

RESEARCH ARTICLE

Modelling population dynamics and seasonal movement to assess and predict the burden of melioidosis

Wiriya Mahikul¹, Lisa J. White^{2,3}, Kittiyod Poovorawan⁴, Ngamphol Soonthornworasiri¹, Pataporn Sukontamarn⁵, Phetsavanh Chanthavilay^{2,6}, Graham F. Medley⁷, Wirichada Pan-ngum^{1,2*}

1 Department of Tropical Hygiene, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, **2** Mahidol-Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, **3** Centre for Tropical Medicine, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom, **4** Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand, **5** College of Population Studies, Chulalongkorn University, Bangkok, Thailand, **6** Institute of Research and Education Development, UHS, Vientiane, Lao PDR, **7** Centre for Mathematical Modelling of Infectious Disease & Department of Global Health and Development, London School of Hygiene and Tropical Medicine, London, United Kingdom

* pan@tropmedres.ac



OPEN ACCESS

Citation: Mahikul W, White LJ, Poovorawan K, Soonthornworasiri N, Sukontamarn P, Chanthavilay P, et al. (2019) Modelling population dynamics and seasonal movement to assess and predict the burden of melioidosis. *PLoS Negl Trop Dis* 13(5): e0007380. <https://doi.org/10.1371/journal.pntd.0007380>

Editor: Alfredo G Torres, University of Texas Medical Branch, UNITED STATES

Received: August 17, 2018

Accepted: April 10, 2019

Published: May 9, 2019

Copyright: © 2019 Mahikul et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: All relevant data are within the manuscript and its Supporting Information files.

Funding: WM and WP received funding from the Thailand Research Fund through the Royal Golden Jubilee PhD Program (grant no. PHD/0123/2557). This study was part of the Wellcome-Trust Major Overseas Programme in SE Asia (grant number 106698/Z/14/Z). This study was financially supported by the Thailand Research Fund through

Abstract

Background

Melioidosis is an infectious disease that is transmitted mainly through contact with contaminated soil or water, and exhibits marked seasonality in most settings, including Southeast Asia. In this study, we used mathematical modelling to examine the impacts of such demographic changes on melioidosis incidence, and to predict the disease burden in a developing country such as Thailand.

Methodology/Principal findings

A melioidosis infection model was constructed which included demographic data, diabetes mellitus (DM) prevalence, and melioidosis disease processes. The model was fitted to reported melioidosis incidence in Thailand by age, sex, and geographical area, between 2008 and 2015, using a Bayesian Markov Chain Monte Carlo (MCMC) approach. The model was then used to predict the disease burden and future trends of melioidosis incidence in Thailand. Our model predicted two-fold higher incidence rates of melioidosis compared with national surveillance data from 2015. The estimated incidence rates among males were two-fold greater than those in females. Furthermore, the melioidosis incidence rates in the Northeast region population, and among the transient population, were more than double compared to the non-Northeast region population. The highest incidence rates occurred in males aged 45–59 years old for all regions. The average incidence rate of melioidosis between 2005 and 2035 was predicted to be 11.42 to 12.78 per 100,000 population per year, with a slightly increasing trend. Overall, it was estimated that about half of all

the Royal Golden Jubilee PhD Program. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing interests: The authors have declared that no competing interests exist.

cases of melioidosis were symptomatic. In addition, the model suggested a greater susceptibility to melioidosis in diabetic compared with non-diabetic individuals.

Conclusions/Significance

The increasing trend of melioidosis incidence rates was significantly higher among working-age Northeast and transient populations, males aged ≥ 45 years old, and diabetic individuals. Targeted intervention strategies, such as health education and awareness raising initiatives, should be implemented on high-risk groups, such as those living in the Northeast region, and the seasonally transient population.

Author summary

Melioidosis is an infectious disease caused by the Gram-negative bacillus *Burkholderia pseudomallei*, which exhibits marked seasonality in most settings where it occurs, such as Southeast Asia and Northern Australia. Most of the population at risk of contracting melioidosis lives in rural areas; particularly at risk are those who are exposed to soil and water, such as rice farmers. Thailand's demography is in a transient phase, with older age groups set to double within a decade. Social impacts of lifestyle changes are reflected in seasonal movement and increasing urbanization. In this study, we used mathematical modelling to examine the impacts of such demographical changes on an important infectious disease and to dynamically predict the disease burden in a developing country setting, namely Thailand. We found that melioidosis incidence was significantly higher among working-age Northeast and transient populations, specifically among males aged ≥ 45 years old and individuals with diabetes. Improved health education and awareness raising should be implemented on a national scale, with a focus on high-risk groups living in endemic areas, as well as those who move seasonally between these and other areas.

Introduction

Melioidosis is an infection caused by the Gram-negative bacillus *Burkholderia pseudomallei*, which exhibits marked seasonality in most settings where it is endemic, including Southeast Asia and Northern Australia [1]. Melioidosis is a communicable disease that is usually transmitted via contaminated soil or water, and is highly prevalent in Northeast Thailand [2]. Most of the population at risk of melioidosis lives in rural areas, especially those people who frequently come into contact with soil or water, such as rice farmers [3, 4]. In Thailand, the highest number of melioidosis reported cases are often in January and October [5]. Infection with *B. pseudomallei* shows great clinical diversity, spanning asymptomatic infections, localized skin ulcers or abscesses, chronic pneumonia mimicking tuberculosis, and fulminant septic shock with abscesses in multiple internal organs [6]. Both humans and animals are susceptible to *B. pseudomallei*, and may be infected by percutaneous inoculation, inhalation, or ingestion. Person-to-person spread and zoonotic infections of humans are very rare [7]. The incubation period is between 1–21 days (average 9 days) [8], and is believed to be influenced by the inoculation dose, mode of infection, host risk factors, and probably differential virulence of the infecting organisms. Most cases result from recent infections, although latency with reactivation has been described up to 62 years following exposure [8], while the median times to

relapse and reinfection are 21 weeks and 111 weeks, respectively. The risk of relapse is related to a patient's adherence to treatment and the initial extent of disease, but not to any underlying conditions [9–11]. Melioidosis seems to be more severe in older people with lower immunity or chronic underlying conditions, such as diabetes [12]. The risk of contracting melioidosis in diabetic individuals is 12 times higher than for non-diabetic individuals [13, 14]. Currently, the global burden of melioidosis is estimated to be 165,000 cases per year (95% credible interval 68,000–412,000), with 89,000 deaths (36,000–227,000) [15].

Thailand's Bureau of Epidemiology (BoE) launched a melioidosis surveillance system in 2001 (Report 506) [5]. Approximately 80% of reported melioidosis cases were from Northeast Thailand [5]. In the past, the number of cases shown in the surveillance system was heavily relied on provincial and regional hospitals voluntarily report, very few were reported from private hospitals [16]. In general, melioidosis is diagnosed by testing for antibodies to *B. pseudomallei* using an indirect hemagglutination (IHA) technique, which has been found to have low sensitivity and specificity [17]. This surveillance system was revised in 2010 in order to capture more health data items. There has been an increase in usage of bacterial culture [16] which could give rise to an increase in total number of culture-confirmed cases. In addition, there has been an improvement to access to healthcare. Nevertheless, the true number of cases is still under-reported because of diverse clinical manifestations and inadequate bacterial identification methods. A previous estimation suggested cases in Thailand were in excess of 7,000 cases per year [15], while the BoE reported just 3,242 cases in 2015 [5].

