**Open Access Library Journal**
2021, Volume 8, e7537
ISSN Online: 2333-9721
ISSN Print: 2333-9705

# Incidences, Case Fatality Rates and Epidemiology of Melioidosis Worldwide: A Review Paper

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**How to cite this paper:** Fong, J.H., Pillai, N., Yap, C.G. and Jahan, N.K. (2021) Incidences, Case Fatality Rates and Epidemiology of Melioidosis Worldwide: A Review Paper. *Open Access Library Journal*, **8**: e7537.
https://doi.org/10.4236/oalib.1107537

**Received:** May 18, 2021
**Accepted:** June 21, 2021
**Published:** June 24, 2021



## Abstract

Melioidosis is an uncommon, opportunistic disease caused by *Burkholderia pseudomallei* that lives freely in soil, water, and harsh environments. Transmission occurs from direct exposure of the bacteria to soil or contaminated water supplies. The case fatality rate (CFR) of Melioidosis is high and increases in children and underdeveloped countries. Unfortunately, the disease remains understudied around the world. We carried out an extensive literature review in a systematic approach. A detailed search strategy and PRISMA chart was used to select the relevant articles from reliable medical databases. Articles published from 2016 to 2020 that addressed the incidences, case fatality rates and epidemiology of Melioidosis are selected based on selection criteria. Finally, a total of 34 articles were included in this review. We identified 15,202 cases of Melioidosis globally from 1913-2018 with a total CFR of 33.9%. We calculated the global incidence of ~2607 per year and a CFR of ~814 (35.4%) per year. There are 80% (n = 2476) of adult cases and 20% (n = 620) of paediatric cases. The total (n = 12,413) male to female ratio of Melioidosis is 2.21:1. We also found that the male to female ratio of adult cases (n = 804) is 3.57:1, whereas that of paediatric cases (n = 318) is 1.39:1. The number of patients found working in the agricultural sector was 36.5% (n = 1068). We found a higher incidence and a lower total CFR which are consistent with previously reported studies. We also found that the percentage of paediatric cases was higher than in previous studies, and there is a considerable difference in male to female ratio between adult cases and paediatric cases. This review provides significant evidence to the public health policy makers to develop an effective preventable intervention to reduce the incidence and case fatality of this neglected tropical disease.

**Subject Areas**

Epidemiology

**Keywords**

Melioidosis, Incidences, Case Fatality Rates, Epidemiology

## 1. Introduction

Melioidosis, or Whitmore's disease, is an uncommon infectious disease caused by *Burkholderia pseudomallei*, a gram-negative bacterium [1]. Not known to many, this tropical disease is discovered in 1911 by Alfred Whitmore and his assistant Krishnaswami in modern-day Myanmar [2]. What makes Melioidosis stands out from other tropical diseases is its high fatality rate, and the bacteria are naturally resistant to multiple antibiotics [3]. Unfortunately, the disease remains neglected and understudied worldwide; even within the World Health Organisation (WHO), until the formation of the International Melioidosis Society in 2015 [4] [5].

*Burkholderia pseudomallei* is a member of the large Burkholderia genus with over 80 formally named species [6]. They are a genus of Gram-negative bacilli that shares the common characteristics of being aerobic, non-spore-forming and nonfermenting. Members of the genus are usually motile with a singular or multiple polar flagella except for *Burkholderia mallei*, the bacteria responsible for glanders [7]. *Burkholderia pseudomallei* is a saprophytic organism previously known to inhabit both land and water, predominantly in humid soil, rhizosphere, surface water and groundwater [8]. It was reported that *Burkholderia pseudomallei* could survive in nutrient-depleted conditions, such as in distilled water for more than 16 years and in the desert [5]. Current studies showed that the bacteria could be detected in unchlorinated water supplies, drinking water, filtered air and even in contaminated wound irrigation fluid, antiseptics, and hand wash detergent [9] [10] [11].

Due to the high incidence of Melioidosis, the Southeast Asia region has always been considered as the origin of *Burkholderia pseudomallei*. However, a recent genetic study on *Burkholderia pseudomallei* discovered that the bacteria originated from Australia and had migrated into Southeast Asia by one incident during the latest glacial period [12]. Recent predictive modelling studies had proposed that the bacteria has now spread and can be found across the tropics of different continents [5].

Since *Burkholderia pseudomallei* is a free-living inhabitant found in both soil and water, the infection could be acquired directly from external environments [13]. The exposure could occur through recreation or occupation and is usually by accident [14]. Most of the infection starts from direct exposure to soil or contaminated water supplies, with being inoculated directly in pre-existing skin abrasions or minor wounds [14]. The increase in ingestion and inhalation of the bacteria was also noted to be associated heavily with climates such as heavy rainfall, flooding and cyclones [14] [15]. The pattern of association of Melioidosis and heavy rainfall could be observed in the Southeast Asia region due to monsoon season [16].

Limmathurotsakul *et al.* (2016) estimated an incidence rate of 5.0 per 100,000 people at risk per year for Melioidosis [17]. People of indigenous ethnicity were more likely to be infected by *Burkholderia pseudomallei*, with an increase of 10% prevalence noted [17]. In terms of demography related risk factors, being of the male gender, age of more than 45 years old, and having agricultural occupation put a person at risk of acquiring Melioidosis [14] [18] [19].

Melioidosis is considered as an opportunistic infection because of its association with risk factors that lower the immune system, such as diabetes mellitus, which accounts for more than half of all patients diagnosed with Melioidosis [13] [20] [21]. Patients with diabetes mellitus are 12 times at risk of getting Melioidosis than those who do not have diabetes mellitus after adjusting other risk factors, making diabetes the most common predisposing factors of Melioidosis [20] [21]. Besides diabetes, comorbidities including liver disease, chronic lung disease, chronic kidney disease and thalassaemia also increase the risk of getting Melioidosis [18] [22] [23]. All of which results in the impairment of the immune system, making infections highly likely to occur. Excessive alcohol consumption, prolonged steroid use and immunosuppression due to malignancy, treatment of HIV are known as risk factors for Melioidosis [14] [18] [19]. Interesting to note, more than 80% of children and 20% of adults have no associated risk factors [20] [21] [22] [23]. They are exposed to the bacteria in more significant amounts, such as aspiration of surface water as seen in drowning patients [24].

The case fatality rate (CFR) of Melioidosis is around 10% - 50% [5]. It was estimated that 89,000 people would die from Melioidosis in 2015 [17]. Many prognostic factors that were proposed to be associated with increasing the CFR of Melioidosis were studied. Among the factors, being under the age of five increases the chances of die per 1000 live births by ten times [17]. Besides age, CFR is increased in low- and middle-income countries and decreases in high-income countries [17]. Recurrence of the Melioidosis was noted to be of 5% - 28% among patients who survive the infection. The reason for recurrence could be due to incomplete clearance of the existing infection, or reinfection by the same bacteria but a different strain [5].

