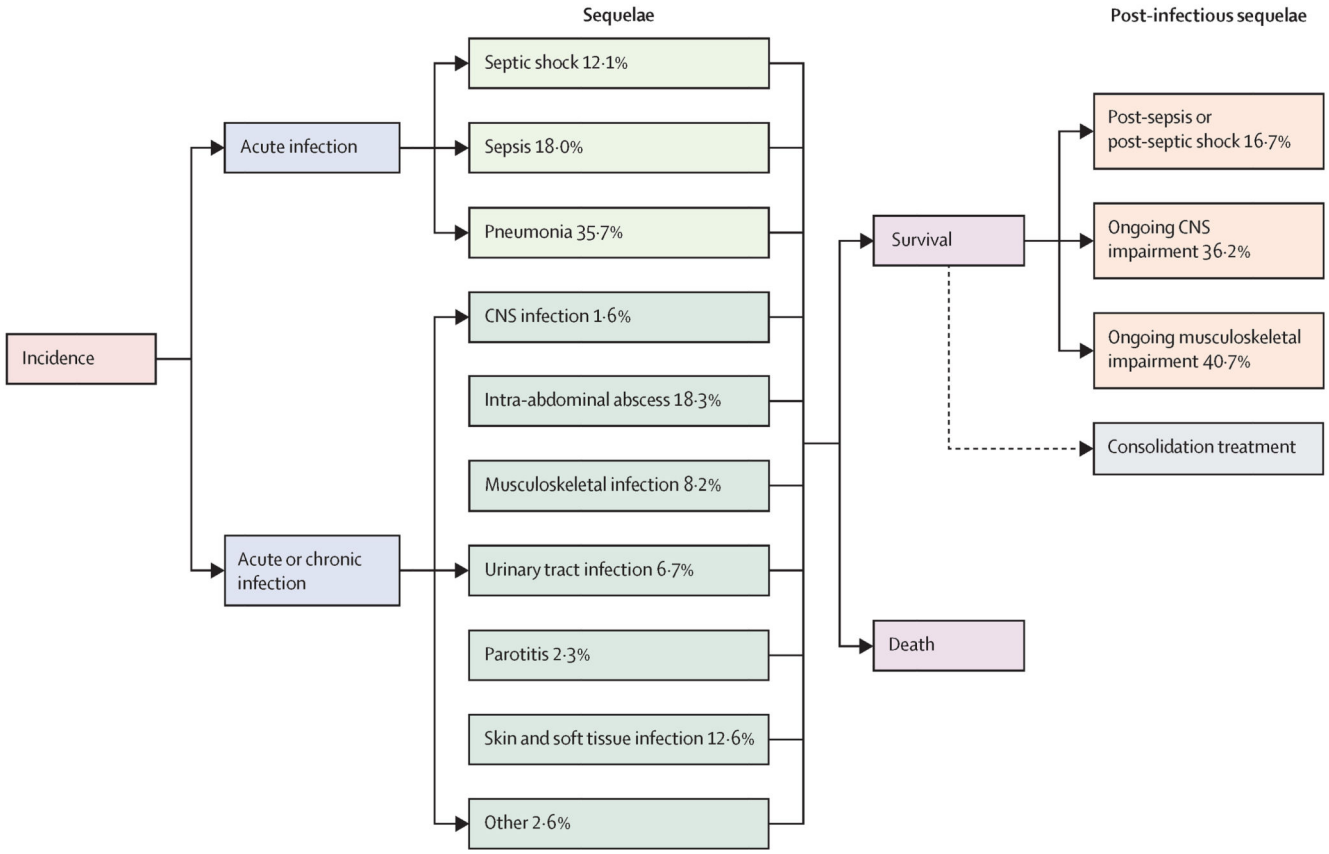

Figure 1. Simplified disease model used to estimate the global burden of melioidosis

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.