B. pseudomallei is resistant to a wide range of antimicrobials, and ineffective treatment may result in death in 70% of cases [18]. The treatment for melioidosis consists of an intensive phase of at least 10–14 days of ceftazidime, meropenem, or imipenem, administered intravenously, followed by oral eradication therapy, usually with trimethoprim–sulfamethoxazole (TMP-SMX) for 3–6 months [19]. There is currently no vaccine against melioidosis [20, 21].

The demographics of Thailand are currently in a transition phase, becoming more like those of developed countries, with rapid changes in population structure, reductions in birth and mortality rates, and a low rate of population growth. Urbanization is accelerating, and there are large annual population movements. These types of changes have been shown to have important impacts on public health and the disease burden of both non-communicable [22] and communicable diseases [23]. The population at highest risk of contracting melioidosis is the working age group. There is appreciable seasonal movement among this group as they go about their working lives. The internal migration of Thai people involves a number of distinct forms of movement within each year. Three forms have been identified in previous research [24]: a single movement, seasonal movement, and repeated movement. Seasonal migration involves people moving from the North and Northeast regions of Thailand towards the Bangkok metropolis and the Central region during the dry season (from March through to June), and in the reverse direction during the wet season (June to September) [24]. 40% of people from the Northeast are classified as seasonal migrants (a transient population) [25]. It is obvious that for person-to-person transmissible infections, there are significantly more infections when such transient individuals are considered [26–29]. However, very few studies were trying to look at the effect of transient populations on an infectious disease from a primarily environmental source which will help better describe the temporal and spatial changes of the incidence of such a disease [30]. Developed countries are also observing an emergence of melioidosis related to travelling and importation of cases [1].

To date, only a few approaches have been applied to determine the melioidosis burden, including simple maps of melioidosis [1], maps of the global distribution of *B. pseudomallei*, and estimates of the total incidence and mortality due to melioidosis worldwide using a statistical model [15]. Only one study has used mathematical modelling, exploring the use of

childhood seroprevalence data as a marker of intensity of exposure [31]. In this study, we used mathematical modelling to predict the incidence of melioidosis in the Thai population, taking account of population changes, seasonal movement, and incidence of diabetes. The model provides multi-dimensional forecasting of melioidosis, which could be useful for targeting intervention strategies in this setting.

Methods

Demographic and seasonal movement sub-models

We generated a deterministic demographic sub-model to predict the size of the total population (see S1 Figure A). We stratified the population by age and sex into 100 annual interval classes, from 0 to 100 years old. The population in each class followed the actual population structure of Thailand between 1980 and 2015, based on birth, death, and migration rate data from the Population and Housing Census [32, 33], and using the 1980 census data as the initial condition. All females in the age classes between 15 to 50 years old were considered to be capable of reproduction, with the fertility rate (fr) [34], while the death rate was age-related [35]. Members of the population were assumed to die upon reaching 100 years of age. Crude net migration rates (immigrant minus emigrant per 1,000 population) for each year had an impact on all age and sex compartments [36]. Most of the at-risk population for melioidosis lives in rural areas, especially in Northeast Thailand, so we modelled internal migration by classifying the population of Thailand into three independent groups. These were: those from the Northeast region who live at home for more than 6 months in a year (NE), the transient group or the people from the Northeast region who move seasonally between home and other parts of the country and spend less than 6 months in a year at home (T) and lastly the non-Northeast group, who live somewhere other than the Northeast (Non_NE). We created the seasonal movement sub-model to overlay with the demographic sub-model to estimate the rates of movement among them (see S1 Figure B). We solved a large set of ordinary differential equations (ODE) for the deterministic demographic sub-model and the seasonal movement sub-model, defined in S1 Information on Demographic sub-model and Seasonal movement sub-model, respectively.

Melioidosis infection model

The demographic and seasonal movement sub-model was overlaid with the melioidosis infection model, defined in S1 Information on Melioidosis infection sub-model. In the melioidosis infection model (a susceptible, exposed, infected, recovered, susceptible, or SEIRS, model), the population was further divided into eight health compartments: susceptible (S), diabetic susceptible (SDM), exposed (E), symptomatic (Sym), asymptomatic ($Asym$), severe (Sev), treatment ($Treat$), and recovered (R) (see Fig 1).

Melioidosis case data stratified by age, sex, and geographical area were obtained from the Thai annual epidemiological surveillance reports from 2008 to 2015 [5]. Key assumptions for our model were as follows. First, the transient population data used within this model referred only to the movement of the Thai population. The movement of migrant workers from other countries could be significant but was omitted in this study for simplicity [24]. Second, diabetes progression was assumed to be irreversible, i.e. people could not move from diabetic to non-diabetic. Third, we did not consider pre-diabetes or impaired glucose tolerance. Fourth, we assumed that incidence rates of diabetes were constant over time but varied by age. Fifth, we did not focus on chronic symptoms (those of duration greater than two months), including such presentations as chronic skin infections, chronic lung nodules, or pneumonia, which