In this review paper, we would like to analyse the incidences, case fatality rates and epidemiology of Melioidosis between male and female, also between adult cases and paediatric cases globally with the hope that it will provide significant evidence to the public health policy makers to develop an effective preventable intervention to reduce the incidence and case fatality of this neglected tropical disease.

# 2. Methods

## 2.1. Search Strategy

We conducted a wide-ranging literature search following a very systematic approach to identify the related studies of Melioidosis, specifically focused on the incidences, case fatality rates and epidemiology of the disease. Five reliable medical databases are searched to obtain relevant articles. They are PubMed, Ovid, EMBASE, Scopus and Web of Science. The search strategy involved the Medical Subject Heading or free terms/keywords as its synonyms such as ((“Melioidosis” OR “Whitmore’s disease” OR “*Burkholderia pseudomallei* infection” OR “Pseudoglanders” OR “Nightcliff gardener’s disease”) AND (“incidence*” OR “incidence rate*”) AND (“mortality” OR “case fatality rate*”) AND “epidemiology”)) to ensure the complete coverage, so that there will not be any article miss out during the search.

## 2.2. Inclusion and Exclusion Criteria

Studies on human subjects were included in this review *i.e.* studies on animal subjects such as livestock and animal models are left out. We also excluded the articles related to non-living subjects such as soil properties and water properties. We included only those articles which were written in English and published from 2016 to 2020. We incorporated studies with patients of both genders into the review. While selecting the articles, we focused on review papers, case reports and research articles. Book chapters, conference abstracts, editorials, correspondences, and encyclopaedias are excluded. Journals that are of veterinary, dentistry and agricultural science are omitted as well. Finally, articles with information that cover incidences, case fatality rates and epidemiology of Melioidosis from all parts of the world are included.

## 2.3. Selection of Research Articles

The selection of the articles was carried out using the PRISMA chart, as shown in **Figure 1**. The articles were assessed in three stages: at the beginning, filters are applied through the database system of PubMed, Ovid, EMBASE, Scopus and Web of Science to ensure that the articles matched the inclusion criteria. Then, in the first stage, the articles were retrieved to remove the duplicates by using Endnote software. Next, the articles were screened based on the title and abstract in the second stage and in the third stage, we moved on to evaluate the articles based on the full-text articles.

## 2.4. Data Extraction and Management

Data were extracted by two independent reviewers (JHF and NKJ[1]) by following a standardized form which includes regions/sub-regions, country where the study has been conducted, list of authors, data on the time period which is covered in each individual article, types of articles which are reviewed, source of

[1]JHF: Jing Hong Fong; NKJ: Nowrozy Kamar Jahan.

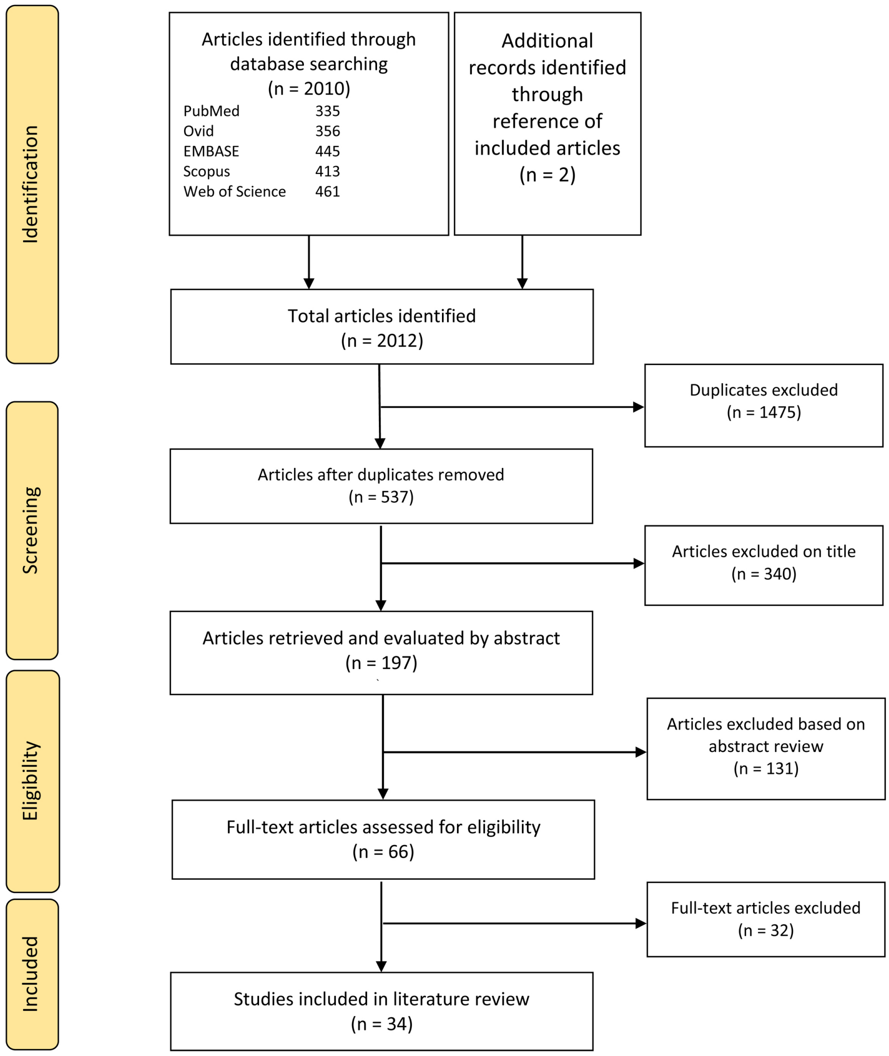


**Figure 1.** PRISMA chart used for the selection of articles.

infection of Melioidosis, sample size, age range of the patients including mean and median age where applicable, gender, case fatality rate in %, and the history of agricultural work. Later on, both the reviewers compared the extracted data to come to a general consensus. They invited the 3rd reviewer either CGY or NKP[2] to contribute when they failed to make the decision. The articles that are finalised by the decisions of the reviewers were then included in the review.

## 3. Results

We identified a total of 34 articles published between the year 2016-2020 that fulfils the criteria. The countries in which the data covered is, as shown in Figure 2. In the figure, countries that reported cases of Melioidosis that are imported are shaded in blue colour, whereas countries that report local cases or local cases with imported cases are shaded in red. All data were arranged, as shown in Tables 1-3. Two articles reported solely imported cases, one from

[2]CGY: Christina Gertrude Yap; NKP: Naganathan Kathiresan Pillai.