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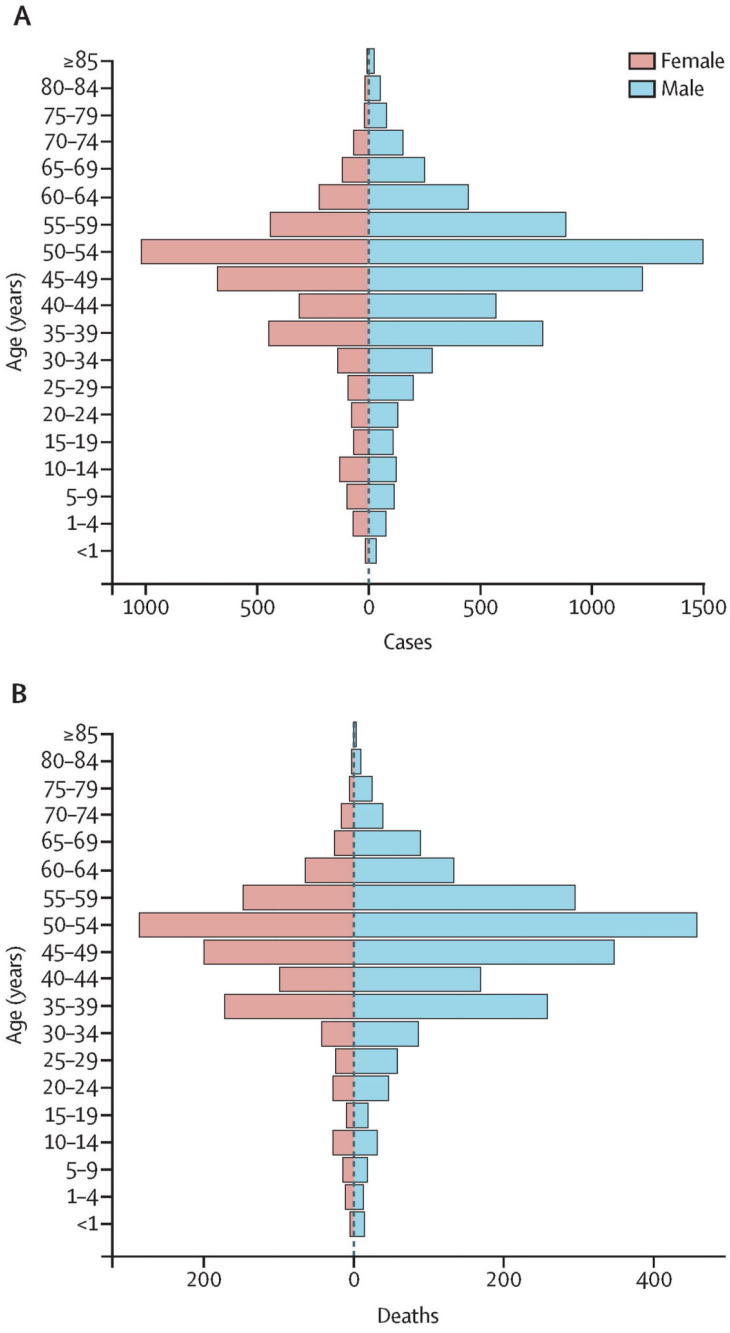

Figure 2. Age and sex distribution of melioidosis incident and fatal cases

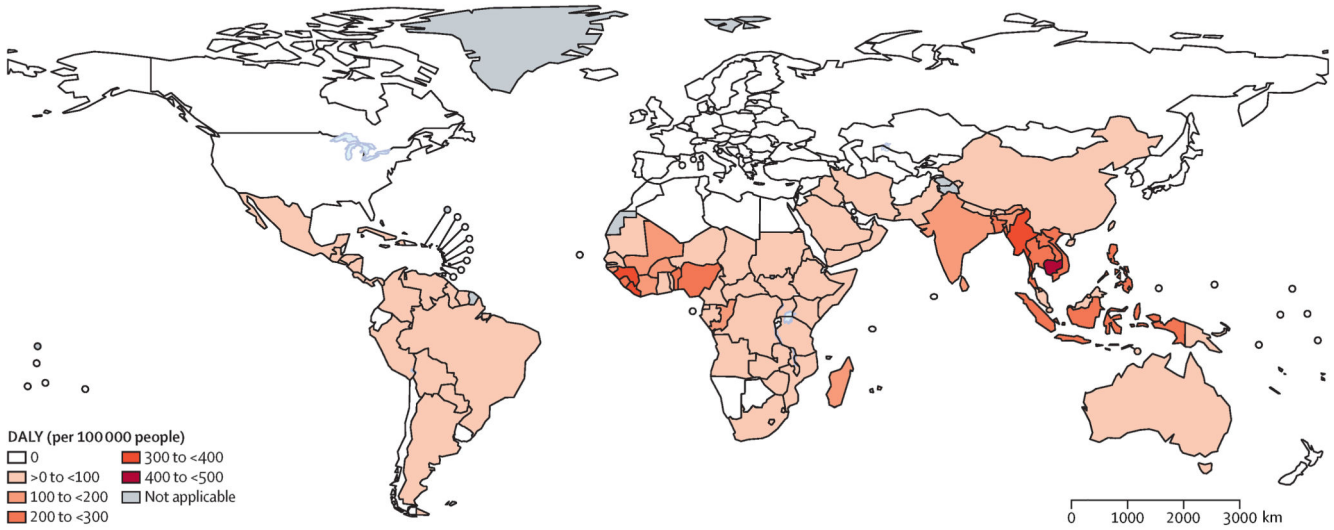

Figure 3. Disability-adjusted life years per 100 000 people for melioidosis by country in 2015

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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)

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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.

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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)

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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)
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)

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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)
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)

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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)
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.