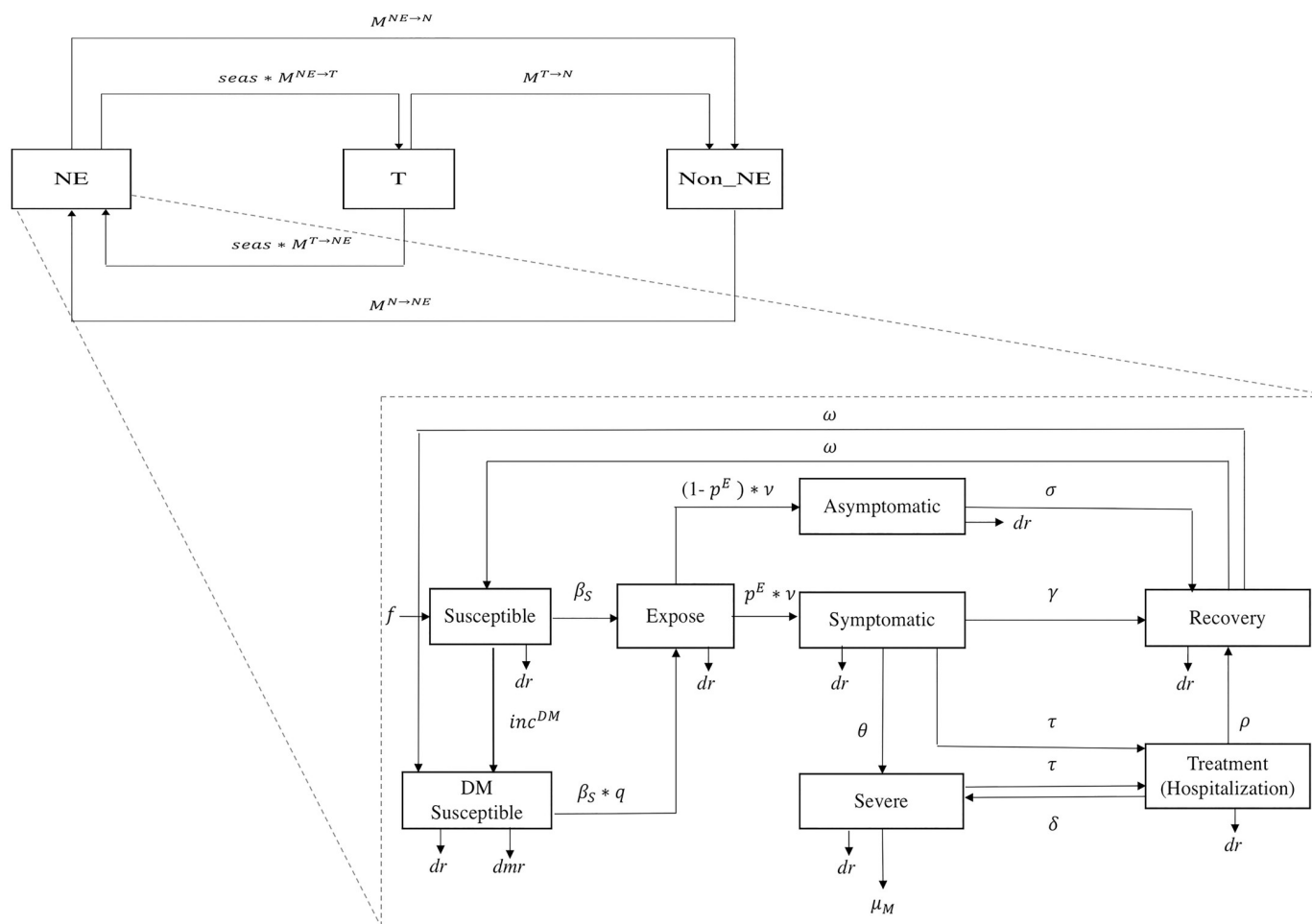


Fig 1. Schematic representation of the melioidosis dynamic sub-model (SEIRS model), with the population further divided into eight health compartments with 100 age categories: Susceptible, diabetic susceptible, exposed, symptomatic, asymptomatic, severe, treatment, and recovery.

<https://doi.org/10.1371/journal.pntd.0007380.g001>

only accounted for around 10% of melioidosis patients [12]. Finally, we did not focus on any behavioral factors such as excessive alcohol use.

We used R software version 3.3.3 to run and analyze the model outputs, and the deSolve package to solve the differential equations [37]. The initial parameter values were calculated from population data and disease burden. Model fitting was carried out using the Markov Chain Monte Carlo (MCMC) method, implemented with the Bayesian Tools R package as defined in S2 Information on the Bayesian framework [38]. The demographic and seasonal movement sub-models were run from 1980 (see S2 Figure A) to calibrate the model by fitting to the average migration data, including the population in the Northeast moving to non-Northeast, and the reverse direction from 2005 to 2015 [25]. We estimated seasonal movement parameters from the transient population model (see S1 Table A) and used them to run the melioidosis infection model from 2005. The model was run and fitted to the annual incidence of melioidosis by age, sex, and area by year, and seasonally by month, from 2008 to 2015 [5]. For model fitting, the DEzs method in the Bayesian Tools package allowed automatic parallelization on three cores to be used for sampling. This method allowed fewer chains to be used for estimated a large number of parameters and thus optimized the computational time [39]. Number of iterations and burn in were decided upon the model convergence by analyzing the

differences between multiple Markov chains. The convergence was assessed by several measures including the standard procedure of Gelman-Rubin [40, 41] and the target acceptance rates [42]. Thirty-three parameters were estimated and the median values and credibility intervals were reported. These parameters were those representing the infection rates among both sexes in the Northeast, transient, and non-Northeast populations, (β_a^{NE} , β_a^T , β_a^N) respectively, proportion of symptomatic cases (p^E), recovery rate from asymptomatic (σ), recovery rate from symptomatic (γ), Relative susceptibility to melioidosis among diabetic individuals when compare with non-diabetic (q), mortality/death rate for melioidosis (μ_M), amplitude (A_{inc}), phase angle (ϕ_{inc}) and proportion of reporting (*Report*) (see S1 Table A). Note that the proportion ($1 - \text{Report}$) was defined as “Under-reporting” i.e. those symptomatic melioidosis patients that have been seen by a physician, but the physician did not report them to the public health authority for some reasons e.g. improperly diagnosis or missing report. The model was further used to predict the 20-year age-specific incidence of melioidosis among males and females in Thailand, sampling all 33 parameters from the posterior chains. The model predictions were reported as age, gender, and area-specific incidence rates over time.

Results

The demographic sub-model was able to reproduce the past population structure of Thailand from 1980 to the present (see S2 Figure A). The parameters that characterized seasonal movement were estimated by fitting the model to the population movement data (see S2 Figure B). The model showed that majority of movements were made by Northeast individuals who moved to non-Northeast areas, approximately 13,600 persons per 100,000 population per month, or 34% of all movements within a month (see S1 Table A). Moreover, the majority of movements were among those aged between 15 and 60 years old, about 19,000 persons per 100,000 population per month, or 51% of all movements within a month (see S2 Figure C).

The fitting performance is shown in Fig 2. Melioidosis cases occurred seasonally, with a peak in the wet season that lasted from May to October. The infection parameters that minimized the fit statistic, using the Bayesian method, are shown in Table 1. The highest infection rate was estimated to be 6 cases per 100,000 population per month among males aged 45–59 years old in the Northeast. The lowest rate was 0.4 cases per 100,000 population per month among females aged 15–44 years old in the non-Northeast region. Surprisingly, we found that the infection rate among the transient male population aged 15–44 years was higher than the non-Northeast population (0.8 compared with 0.08 per 100,000 persons per month). Overall 46% of melioidosis cases were symptomatic. Recovery rates for untreated symptomatic cases and asymptomatic patients were estimated by the model, with the average period of infection estimated at around 9 and 5 months, respectively. The susceptibility to melioidosis among DM population is 10.84 [95% CI 8.42–12.23] times greater than the non-DM population. If patients’ treatment failed and they developed severe melioidosis, they could die within two weeks. We estimated 80% and 50% under-reporting of cases in 2008–2009 and 2010–2015, respectively.

Projections of the numbers of melioidosis cases between 2015 and 2035 are given in Fig 3. Total melioidosis incidence per year was projected to increase by 70%, from 6,569 (4,834–8,701) in 2015 to 11,173 (8,207–14,773) in 2035. The largest increase of melioidosis was projected to occur among the population aged 45–59 years old. The predicted incidence among males was two-fold greater than that of females. The majority of melioidosis cases were seen to occur in the population from the Northeast region of Thailand. The predicted incidence among non-diabetic was two-fold greater than that of diabetic population.