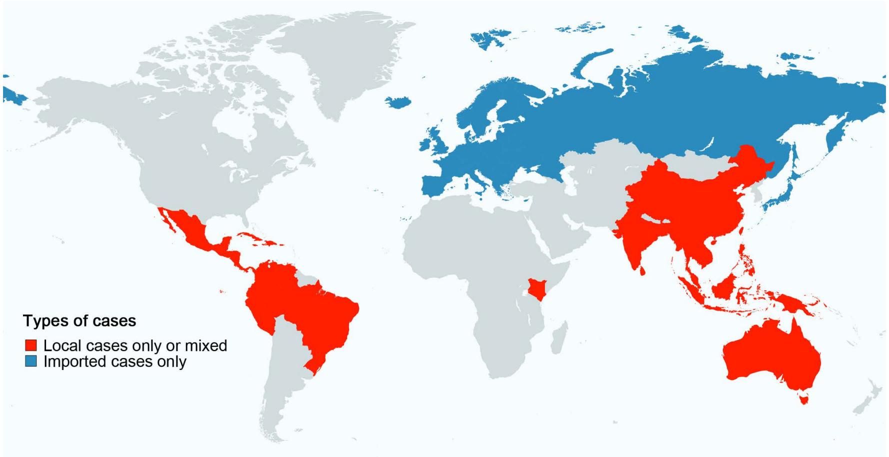


**Figure 2.** Map showing the countries covered by the selected articles.

Japan [25] and two from Europe [3] [26]. One article reported aboriginal cases from Australia [27].

### 3.1. Incidence

From the 34 articles [23] [25]-[56], we identified a total of 15,202 cases of Melioidosis around the world from 1913-2018. The incidences vary widely, from 5 cases [38] to 7126 cases [34] (see **Table 1**). Among the sub-regions, Southeast Asia reports the most cases at 12,518 cases (82.5% of all cases) [23] [28] [30] [33] [34] [36] [39] [40] [41] [43] [48] [49] [51] [53] [54] [55] (see **Table 2**, **Figure 3**), with Thailand being the country of most cases at a total of 7690 cases (50.7% of all cases) [34] (see **Table 1**). Oceania and East Asia then follow Southeast Asia with a number of 1066 cases [27] [45] [46] [47] and 994 cases [25] [35] [37] [50] [56], respectively (see **Table 2**). The lowest number of reported cases comes from Kenya, a country in Africa, at 5 cases [38]. Europe follows this with 110 cases [26] and America with 123 cases [29] [42] [44] (see **Table 2**).

The period of study of each article varies, from the year 1913 to 2018 (see **Table 1**). The number of cases reported by each article was then divided by their respective number of observational years. The article that reports the most cases per observation year (1781.5 cases per observation year) is Hantrakun *et al.* from Thailand [34]. After our calculation, it was noted that there is ~2607 incidence per observation year in the world.

### 3.2. Case Fatality Rate (CFR)

Data on the case fatality was not reported in four articles [30] [33] [35] [48] (see **Table 1**). Among those articles that reported case fatality, CFR was calculated. The case fatality rate per year is calculated by taking the total number of fatal cases reported and divide it with the total number of years observed. The calculated total case fatality rate of the 30 articles was 33.9% (see **Table 2**). The CFR of different continents ranges from 8.2% in Europe to 60.0% in Africa. The CFR calculated from each article also varies, from CFR of 0.00% from China to CFR

**Table 1.** List of articles included and details.

| Region/ Sub-region/ Country | Author | Data Period | Types of article | Source of infection | Sample size (n) | Age Range | Agriculture work | Case fatality (%) | Ref. no. |
|---|---|---|---|---|---|---|---|---|---|
| China | Zheng *et al.* | 2002-2016 | Surveillance Data | Local | 396 | 0 - 84 | 118 | 23.1 | [56] |
| | Tang *et al.* | 2006-2015 | Review | Local | 7 | 36 - 63 | 3 | 0.0 | [50] |
| Hong Kong | Lui *et al.* | 1998-2017 | Review | Local | 61 | 8 - 100 | NA | 31.1 | [37] |
| Taiwan | Hsueh *et al.* | 2000-2017 | Surveillance Data | Local | 516 | NA | (86%) | NA | [35] |
| Japan | Hadano *et al.* | 1993-2017 | Review | Imported | 14 | 33 - 69 | NA | 14.3 | [25] |
| Brunei | Pande *et al.* | 2015-2016 | Review | Local | 115 | 2 - 86 | NA | 27.0 | [40] |
| Cambodia | Turner *et al.* | 2009-2013 | Retrospective study | Local | 173 | 0.02 - 15.9 | NA | 15.0 | [23] |
| | Suttisunhakul *et al.* | 2011 | Serological study | Local | 163 | NA | (22.5%) | NA | [48] |
| Indonesia | Tauran *et al.* | 2012-2017 | Review | Local | 42 | 0 - 78 | NA | 43.0 | [51] |
| Laos | Bulterys *et al.* | 1999-2015 | Review | Local | 870 | NA | 254 | NA | [30] |
| | Dance *et al.* | 1999-2017 | Review | Local | 1359 | NA | NA | NA | [33] |
| Malaysia | Yazid *et al.* | 2001-2011 | Laboratory database | Local | 98 | 0 - 60+ | 33% | 36.0 | [55] |
| | Nathan *et al.* | 1975-2015 | Review | Local | 697 | 0 - 60+ | NA | 41.9 | [39] |
| | Tang *et al.* | 2013-2017 | Retrospective Study | Local | 46 | 0 - 65 | 10 | 52.2 | [49] |
| | Hassan *et al.* | 2005-2011 | Case-control | Local | 242 | (46.6) | 41 | 41.8 | [28] |
| Myanmar | Win *et al.* | 1913-2018 | Review | Local | 298 | NA | NA | 87.9 | [54] |
| Philippine | San Martin *et al.* | 1948-2018 | Review | Local | 41 | 21 - 82 | 6 | 14.6 | [43] |
| Singapore | Pang *et al.* | 2003-2014 | Surveillance Data | Local | 614 | 31 - 96 | NA | 18.4 | [41] |
| Thailand | Jatapai *et al.* | 2009-2013 | Serological study | Local | 564 | 1 - 93 | NA | 14.0 | [36] |
| | Hantrakun *et al.* | 2012-2015 | Retrospective study | Local | 7126 | 0 - 100 | NA | 39.0 | [34] |
| Vietnam | Trinh *et al.* | 2015 | Laboratory database | Local | 70 | 1 - 90 | 43 | 25.7 | [53] |
| Bangladesh | Chowdhury *et al.* | 1961-2017 | Review | Local | 51 | 8 - 90 | 14 | 27.0 | [31] |
| India | Tipre *et al.* | 1953-2016 | Review | Local | 85 | 0 - 71 | 14 | 27.0 | [52] |
| Sri Lanka | Corea *et al.* | 2006-2017 | Review | Local | 250 | 2 - 92 | 44 | 20.4 | [32] |
| Australia | Stephens *et al.* | 1989-2013 | Melioidosis database | Local | 810 | 50* | NA | 12.2 | [46] |
| | Smith *et al.* | 1998-2017 | Review | Local | 10 | 0 - 14 | NA | 50.0 | [45] |
| | Stewart *et al.* | 1998-2016 | Review | Local | 197 | 0 - 92 | NA | 15.0 | [47] |
| | Hempenstall *et al.* | 1997-2017 | Review | Aboriginal | 49 | 44.9* | NA | 8.0 | [27] |
| Europe | Le Tohic *et al.* | 2000-2018 | Review | Imported | 77 | 29 - 63 | 6 | 6.0 | [26] |
| Netherlands | Birnie *et al.* | 2003-2018 | Registry data | Imported | 33 | 21 - 83 | NA | 12.0 | [70] |
| Panama | Arauz *et al.* | 2007-2017 | Review | Local | 12 | 29 - 72 | 2 | 41.7 | [29] |
| Mexico, Central America, and the Caribbean | Sanchez-Villamil *et al.* | 1945-2017 | Review | Local | 63 | 4 - 88 | NA | | [44] |
| South America | Rolim *et al.* | 1962-2017 | Review | Local | 48 | 3 - 100 | NA | 47.9 | [42] |
| Kenya | Muthumbi *et al.* | 2002-2014 | Review | Local | 5 | 0 - 68 | NA | 60.0 | [38] |

NA: Not available; *: Median age.