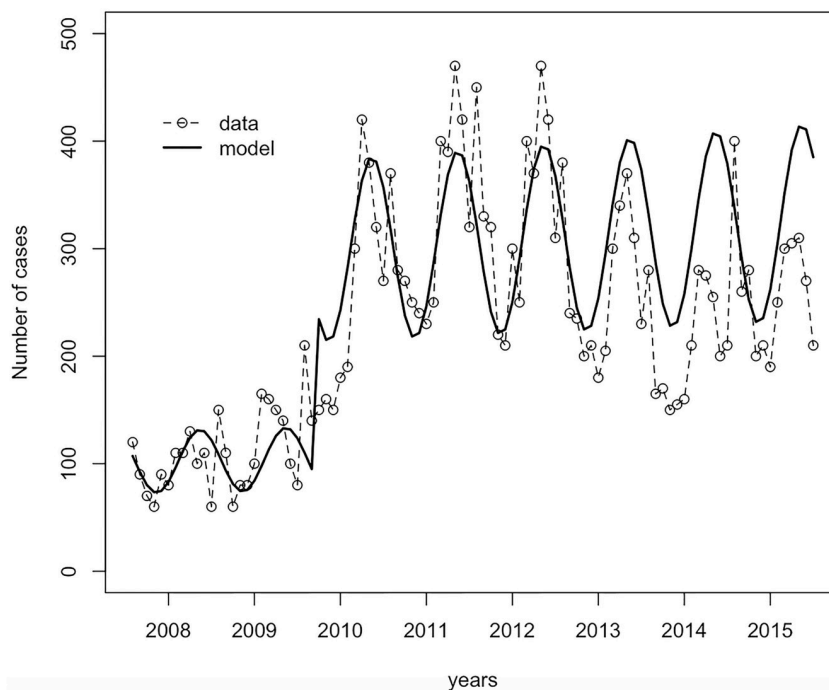


Fig 2. Comparing the observed and model estimates of monthly melioidosis cases between 2005 and 2015.

<https://doi.org/10.1371/journal.pntd.0007380.g002>

In Fig 4, total melioidosis incidence rates were projected to increase by approximately 10% by 2035, from 11.42 (8.5–13.4) in 2015 to 12.78 (9.6–14.9) per 100,000 population in 2035 (see Table 2). The highest incidence rates were predicted to be among those aged between 45–59 years old, followed by those age 60 years old and above. The incidence was almost double among males compared with females in both Northeast and other regions. The incidence rate among the Northeast population was more than double compared with the transient population, and almost ten times higher when compared with the other regions. This study also highlighted the importance of melioidosis among the transient population who temporally live in the risk area but had almost six times higher incidence compared with other regional populations. From diabetes prospective, the incidence of melioidosis among diabetes was predicted to be as high as 60 per 100,000 population. To summary, the risk of melioidosis among the aging population with some chronic diseases such as diabetes is presenting an increasing trend. The risk of infection among transient population, who temporary get some disease exposure during the agricultural seasons, cannot be ignored.

Discussion

Few models have been used to predict the incidence of melioidosis on either a national or global scale [14, 15, 43]. We applied population dynamics, seasonal movement, and the impact of diabetes to study melioidosis epidemiology in Thailand. Other approaches such as decision tree or Markov model can also be used to study melioidosis epidemiology given that the rate of transmission is constant and the system is linear. Our model fits a dynamic model for a non-transmissible disease to data on notifications only, which should allow reasonable predictions to be made as to the future course of the epidemic. However, drawing strong inferences regarding parameter values that pertain to transitions through infection/disease states after the point of infection is less safe, such that particular caution should be exercised in regards to

Table 1. Results of estimated parameters of the melioidosis model.

Parameter	Symbol	Value (95% Credible Interval)
Infection rate (10^{-5}) among males in the Northeast (per capita per month)	β_{ma}^{NE}	Aged 0–14 = 0.7 (0.6–0.8) Aged 15–44 = 0.7 (0.5–0.8) Aged 45–59 = 6.1 (4.2–7.3) Aged > = 60 = 1.7 (1.3–1.8)
Infection rate (10^{-5}) among females in the Northeast (per capita per month)	β_{fa}^{NE}	Aged 0–14 = 0.5 (0.4–0.6) Aged 15–44 = 0.3 (0.2–0.4) Aged 45–59 = 2.8 (1.1–2.9) Aged > = 60 = 0.8 (0.6–0.9)
Infection rate (10^{-5}) among males in the transient population (per capita per month)	β_{ma}^T	Aged 0–14 = 0.3 (0.1–0.5) Aged 15–44 = 0.8 (0.5–1.2) Aged 45–59 = 0.8 (0.2–1.2) Aged > = 60 = 1.1 (0.2–1.3)
Infection rate (10^{-5}) among females in the transient population (per capita per month)	β_{fa}^T	Aged 0–14 = 1.6 (0.1–1.8) Aged 15–44 = 0.3 (0.1–1.1) Aged 45–59 = 0.3 (0.1–0.6) Aged > = 60 = 0.7 (0.2–1.2)
Infection rate (10^{-5}) among males in the non-Northeast (per capita per month)	β_{ma}^N	Aged 0–14 = 0.06 (0.05–0.08) Aged 15–44 = 0.08 (0.04–0.09) Aged 45–59 = 0.47 (0.4–0.65) Aged > = 60 = 0.13 (0.12–0.2)
Infection rate (10^{-5}) among females in the non-Northeast (per capita per month)	β_{fa}^N	Aged 0–14 = 0.09 (0.03–0.17) Aged 15–44 = 0.04 (0.02–0.05) Aged 45–59 = 0.19 (0.15–0.3) Aged > = 60 = 0.08 (0.04–0.09)
Proportion of symptomatic cases from exposers	p^E	0.46 (0.38–0.53)
Recovery rate from asymptomatic (per capita per month)	σ	0.21 (0.005–0.24)
Recovery rate from untreated symptomatic (per capita per month)	γ	0.11 (0.01–0.15)
Relative susceptibility to melioidosis among diabetic individuals	q	10.84 (8.42–12.23)
mortality/death rate for melioidosis (per capita per month)	μ_M	0.6 (0.4–0.75)
Proportion of reporting	Report	Report (in 2005–2009) = 0.17 (0.15–0.22) Report (in 2010–2015) = 0.43 (0.39–0.54)
Amplitude	A_{inc}	1.7 (1.3–1.8)
Phase angle	ϕ_{inc}	20.6 (20.3–21.0)

<https://doi.org/10.1371/journal.pntd.0007380.t001>

parameters, especially those discussed here. Our findings have some similarities and differences compared with previously published work. Limmathurotsakul and colleagues used a negative binomial model to derive estimates of 7,572 (3,396–17,685) cases for global melioidosis incidence in the year 2015 [15]. This figure was similar to the incidence of melioidosis estimated in our study, which was 7,569 cases (4,834–8,701) for 2015. Both studies reached similar estimates of approximately 50% for case reporting and 40–45% for mortality/death rate for melioidosis (see S2 Table A), while the risk factors identified for melioidosis were also in agreement, i.e. being male, aged more than 44 years old, and having diabetes [13]. Two previous studies by both Thai and Australian researchers consistently showed that type 2 diabetes increased the risk of melioidosis by more than 10 times when compared with those non-diabetics [13, 44], this figure is similar to our model estimates. Buckee and colleagues pointed out that seasonal disease incidence could be driven by the mobility and aggregation of human populations, which spark outbreaks and sustain transmission [30]. Northeast and transient males aged more than 45 years old were also predicted by our model to be a highest risk groups for melioidosis. Apart from reporting and mortality/death rates for melioidosis, the model also gave the estimates for some natural history of disease parameters which would be hard to