Table 2. Epidemiological data based on continents.

| Region/ Sub-region | References | Data Period | | n | Age Range | Agriculture workers | Case fatality (%) |
|---|---|---|---|---|---|---|---|
| East Asia | [25] [35] [37] [50] [56] | 1993-2017 | Mixed | 994 | 0 - 100 | 565 (48.6%) | 11.3% |
| South-east Asia | [23] [28] [30] [33] [34] [36] [39] [40] [41] [43] [48] [49] [51] [53] [54] [55] | 1913-2018 | Local | 12,518 | 0 - 100 | 423 (28%) | 37.3% |
| South Asia | [31] [32] [52] | 1953-2017 | Local | 386 | 0 - 92 | 72 (18.7%) | 22.8% |
| Oceania | [27] [45] [46] [47] | 1989-2017 | Local | 1066 | 0 - 92 | NA | 12.9% |
| Europe | [26] | 2000-2018 | Imported | 110 | 29 - 63 | 6 | 8.2% |
| America | [29] [42] [44] | 1945-2017 | Local | 123 | 3 - 100 | 2 (16.7%) | 46.7% |
| Africa | [38] | 2002-2014 | Local | 5 | 0 - 68 | NA | 60.0% |
| **World total** | **[23] [25]-[56]** | **1913-2018** | **Mixed** | **15,202** | **0 - 100** | **1068 (36.5%)** | **33.9%** |

of 87.9% from Myanmar (see Table 1). After completing our calculation, it was noted that there is minimum ~814 case fatality per observation year to maximum ~2299 incidence per observation year. The case fatality rate per observation year is 35.4%.

### 3.3. Age and Male to Female Ratio

Only two articles, Turner *et al.* [23] and Smith *et al.* [45], investigated Melioidosis in children as they included the age ranges from 0 year to 100 years. Definition of a paediatric case varies from less than 15 years old to less than 21 years old. Calculation on the difference of percentage between adult cases and children cases was also done. Articles that do not include detailed data on adult cases or paediatric cases were excluded from the calculation. Out of 3096 calculated cases, the number of adult cases made up 80% of the total (n = 2476), and paediatric cases (n = 620) was 20.0% (see Table 3).

Calculations on male to female ratio were made as well. Articles that do not have the details information on gender are excluded from the calculation. Of 12,413 adults and paediatric cases identified, there are 8549 males (68.9%) and 3864 females (31.1%), with a male to female ratio of 2.21:1. Of 804 adult cases identified, there are 628 males (78.1%) and 176 females (21.9%), with a male to female ratio of 3.57:1. Out of 318 paediatric cases identified, 58.2% (n = 185) were males and 41.8 % (n = 133) were females. The male to female ratio is 1.39:1. The highest number of male to female ratio calculated is 14:0 (14 males and no females) from China [25] in which all patients reported are adults. The lowest number of male to female ratio calculated is 1.34:1 from Cambodia [23], in which all patients reported are children (see Table 3).

### 3.4. Occupation

Calculations on the number of cases with agricultural work as an occupation were completed. Articles that do not have the details of occupation are excluded

**Table 3.** Epidemiological data of melioidosis between adult and children.

| | Total | | | | Adult | | | | Children | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | M | F | Ratio | n | M | F | Ratio | n | M | F | Ratio |
| [56] | 289 | 245 | 44 | 5.57:1 | | | | | | | | |
| [50] | 7 | 7 | 0 | 7.00:0 | 7 | 7 | 0 | 7.00:0 | 0 | 0 | 0 | |
| [25] | 14 | 14 | 0 | 14.00:0 | 14 | 14 | 0 | 14.00:0 | 0 | 0 | 0 | |
| [23] | 173 | 99 | 74 | 1.34:1 | | | | | 173 | 99 | 74 | 1.34:1 |
| [48] | 42 | 32 | 10 | 3.20:1 | 27 | 22 | 5 | 4.40:1 | 15 | 10 | 5 | 2.00:1 |
| [55] | 697 | 522 | 175 | 2.98:1 | 599 | 463 | 136 | 3.40:1 | 98 | 59 | 39 | 1.51:1 |
| [49] | 242 | 185 | 57 | 3.25:1 | | | | | | | | |
| [54] | 41 | 35 | 6 | 5.83:1 | 41 | 35 | 6 | 5.83:1 | 0 | 0 | 0 | |
| [43] | 614 | 516 | 98 | 5.27:1 | | | | | | | | |
| [36] | 7126 | 4839 | 2287 | 2.12:1 | | | | | | | | |
| [53] | 51 | 41 | 10 | 4.10:1 | | | | | | | | |
| [32] | 810 | 523 | 287 | 1.82:1 | | | | | | | | |
| [46] | 10 | 6 | 4 | 1.50:1 | | | | | 10 | 6 | 4 | 1.50:1 |
| [45] | 197 | 147 | 50 | 2.94:1 | | | | | | | | |
| [47] | 49 | 34 | 15 | 2.27:1 | | | | | | | | |
| [26] | 12 | 9 | 3 | 3.00:1 | 12 | 9 | 3 | 3.00:1 | 0 | 0 | 0 | |
| [70] | 33 | 23 | 10 | 2.30:1 | 33 | 23 | 10 | 2.30:1 | 0 | 0 | 0 | |
| [29] | 40 | 24 | 16 | 1.50:1 | 32 | 20 | 12 | 1.67:1 | 8 | 4 | 4 | 1.00:1 |
| [44] | 48 | 39 | 9 | 4.33:1 | 37 | 34 | 3 | 11.33:1 | 11 | 5 | 6 | 0.83:1 |
| [42] | 5 | 3 | 2 | 1.50:1 | 2 | 1 | 1 | 1.00:1 | 3 | 2 | 1 | 2.00:1 |
| **TOTAL** | **10,500** | **7343** | **3157** | **2.33:1** | **804** | **628** | **176** | **3.57:1** | **318** | **185** | **133** | **1.39:1** |
| | 10,500 | 7343 | 3147 | 2.33:1 | 804 | | | | 318 | | | |
| [40] | 115 | 84 | 31 | 2.71:1 | 111 | | | | 4 | | | |
| [51] | 870 | 513 | 357 | 1.44:1 | 625 | | | | 245 | | | |
| [33] | 86 | 68 | 18 | 3.78:1 | 81 | | | | 5 | | | |
| [34] | 70 | 47 | 23 | 2.04:1 | 66 | | | | 4 | | | |
| [39] | 46 | 35 | 11 | 3.18:1 | 41 | | | | 5 | | | |
| [41] | 564 | 338 | 226 | 1.50:1 | 542 | | | | 22 | | | |
| [31] | 85 | 65 | 20 | 3.25:1 | 74 | | | | 11 | | | |
| [27] | 77 | 56 | 21 | 2.67:1 | 74 | | | | 3 | | | |
| **TOTAL** | **12,413** | **8549** | **3864** | **2.21:1** | **2418** | | | | **617** | | | |
| | 12,413 | | | | 2418 | | | | 617 | | | |
| [37] | 61 | | | | 58 | | | | 3 | | | |
| **TOTAL** | **12,474** | | | | **2476** | **80.0%** | | | **620** | **20.0%** | | |