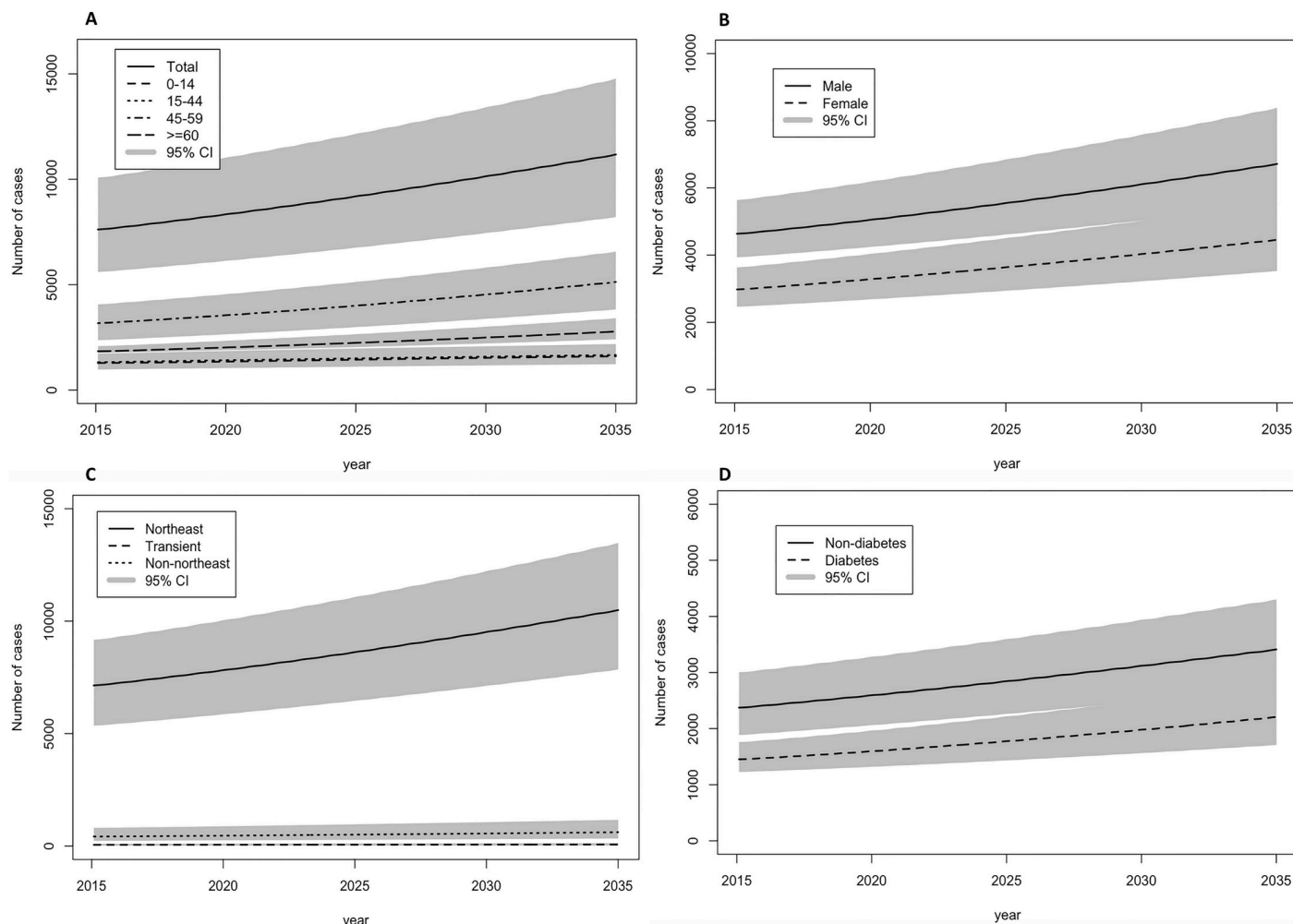


Fig 3. Projections of the numbers of melioidosis cases (95% credible intervals) between 2015 and 2035 in Thailand: (A) By age class (B) By gender (C) By geographical area, and (D) By diabetes status.

<https://doi.org/10.1371/journal.pntd.0007380.g003>

measure i.e. proportion and duration of asymptomatic infections, duration of untreated symptomatic infections, and host susceptibility to melioidosis [45]. With regard to asymptomatic infections, a few studies have tried to characterize and estimate the number of these hidden infections [44–46]. Our model suggested that there could be a significant proportion of asymptomatic infections (54%). Although the parameter values used in the fitting and prediction process are based on annual incidence data only, the variation in the parameter values is included to reflect the uncertainty in the predictions, and the posterior distributions represent sets of collinear parameters that reproduce the observed data. Further studies and more appropriate data are required to refine these parameters.

Our model can provide many benefits for health policy planning. First, the model, in common with previous studies, estimated that only about half of all melioidosis cases were being reported. Under-reporting results in melioidosis being neglected, even more than other neglected diseases such as dengue and leptospirosis [16]. Previous study suggested that melioidosis was the third most frequent cause of death from infectious diseases in northeast Thailand, after HIV/AIDS and tuberculosis [13]. By regarding melioidosis as being less

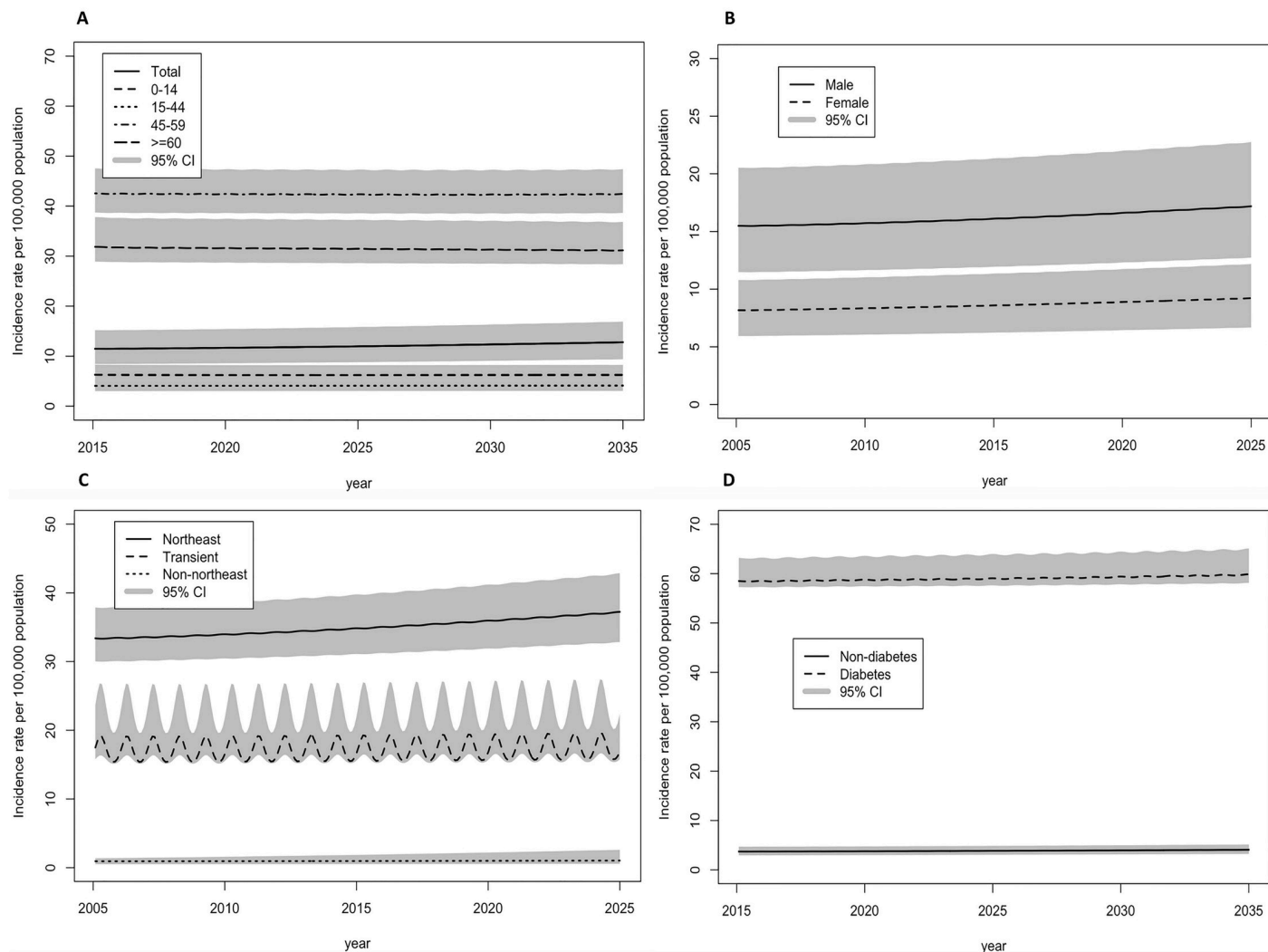


Fig 4. Projections of incidence rate of melioidosis per 100,000 population (95% credible intervals) between 2015 and 2035 in Thailand: (A) By age class (B) By gender (C) By geographical area, and (D) By diabetes status.

<https://doi.org/10.1371/journal.pntd.0007380.g004>

important disease has made it being further under-recognized by healthcare professionals, low health budgets to invest in intensive prevention and control, poor disease knowledge and practices among the population at risk, and finally a lack of research that would enable the development of concrete strategies to improve standards of care. Second, the model can be used to guide the design of targeted interventions i.e. predicting and identifying populations at high risk for morbidity and mortality. In line with the model's predictions, targeted intervention strategies could be concentrated among the male population of working age who live in the Northeast, as well as the transient population. These strategies could include providing health education to increase protective practices while engaging in agricultural activities, washing after work, and seeking appropriate health advice when feeling sick. To prevent deaths due to infections in older age groups, i.e. 45 years or older (65%) (see S2 Table A), national strategies could focus on early diagnosis and appropriate treatment, as well as improving diabetes screening programmes, since elderly people with diabetes may be prone to severe melioidosis.

Table 2. Projection of melioidosis incidence rates per 100,000 people in males and females by age group for selected years in each area.

Year	Age group (years)								Total
	0–14		15–44		45–59		≥60		
	Male	Female	Male	Female	Male	Female	Male	Female	
Total									
2005	7.73	4.27	5.82	2.82	63.97	29.82	43.61	24.82	11.42
2010	7.74	4.27	5.82	2.82	63.79	29.78	43.59	24.77	11.39
2015	7.67	4.25	5.83	2.83	63.66	29.75	43.48	24.65	11.46
2035	7.64	4.25	5.86	2.85	63.58	29.74	42.94	24.59	12.78
Northeast									
2005	22.43	11.86	16.77	8.18	185.24	86.27	124.61	70.34	33.24
2010	22.44	11.84	16.75	8.18	184.75	86.14	124.55	70.22	33.20
2015	22.24	11.81	16.76	8.19	184.36	86.06	124.22	69.87	33.40
2035	22.16	11.79	16.87	8.25	184.15	86.02	122.70	69.70	37.22
Transient									
2005	11.57	32.95	17.49	7.10	73.46	30.33	65.85	52.83	16.24
2010	11.99	34.21	18.32	7.43	75.71	31.01	67.19	54.25	16.01
2015	11.89	34.11	18.34	7.44	75.37	30.97	67.01	53.89	15.83
2035	11.88	34.10	18.48	7.49	74.08	30.98	66.95	53.74	16.93
Non-Northeast									
2005	0.62	0.46	0.54	0.27	4.79	2.26	3.33	2.15	0.93
2010	0.62	0.46	0.55	0.26	4.78	2.26	3.33	2.15	0.94
2015	0.61	0.45	0.55	0.26	4.77	2.26	3.32	2.14	0.94
2035	0.61	0.45	0.56	0.26	4.76	2.25	3.28	2.13	1.04

<https://doi.org/10.1371/journal.pntd.0007380.t002>

Our model has some limitations. For simplicity we assumed that diabetes influenced the likelihood of melioidosis infection alone and therefore once the person is infected with melioidosis, the diagnosis and disease progression are independent of diabetes status. Although diabetes has been shown to play roles in increasing severity and/or that medication of diabetes may also affect susceptibility and presentation of melioidosis [47, 48]. We also assumed that mortality/death rates for melioidosis, incidence rates of diabetes, and seasonal movement rates were constant over time, although they varied by age. It has been suggested that mortality/death rate for melioidosis due to diabetes have decreased over time because of improved access to hospitals [49], and lifestyle changes might also have affected incidence rates [50]. In this model we classified the population into those living in the Northeast and non-Northeast, which meant that the model was unable to predict the incidence of melioidosis in locations more specifically than non-Northeast. It is important to keep in mind that melioidosis is probably prevalent in all regions of Thailand, the lack of knowledge, disease awareness and diagnosis tools led to heavily report of cases by the Northeast region only [16]. We assumed that the estimates of reporting among both males and females were the same. The annual epidemiological surveillance reports of melioidosis data used in the model included cases from all provinces around Thailand, except for those cases seen in private hospitals, which account for about 30% of hospital provision, although there is no information on the relative likelihood of melioidosis being diagnosed in different sectors. Melioidosis diagnoses reported annually by the BoE are made using an indirect hemagglutination (IHA) technique to test for antibodies to *B. pseudomallei*, which has been found to have low sensitivity and specificity. It could therefore potentially under-predict the number of cases.

Conclusion

Population dynamics, seasonal movement, melioidosis infection rates, and under-reporting are important components of melioidosis incidence patterns. The increases seen in melioidosis cases are partly attributable to demographic changes as working, transient, and aging population groups are more prone to develop melioidosis. The key findings from our study are firstly, the increasing trend of melioidosis incidence, especially among males aged 45–59 years old, is predicted to continue; and secondly, the male, Northeast, and transient populations aged 45–59 years old were at the highest risk of melioidosis infection.

We anticipate that the modelling methods described here could be used in similar settings, especially those with reliable census data, to estimate the future melioidosis burden, as well as the potential effects of under-reporting. In addition, this modelling approach could be adapted to study other infectious diseases, behavioral changes, and seasonal movements, where demographic factors are important drivers of a population's disease burden.