Note: n = sample size; M = male and F = female.

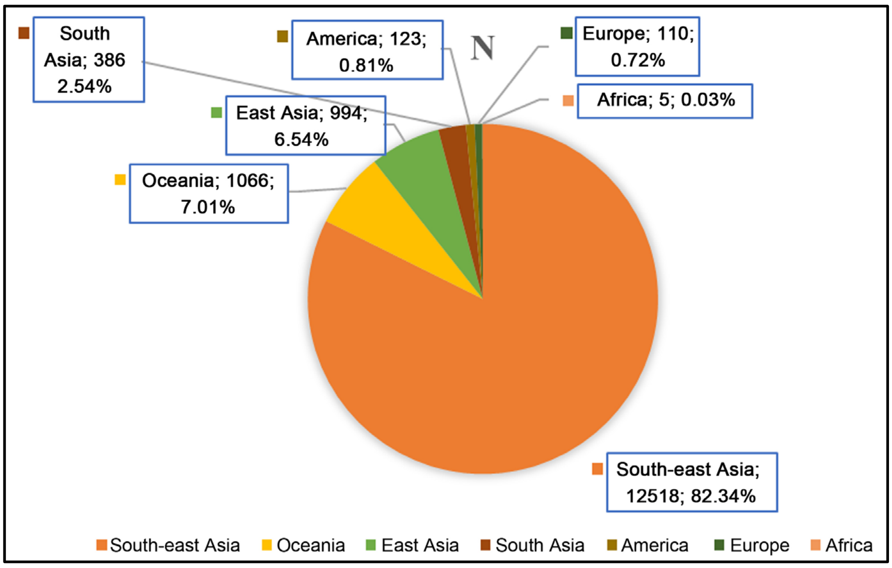


**Figure 3.** Pie chart on the number of incidence of Melioidosis across continents.

from the calculation. Of 2926 cases identified, the number of patients working in the agricultural sector was 36.5% (n = 1068) (Table 2). Among different continents, the highest percentage of agriculture workers was found in East Asia at 48.6%, followed by South-east Asia by 28%. Of all agriculture workers, the agriculture workers from Asia spans a percentage of 99.3%. There was no data in this regard from Oceania and Africa.

## 4. Discussion

### 4.1. Incidence

This review provides an update on the incidences, case fatality rates and epidemiology of Melioidosis around the world. As global awareness towards Melioidosis increases after 2015, many evidences were published in all efforts, reviewing, and updating the number of Melioidosis cases happened in different countries. Comparing our review data with the data shared by Perumal Samy *et al.* [3], the number of incidences has found to be higher in at least 16 countries and in the continent of Europe and South America (see Table 4). The only exceptions are in India with an incidence of 85 as compared to 95 recorded in 2017 and Vietnam with an incidence of 300 as compared to 70 recorded in 2017 [3]. This increase in the number had proven that Melioidosis was underdiagnosed before.

It could remain underdiagnosed as Melioidosis is listed as a notifiable disease in only a few countries/regions such as Thailand [34], Singapore [57], Taiwan [35] and Australia [58]. Data from the Laos Democratic Republic, in which it was previously absent, was also reported; this could be justified by the increasing recognition and awareness of Melioidosis in the country after the establishment of Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit (LOMWRU). LOMWRU had supported the improvement of diagnostic tests such as reagents

**Table 4.** Our study outcome in comparison to Perumal *et al.* (2017) [3].

| Country/ Region | 2017 [3] | 2020 | Country/ Region | 2017 [3] | 2020 | Country/ Region | 2017 [3] | 2020 |
|---|---|---|---|---|---|---|---|---|
| Myanmar | 100 | 298 | Taiwan | 40 | 516 | Japan | 1 | 14 |
| Malaysia | 406 | 1083 | Cambodia | 5 | 336 | Philippines | 1 | 41 |
| Singapore | 372 | 614 | Hong Kong | 6 | 61 | Sri Lanka | 1 - 3 | 250 |
| Thailand | 800 | 7690 | Southern China | 8 per year | 403 | Mexico and Central America | 3 | 75 |
| Vietnam | 300 | 70 | Bangladesh | 5 | 51 | South America | 5 | 48 |
| Australia | 252 | 1066 | India | 95 | 85 | Kenya | 0 | 5 |
| Brunei | 45 | 115 | Indonesia | 4 | 42 | Europe | 39 - 55 | 110 |

Countries included in 2017 but not in 2020: Guam, Pakistan, Papua New Guinea, Iran, Madagascar, Niger, South Africa, United States of America, Egypt, South Korea, Turkey, Saudi Arabia, United Arab Emirates, Cote d'Ivoire, Uganda

Countries included in 2020 but not in 2017: Laos

and selective culture media [33]. The support is given by Centre d'Infectiologie Christophe Mérieux du Laos (CICML) in 2009 in staff training; also the European Union provided €3,000,000 support for the development of diagnostic capacity to help in diagnosis and reporting of Melioidosis cases [33].

Our findings are consistent with the predicted data of Limmathurotsakul *et al.* in 2016. It was estimated that in 2015, there would be a global burden of 165,000 cases at an incidence rate of 5.0 per 100,000 people being at risk per year [17]. As per our calculation, there will be ~2614 incidence per observation year globally, which is lower than the predicted value. The reason could be as because Melioidosis is still being underdiagnosed and underreported in most of the countries. The predicted incidence estimated for Indonesia, Bangladesh and India was ~20,000, ~16,900 and ~52,500 cases per year, respectively [17]. Our data has shown to be lower than predicted, at 7.00, 0.89 and 1.32 cases per year, respectively.

Limmathurotsakul *et al.* (2016) mentioned that the United States of America and Japan have areas that favour the growth of *Burkholderia pseudomallei*, but no cases of Melioidosis were yet reported. Our findings reveal that there are recently reported cases in Japan but not in the United States of America. However, there are still no local cases reported from Japan as most of the cases reported recent travel history to South-east Asia [25].