Supporting information

S1 File. Figure (A). Schematic representation of the deterministic demographic model. Figure (B). Schematic representation of the seasonal movement sub-model. Table (A). Parameter table for melioidosis infection model. **Demographic sub-model.** Set of ordinary differential equations (ODE) for the demographic sub-model. **Seasonal movement sub-model.** Set of ordinary differential equations (ODE) for the seasonal movement sub-model. **Melioidosis infection sub-model.** Set of ordinary differential equations (ODE) for the melioidosis dynamics sub-model. (DOCX)

S2 File. Figure (A). Projection of the population size of Thailand between 1980 and 2035. Figure (B). Observed data and model estimates of the annual population (in millions) in Northeast and non-Northeast Thailand during 2005–2010. Figure (C). Estimation of the transient population by age (in thousands) in Thailand, from 2005 to 2015. Figure (D). Posterior distributions from the melioidosis infection model, that each row corresponds to the separate parameter, the left-hand column contains traces with 6 color chains and the right-hand column contains the posterior distribution, corresponding to each parameter. Table (A). Estimation of the number of deaths of males and females from melioidosis by age group for selected years. **Bayesian framework.** Bayes theorem, Prior distribution, Likelihood function and Posterior estimation. (DOCX)

Acknowledgments

This publication fulfills a part of the degree program of Doctor of Philosophy (Tropical Medicine), Faculty of Tropical Medicine, Mahidol University. We would also like to thank staff from the Mahidol-Oxford Tropical Medicine Research Unit, Department of Tropical Hygiene, Mathematical and Economic MODelling (MAEMOD) and Viriya Hantrakun for all advices and supports.

Author Contributions

Conceptualization: Wiriya Mahikul, Graham F. Medley, Wirichada Pan-ngum.

Data curation: Wiriya Mahikul, Wirichada Pan-ngum.

Formal analysis: Wiriya Mahikul, Graham F. Medley.

Methodology: Wiriya Mahikul, Graham F. Medley, Wirichada Pan-ngum.

Supervision: Graham F. Medley, Wirichada Pan-ngum.

Validation: Wiriya Mahikul, Wirichada Pan-ngum.

Writing – original draft: Wiriya Mahikul, Graham F. Medley, Wirichada Pan-ngum.

Writing – review & editing: Lisa J. White, Kittiyod Poovorawan, Ngamphol Soonthornworasiri, Pataporn Sukontamarn, Phetsavanh Chanthavilay, Graham F. Medley, Wirichada Pan-ngum.

References

- Currie BJ, Dance DA, Cheng AC. The global distribution of *Burkholderia pseudomallei* and melioidosis: an update. *Trans R Soc Trop Med Hyg.* 2008; 102 Suppl 1:S1–4. [https://doi.org/10.1016/S0035-9203\(08\)70002-6](https://doi.org/10.1016/S0035-9203(08)70002-6) PMID: 19121666.
- Wiersinga WJ, Currie BJ, Peacock SJ. Melioidosis. *N Engl J Med.* 2012; 367(11):1035–44. Epub 2012/09/14. <https://doi.org/10.1056/NEJMra1204699> PMID: 22970946.
- Cheng AC, Currie BJ. Melioidosis: epidemiology, pathophysiology, and management. *Clinical microbiology reviews.* 2005; 18(2):383–416. <https://doi.org/10.1128/CMR.18.2.383-416.2005> PMID: 15831829.
- Dance DA. Melioidosis: the tip of the iceberg? *Clinical microbiology reviews.* 1991; 4(1):52–60. PMID: 2004347.
- Suwanchairob O. Annual Epidemiological Surveillance Report 2015. Ministry of Public Health, Thailand: Bureau of Epidemiology, 2015.
- Wiersinga WJ, Virk HS, Torres AG, Currie BJ, Peacock SJ, Dance DAB, et al. Melioidosis. *Nat Rev Dis Primers.* 2018; 4:17107. Epub 2018/02/02. <https://doi.org/10.1038/nrdp.2017.107> PMID: 29388572.
- Currie BJ. Melioidosis: evolving concepts in epidemiology, pathogenesis, and treatment. *Semin Respir Crit Care Med.* 2015; 36(1):111–25. Epub 2015/02/03. <https://doi.org/10.1055/s-0034-1398389> PMID: 25643275.
- Currie BJ. *Burkholderia pseudomallei* and *Burkholderia mallei*: Melioidosis and Glanders. Australia: Bentham Science Publishers; 2007.
- Chaowagul W, Suputtamongkol Y, Dance DA, Rajchanuvong A, Pattara-arechachai J, White NJ. Relapse in melioidosis: incidence and risk factors. *The Journal of infectious diseases.* 1993; 168(5):1181–5. PMID: 8228352.
- Limmathurotsakul D, Chaowagul W, Chierakul W, Stepniewska K, Maharjan B, Wuthiekanun V, et al. Risk factors for recurrent melioidosis in northeast Thailand. *Clin Infect Dis.* 2006; 43(8):979–86. Epub 2006/09/20. <https://doi.org/10.1086/507632> PMID: 16983608.
- Sarovich DS, Ward L, Price EP, Mayo M, Pitman MC, Baird RW, et al. Recurrent melioidosis in the Darwin Prospective Melioidosis Study: improving therapies mean that relapse cases are now rare. *J Clin Microbiol.* 2014; 52(2):650–3. Epub 2014/01/31. <https://doi.org/10.1128/JCM.02239-13> PMID: 24478504.
- Perumal Samy R, Stiles BG, Sethi G, Lim LHK. Melioidosis: Clinical impact and public health threat in the tropics. *PLoS Negl Trop Dis.* 2017; 11(5):e0004738. Epub 2017/05/12. <https://doi.org/10.1371/journal.pntd.0004738> PMID: 28493905.
- Limmathurotsakul D, Wongratanacheewin S, Teerawattanasook N, Wongsuvan G, Chaisuksant S, Chetchotisakd P, et al. Increasing incidence of human melioidosis in Northeast Thailand. *The American journal of tropical medicine and hygiene.* 2010; 82(6):1113–7. <https://doi.org/10.4269/ajtmh.2010.10-0038> PMID: 20519609.
- Currie BJ, Jacups SP, Cheng AC, Fisher DA, Anstey NM, Huffam SE, et al. Melioidosis epidemiology and risk factors from a prospective whole-population study in northern Australia. *Trop Med Int Health.* 2004; 9(11):1167–74. Epub 2004/11/19. <https://doi.org/10.1111/j.1365-3156.2004.01328.x> PMID: 15548312.
- Limmathurotsakul D, Golding N, Dance DA, Messina JP, Pigott DM, Moyes CL, et al. Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis. *Nature microbiology.* 2016; 1(1). <https://doi.org/10.1038/nmicrobiol.2015.8> PMID: 26877885.
- Hinjoy S, Hantrakun V, Kongyu S, Kaewrakmuk J, Wangrangsimakul T, Jitsuronk S, et al. Melioidosis in Thailand: Present and Future. *Trop Med Infect Dis.* 2018; 3(2):38. Epub 2018/05/05. <https://doi.org/10.3390/tropicalmed3020038> PMID: 29725623.