## 4.2. Case Fatality Rate (CFR)

The case fatality rate of Melioidosis was reported as 10% - 50% [5] [14]. Based on our calculation, it was noted that the total case fatality rate of the 29 articles was 31.5%. We calculated the minimum ~814 cases per year to maximum ~2298 cases per year which are fatal at the percentage of 35.4; this also falls within the range of 10% - 50%. As per our calculation, lower 22.4% were apparent relative to the estimated result of 89,000 (53.9%) by Limmathurotsakul *et al.* (2016). It was also predicted that the number of case fatality for high-income countries like Australia, Brunei and Singapore would be less than 1% of total deaths, whereas more than 99% would come from low- to middle-income countries [17]. However, that is not the actual case as our result showed that the calculated CFR per year for Australia, Brunei and Singapore combined is 37.98% of total deaths. It could be due to the impact of underreporting from other countries as compared to Australia, Brunei, and Singapore.

It was known that diabetes is a significant comorbidity of Melioidosis. Therefore, the decrease in case fatality of people with Melioidosis was proposed due to the use of Glibenclamide, a diabetic drug. Being one of the established comorbidities of Melioidosis, treating patients with Melioidosis was often associated with treating their diabetes mellitus as well [5] [59]. Another reason of decrease in case fatality rate was reported by Fong *et al.* [18]. Among thalassaemic patients with comorbidity of Melioidosis, the introduction of iron chelation therapy and early diagnosis of Melioidosis helped in lowering the case fatality rate significantly [18].

The lowest CFR was found from Europe at 8.2%. Lower prevalence of comorbidities like diabetes and occurrence of bacteraemia could play a role in the low CFR rate from Europe [26]. On the other end of the spectrum is Africa at 60.0% of CFR, almost eight times to that of Europe [38]. Other than factors of comorbidity and healthcare facilities, the reason for high CFR could be due to underreporting as the whole continent is represented by the data from only Kenya [38].

The zero-fatality rate was found in China and this could be due to the intensive therapy of antibiotics given and frequent follow-ups. Moreover, all of the patients received insulin therapy, and surgical drainage was performed on those who needed [50]. The country with the highest reported CFR is Myanmar at 87.9%. The condition is attributed to the lack of awareness among healthcare providers, incomplete utilisation of facilities and lack of resources. The absence of experienced microbiologist as well as a standard treatment guideline could be the reason as well [54].

### 4.3. Age of the Respondents

The age range from 0 to 100 years old indicated that Melioidosis is not an age-specific disease as all the age groups can be affected. Of 3096 cases calculated, the number of adult cases are 2476, at 80.0% of total cases, whereas the number of paediatric cases is 620, at 20.0% (**Table 3**). Compared with the previous studies conducted in Australia and Thailand with 5% - 10% of patients of <15 years of age, our calculation found a higher percentage of paediatric cases of 20.0% [20] [22] [60]. The incidence of Melioidosis among children of Laos and Cambodia is also 3-fold higher compared to that of adults because of the association with high humidity in Laos and Cambodia [30].

Paediatric cases have a higher tendency to be underreported. In seven out of 34 articles, we did not find any information of paediatric cases which includes incidences, gender, and case fatality [32] [36] [43] [45] [47] [49] [53] [56]. Previous reports showed that Melioidosis is more common in adults than in children [61], which are consistent with our review findings. Reporting of paediatric cases as a separate entity is important. This is because most of the paediatric cases can develop an acute pulmonary infection which then followed by multiple abscesses [3]. This may cause them more likely to be highly associated with septicaemia and thus, higher case fatality rates [39]. Paediatric cases of Melioidosis are generally not associated with comorbidities, especially those that occurred mostly in adults like type 2 diabetes mellitus [22].

Besides that, they do not present themselves as a classic case of Melioidosis because symptomatic Melioidosis is uncommon in children [62]. Various factors controlled the occurrence and types of symptoms in children, such as types of transmission and host susceptibility [61]. The factors mentioned above causes the typical presentation of paediatric Melioidosis; these may be varying significantly across different geographic locations as a contrast to the adult presentation. For example, most paediatric Melioidosis reported in Darwin, Australia had an inoculation event and was usually associated with cutaneous presentation and soft tissue infection [22] [61] [63].

On the other hand, paediatric Melioidosis in South-east Asia was highly associated with acute suppurative parotitis and liver abscesses because the transmission route of Melioidosis is likely through ingestion [23] [61] [63] [64] [65]. The exception to that is Malaysia, where parotid infections are rare and only documented in 3% of children as compared to >25% of children reported in Cambodia and Thailand [23] [39] [66]. Moreover, the likelihood of bacteraemia is noted to be higher in South-east Asia than in Australia [22].

Thirdly, poor adherence to treatment and follow up is higher in children. The rate of completion of eradication treatment was only 13.7% in hospital-discharged children [23]. Poor adherence of paediatric cases to follow-up was reported in India [67]. However, more studies should be performed to understand the difference in adherence between children and adults. Lastly, paediatric cases have a lower association with gender compared to adult cases.

### 4.4. Male to Female Ratio and Occupation of the Respondents

A systematic review done by Birnie *et al.* (2019) estimated that the incidence, mortality, and disability-adjusted life year (DALY) of Melioidosis is two times higher in men than in women [68]. Our findings are also consistent with reported data. We have calculated a male to female ratio of 2.21:1 in which males have a percentage of 68.9% in 12,380 cases. There is a huge difference in male to female ratio between adult cases and paediatric cases, with a male to female ratio of 3.57:1 and 1.39:1, respectively. The difference in incidence between male and female was explained by many factors. This includes differences in genetics, risk factors, occupational preferences and exposure, access to health care [5] [14] [68]. The differences in occupational exposures apply to paediatric cases as well, as they have not had any occupation. Hence their differences in male to female ratio are lower.

In terms of the association of occupational exposures towards Melioidosis, workers from the agricultural sector are identified from each article. Of 2926 cases identified, the number of patients working in the agricultural sector is 1068 (36.5%). The high cases of agriculture workers were found in Asia, specifically in East Asia; this could be due to the cultural habit of consuming rice. Previous results only showed that Melioidosis cases from South-east Asia are highly associated with paddy field workers [14] [69]. Our review findings also have proven that Melioidosis occurred in East Asia and South Asia, and were highly associated with rice farming too. This could be due to the similar cultures that as people in South-east Asia shared with people in East Asia and South Asia. The implication of the results could be applied in choosing target groups for prevention and control of Melioidosis.

## 5. Conclusion

Melioidosis is still considered as a neglected tropical disease. In order to reduce its burden, both at the regional and global levels, significant amount of evidences needs to be generated either through conducting review or original research both at the community and health facility levels. This may help to improve the prevention, diagnosis and management, which in turn also contributes to reduce the under-reporting. We hope that this review finding will also provide significant evidence to the public health policy makers to develop an effective preventable intervention to reduce the incidence and case fatality of this neglected tropical disease globally.