17. Yasopa A. Annual Epidemiological Surveillance Report 2016. Ministry of Public Health, Thailand: Bureau of Epidemiology, 2016.
18. White NJ, Dance DA, Chaowagul W, Wattanagoon Y, Wuthiekanun V, Pitakwatchara N. Halving of mortality of severe melioidosis by ceftazidime. *Lancet*. 1989; 2(8665):697–701. Epub 1989/09/23. PMID: [2570956](#).
19. White NJ. Melioidosis. *Lancet*. 2003; 361(9370):1715–22. PMID: [12767750](#).
20. Peacock SJ, Limmathurotsakul D, Lubell Y, Koh GC, White LJ, Day NP, et al. Melioidosis vaccines: a systematic review and appraisal of the potential to exploit biodefense vaccines for public health purposes. *PLoS neglected tropical diseases*. 2012; 6(1):e1488. <https://doi.org/10.1371/journal.pntd.0001488> PMID: [22303489](#).
21. Patel N, Conejero L, De Reynal M, Easton A, Bancroft GJ, Titball RW. Development of vaccines against burkholderia pseudomallei. *Frontiers in microbiology*. 2011; 2:198. <https://doi.org/10.3389/fmicb.2011.00198> PMID: [21991263](#).
22. Boyle JP, Honeycutt AA, Narayan KM, Hoerger TJ, Geiss LS, Chen H, et al. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care*. 2001; 24(11):1936–40. Epub 2001/10/27. PMID: [11679460](#).
23. Geard N, Glass K, McCaw JM, McBryde ES, Korb KB, Keeling MJ, et al. The effects of demographic change on disease transmission and vaccine impact in a household structured population. *Epidemics*. 2015; 13:56–64. Epub 2015/12/01. <https://doi.org/10.1016/j.epidem.2015.08.002> PMID: [26616042](#).
24. Guest P, Chamratrithirong A, Archavanitkul K, Piriathamwong N, Richter K. Internal migration in Thailand. *Asian Pac Migr J*. 1994; 3(4):531–45. Epub 1994/01/01. PMID: [12346388](#).
25. NSO. The Migration Survey of Thailand. Thailand: National Statistical Office Thailand, 2016.
26. Parikh N, Youssef M, Swarup S, Eubank S. Modeling the effect of transient populations on epidemics in Washington DC. *Sci Rep*. 2013; 3:3152. Epub 2013/11/07. <https://doi.org/10.1038/srep03152> PMID: [24193263](#).
27. Ferguson NM, Cummings DA, Fraser C, Cajka JC, Cooley PC, Burke DS. Strategies for mitigating an influenza pandemic. *Nature*. 2006; 442(7101):448–52. Epub 2006/04/28. <https://doi.org/10.1038/nature04795> PMID: [16642006](#).
28. Colizza V, Barrat A, Barthélemy M, Vespignani A. The role of the airline transportation network in the prediction and predictability of global epidemics. *Proc Natl Acad Sci U S A*. 2006; 103(7):2015–20. Epub 2006/02/08. <https://doi.org/10.1073/pnas.0510525103> PMID: [16461461](#).
29. Fulford GR, Roberts MG, Heesterbeek JA. The metapopulation dynamics of an infectious disease: tuberculosis in possums. *Theor Popul Biol*. 2002; 61(1):15–29. Epub 2002/03/16. <https://doi.org/10.1006/tpbi.2001.1553> PMID: [11895380](#).
30. Buckee CO, Tatem AJ, Metcalf CJE. Seasonal Population Movements and the Surveillance and Control of Infectious Diseases. *Trends Parasitol*. 2017; 33(1):10–20. Epub 2016/11/21. <https://doi.org/10.1016/j.pt.2016.10.006> PMID: [27865741](#).
31. Cheng AC, Wuthiekanun V, Limmathurotsakul D, Chierakul W, Peacock SJ. Intensity of exposure and incidence of melioidosis in Thai children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. 2008; 102 Suppl 1:S37–9. [https://doi.org/10.1016/S0035-9203\(08\)70010-5](https://doi.org/10.1016/S0035-9203(08)70010-5) PMID: [19121683](#).
32. USCB. International Data Base United States Census Bureau: United State; 2016 [cited 2016 21 August]. <https://www.census.gov/population/international/data/idb/informationGateway.php>.
33. NSO. The 2010 population and housing census. Thailand: National statistical office, office of the prime minister; 2010.
34. MoPH. Public health statistics A.D.2010. Thailand: Ministry of Public health; 2010.
35. Leoprapai B. Thailand's Population Thailand: Mahidol university; 2014.
36. Huguet JW. Thailand Migration Report 2011. Thailand: International Organization for Migration, 2011.
37. Karlne Soetaert TP R. Woodrow Setzer. Solving Differential Equations in R: Package deSolve. *Journal of Statistical Software*. 2010; 33(9):1–25. <https://doi.org/10.18637/jss.v033.i09>
38. Hartig F, Minunno, F., Paul, S., BayesianTools: General-Purpose MCMC and SMC Samplers and Tools for Bayesian Statistics. R package version. R package version 0.1.3. 2017. <https://cran.r-project.org/web/packages/BayesianTools/index.html>.
39. Ter Braak CJ, Vrugt J.A. Differential evolution Markov chain with snooker updater and fewer chains. *Stat Comput* 2008; 18:435–46.
40. Gelman A. Inference from Iterative Simulation Using Multiple Sequences. *statistical science*. 1992; 7:457–551.
41. Balov N. Gelman–Rubin convergence diagnostic using multiple chains 2016. <https://blog.stata.com/2016/05/26/gelman-rubin-convergence-diagnostic-using-multiple-chains/>.

42. Rosenthal JS. Optimising and Adapting the Metropolis Algorithm. 2014.
43. Hassan MR, Pani SP, Peng NP, Voralu K, Vijayalakshmi N, Mehanderkar R, et al. Incidence, risk factors and clinical epidemiology of melioidosis: a complex socio-ecological emerging infectious disease in the Alor Setar region of Kedah, Malaysia. *BMC Infect Dis*. 2010; 10:302. Epub 2010/10/23. <https://doi.org/10.1186/1471-2334-10-302> PMID: 20964837.
44. 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. Epub 2010/12/15. <https://doi.org/10.1371/journal.pntd.0000900> PMID: 21152057.
45. Currie BJ, Fisher DA, Anstey NM, Jacups SP. Melioidosis: acute and chronic disease, relapse and re-activation. *Trans R Soc Trop Med Hyg*. 2000; 94(3):301–4. Epub 2000/09/07. PMID: 10975006.
46. Wuthiekanun V, Chierakul W, Langa S, Chaowagul W, Panpitpat C, Saipan P, et al. Development of antibodies to *Burkholderia pseudomallei* during childhood in melioidosis-endemic northeast Thailand. *The American journal of tropical medicine and hygiene*. 2006; 74(6):1074–5. Epub 2006/06/09. PMID: 16760522.
47. Liu X, Foo G, Lim WP, Ravikumar S, Sim SH, Win MS, et al. Sulphonylurea usage in melioidosis is associated with severe disease and suppressed immune response. *PLoS Negl Trop Dis*. 2014; 8(4): e2795. Epub 2014/04/26. <https://doi.org/10.1371/journal.pntd.0002795> PMID: 24762472.
48. Koh GC, Maude RR, Schreiber MF, Limmathurotsakul D, Wiersinga WJ, Wuthiekanun V, et al. Glyburide is anti-inflammatory and associated with reduced mortality in melioidosis. *Clin Infect Dis*. 2011; 52(6):717–25. Epub 2011/02/05. <https://doi.org/10.1093/cid/ciq192> PMID: 21293047.
49. Johnson JA, Majumdar SR, Simpson SH, Toth EL. Decreased mortality associated with the use of metformin compared with sulfonylurea monotherapy in type 2 diabetes. *Diabetes Care*. 2002; 25(12):2244–8. PMID: 12453968.
50. Appuhamy JA, Kebreab E, France J. A mathematical model for determining age-specific diabetes incidence and prevalence using body mass index. *Ann Epidemiol*. 2013; 23(5):248–54. <https://doi.org/10.1016/j.annepidem.2013.03.011> PMID: 23608303.