## Acknowledgements

Authors would like to acknowledge the Monash University to provide the permission to use Monash University Malaysia library's extensive resources to get access to all required full-text articles. In addition, Monash University also allowed the authors to use Endnote software to remove duplicated articles.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

## References

[1] Wiersinga, W.J., Currie, B.J. and Peacock, S.J. (2012) Melioidosis. *New England Journal of Medicine*, **367**, 1035-1044. https://doi.org/10.1056/NEJMra1204699

[2] Whitmore, A. (1913) An Account of a Glanders-Like Disease Occurring in Rangoon. *Epidemiology & Infection*, **13**, 1-34.

https://doi.org/10.1017/S0022172400005234

[3] Perumal Samy, R., Stiles, B.G., Sethi, G. and Lim, L.H.K. (2017) Melioidosis: Clinical Impact and Public Health Threat in the Tropics. *PLoS Neglected Tropical Diseases*, **11**, e0004738. https://doi.org/10.1371/journal.pntd.0004738

[4] Molyneux, D.H., Savioli, L. and Engels, D. (2017) Neglected Tropical Diseases: Progress towards Addressing the Chronic Pandemic. *The Lancet*, **389**, 312-325. https://doi.org/10.1016/S0140-6736(16)30171-4

[5] Wiersinga, W.J., Virk, H.S., Torres, A.G., Currie, B.J., Peacock, S.J., Dance, D.A.B., *et al.* (2018) Melioidosis. *Nature Reviews Disease Primers*, **4**, Article No. 17107. https://doi.org/10.1038/nrdp.2017.107

[6] Depoorter, E., Bull, M.J., Peeters, C., Coenye, T., Vandamme, P., Mahenthiralingam, E. (2016) *Burkholderia*: An Update on Taxonomy and Biotechnological Potential as Antibiotic Producers. *Applied Microbiology and Biotechnology*, **100**, 5215-5229. https://doi.org/10.1007/s00253-016-7520-x

[7] Lipuma, J.J., Currie, B.J., Peacock, S.J. and Vandamme, P.A. (2015) *Burkholderia*, *Stenotrophomonas*, *Ralstonia*, *Cupriavidus*, *Pandoraea*, *Brevundimonas*, *Comamonas*, *Delftia*, and *Acidovorax*. In: Jorgensen, J.H., Carroll, K.C., Funke, G., Pfaller, M.A., Louise Landry, M., Richter, S.S. and Warnock, D.W., Eds., *Manual of Clinical Microbiology*, 11th Edition, American Society of Microbiology Press, Almere, 791-812. https://doi.org/10.1128/9781555817381.ch43

[8] Kaestli, M., Schmid, M., Mayo, M., Rothballer, M., Harrington, G., Richardson, L., *et al.* (2012) Out of the Ground: Aerial and Exotic Habitats of the Melioidosis Bacterium *Burkholderia pseudomallei* in Grasses in Australia. *Environmental Microbiology*, **14**, 2058-2070. https://doi.org/10.1111/j.1462-2920.2011.02671.x

[9] Limmathurotsakul, D., Wongsuvan, G., Aanensen, D., Ngamwilai, S., Saiprom, N., Rongkard, P., *et al.* (2014) Melioidosis Caused by *Burkholderia pseudomallei* in Drinking Water, Thailand, 2012. *Emerging Infectious Diseases*, **20**, 265-268. https://doi.org/10.3201/eid2002.121891

[10] Chen, P.-S., Chen, Y.-S., Lin, H.-H., Liu, P.-J., Ni, W.-F., Hsueh, P.-T., *et al.* (2015) Airborne Transmission of Melioidosis to Humans from Environmental Aerosols Contaminated with *B. pseudomallei*. *PLoS Neglected Tropical Diseases*, **9**, e0003834. https://doi.org/10.1371/journal.pntd.0003834

[11] Merritt, A.J., Peck, M., Gayle, D., Levy, A., Ler, Y.-H., Raby, E., *et al.* (2016) Cutaneous Melioidosis Cluster Caused by Contaminated Wound Irrigation Fluid. *Emerging Infectious Diseases*, **22**, 1420-1427. https://doi.org/10.3201/eid2208.151149

[12] Pearson, T., Giffard, P., Beckstrom-Sternberg, S., Auerbach, R., Hornstra, H., Tuanyok, A., *et al.* (2009) Phylogeographic Reconstruction of a Bacterial Species with High Levels of Lateral Gene Transfer. *BMC Biology*, **7**, Article No. 78. https://doi.org/10.1186/1741-7007-7-78

[13] Currie, B.J. (2015) Melioidosis: Evolving Concepts in Epidemiology, Pathogenesis, and Treatment. *Seminars in Respiratory and Critical Care Medicine*, **36**, 111-125. https://doi.org/10.1055/s-0034-1398389

[14] Cheng, A.C. and Currie, B.J. (2005) Melioidosis: Epidemiology, Pathophysiology, and Management. *Clinical Microbiology Reviews*, **18**, 383-416. https://doi.org/10.1128/CMR.18.2.383-416.2005

[15] Chai, L.Y.A. and Fisher, D. (2018) Earth, Wind, Rain, and Melioidosis. *The Lancet Planetary Health*, **2**, e329-e330. https://doi.org/10.1016/S2542-5196(18)30165-7

[16] Liu, X., Pang, L., Sim, S.H., Goh, K.T., Ravikumar, S., Win, M.S., *et al.* (2015) Association of Melioidosis Incidence with Rainfall and Humidity, Singapore, 2003-2012.

*Emerging Infectious Diseases*, **21**, 159-162. https://doi.org/10.3201/eid2101.140042

[17] Limmathurotsakul, D., Golding, N., Dance, D.A., Messina, J.P., Pigott, D.M., Moyes, C.L., *et al*. (2016) Predicted Global Distribution of *Burkholderia pseudomallei* and Burden of Melioidosis. *Nature Microbiology*, **1**, Article No. 15008. https://doi.org/10.1038/nmicrobiol.2015.8

[18] Fong, S.M., Wong, K.J., Fukushima, M. and Yeo, T.W. (2015) Thalassemia Major Is a Major Risk Factor for Pediatric Melioidosis in Kota Kinabalu, Sabah, Malaysia. *Clinical Infectious Diseases*, **60**, 1802-1807. https://doi.org/10.1093/cid/civ189

[19] Moreno, R.M., Jimenez Jr., V. and Monroy, F.P. (2019) Impact of Binge Alcohol Intoxication on the Humoral Immune Response during *Burkholderia* spp. Infections. *Microorganisms*, **7**, Article No. 125. https://doi.org/10.3390/microorganisms7050125

[20] Limmathurotsakul, D., Wongratanacheewin, S., Teerawattanasook, N., Wongsuvan, G., Chaisuksant, S., Chetchotisakd, P., *et al*. (2010) Increasing Incidence of Human Melioidosis in Northeast Thailand. *The American Journal of Tropical Medicine and Hygiene*, **82**, 1113-1117. https://doi.org/10.4269/ajtmh.2010.10-0038

[21] Currie, B.J., Jacups, S.P., Cheng, A.C., Fisher, D.A., Anstey, N.M., Huffam, S.E., *et al*. (2004) Melioidosis Epidemiology and Risk Factors from a Prospective Whole-Population Study in Northern Australia. *Tropical Medicine & International Health*, **9**, 1167-1174. https://doi.org/10.1111/j.1365-3156.2004.01328.x

[22] McLeod, C., Morris, P.S., Bauert, P.A., Kilburn, C.J., Ward, L.M., Baird, R.W., *et al*. (2015) Clinical Presentation and Medical Management of Melioidosis in Children: A 24-Year Prospective Study in the Northern Territory of Australia and Review of the Literature. *Clinical Infectious Diseases*, **60**, 21-26. https://doi.org/10.1093/cid/ciu733

[23] Turner, P., Kloprogge, S., Miliya, T., Soeng, S., Tan, P., Sar, P., *et al*. (2016) A Retrospective Analysis of Melioidosis in Cambodian Children, 2009-2013. *BMC Infectious Diseases*, **16**, Article No. 688. https://doi.org/10.1186/s12879-016-2034-9

[24] Lim, M., Tan, E., Soh, C. and Chang, T. (1997) *Burkholderia pseudomallei* Infection in the Singapore Armed Forces from 1987 to 1994—An Epidemiological Review. *Annals of the Academy of Medicine*, *Singapore*, **26**, 13-17.

[25] Hadano, Y. (2018) Imported Melioidosis in Japan: A Review of Cases. *Infection and Drug Resistance*, **11**, 163-168. https://doi.org/10.2147/IDR.S154696

[26] Le Tohic, S., Montana, M., Koch, L., Curti, C. and Vanelle, P. (2019) A Review of Melioidosis Cases Imported into Europe. *European Journal of Clinical Microbiology & Infectious Diseases*, **38**, 1395-1408. https://doi.org/10.1007/s10096-019-03548-5

[27] Hempenstall, A.J., Smith, S., Stanton, D. and Hanson, J. (2019) Melioidosis in the Torres Strait Islands, Australia: Exquisite Interplay between Pathogen, Host, and Environment. *American Journal of Tropical Medicine & Hygiene*, **100**, 517-521. https://doi.org/10.4269/ajtmh.18-0806

[28] Abu Hassan, M.R., Aziz, N., Ismail, N., Shafie, Z., Mayala, B., Donohue, R.E., *et al*. (2019) Socio-Epidemiological and Land Cover Risk Factors for Melioidosis in Kedah, Northern Malaysia. *PLoS Neglected Tropical Diseases*, **13**, e0007243. https://doi.org/10.1371/journal.pntd.0007243

[29] Araúz, A.B., Castillo, K., Santiago, E., Quintero, Y., Adames, E., Castillo, B., *et al*. (2020) Geographic Distribution and Incidence of Melioidosis, Panama. *Emerging Infectious Diseases*, **26**, 118-121. https://doi.org/10.3201/eid2601.180870

[30] Bulterys, P.L., Bulterys, M.A., Phommasone, K., Luangraj, M., Mayxay, M., Klo-

progge, S., *et al.* (2018) Climatic Drivers of Melioidosis in Laos and Cambodia: A 16-Year Case Series Analysis. *The Lancet Planetary Health*, **2**, e334-e343. https://doi.org/10.1016/S2542-5196(18)30172-4

[31] Chowdhury, F.R., Shariful Alam Jilani, M., Barai, L., Rahman, T., Saha, M.R., Robed Amin, M., *et al.* (2018) Melioidosis in Bangladesh: A Clinical and Epidemiological Analysis of Culture-Confirmed Cases. *Tropical Medicine and Infectious Disease*, **3**, Article No. 40. https://doi.org/10.3390/tropicalmed3020040

[32] Corea, E.M., De Silva, A.D. and Thevanesam, V. (2018) Melioidosis in Sri Lanka. *Tropical Medicine and Infectious Disease*, **3**, Article No. 22. https://doi.org/10.3390/tropicalmed3010022

[33] Dance, D.A.B, Luangraj, M., Rattanavong, S., Sithivong, N., Vongnalaysane, O., Vongsouvath, M., *et al.* (2018) Melioidosis in the Lao People's Democratic Republic. *Tropical Medicine and Infectious Disease*, **3**, Article No. 21. https://doi.org/10.3390/tropicalmed3010021

[34] Hantrakun, V., Kongyu, S., Klaytong, P., Rongsumlee, S., Day, N.P.J., Peacock, S.J., *et al.* (2019) Clinical Epidemiology of 7126 Melioidosis Patients in Thailand and the Implications for a National Notifiable Diseases Surveillance System. *Open Forum Infectious Diseases*, **6**, Article No. ofz498. https://doi.org/10.1093/ofid/ofz498

[35] Hsueh, P.T., Huang, W.T., Hsueh, H.K., Chen, Y.L. and Chen, Y.S. (2018) Transmission Modes of Melioidosis in Taiwan. *Tropical Medicine and Infectious Disease*, **3**, Article No. 26. https://doi.org/10.3390/tropicalmed3010026

[36] Jatapai, A., Gregory, C.J., Thamthitiwat, S., Tanwisaid, K., Bhengsri, S., Baggett, H.C., *et al.* (2018) Hospitalized Bacteremic Melioidosis in Rural Thailand: 2009-2013. *American Journal of Tropical Medicine & Hygiene*, **98**, 1585-1591. https://doi.org/10.4269/ajtmh.17-0402

[37] Lui, G., Tam, A., Tso, E.Y.K., Wu, A.K.L., Zee, J., Choi, K.W., *et al.* (2018) Melioidosis in Hong Kong. *Tropical Medicine and Infectious Disease*, **3**, Article No. 91. https://doi.org/10.3390/tropicalmed3030091

[38] Muthumbi, E.M., Gordon, N.C., Mochamah, G., Nyongesa, S., Odipo, E., Mwarumba, S., *et al.* (2019) Population-Based Estimate of Melioidosis, Kenya. *Emerging Infectious Diseases*, **25**, 984-987. https://doi.org/10.3201/eid2505.180545

[39] Nathan, S., Chieng, S., Kingsley, P.V., Mohan, A., Podin, Y., Ooi, M.H., *et al.* (2018) Melioidosis in Malaysia: Incidence, Clinical Challenges, and Advances in Understanding Pathogenesis. *Tropical Medicine and Infectious Disease*, **3**, Article No. 25. https://doi.org/10.3390/tropicalmed3010025

[40] Pande, K., Kadir, K.A.A., Asli, R. and Chong, V.H. (2018) Melioidosis in Brunei Darussalam. *Tropical Medicine and Infectious Disease*, **3**, Article No. 20. https://doi.org/10.3390/tropicalmed3010020

[41] Pang, L., Harris, P.N.A., Seiler, R.L., Ooi, P.L., Cutter, J., Goh, K.T., *et al.* (2018) Melioidosis, Singapore, 2003-2014. *Emerging Infectious Diseases*, **24**, 140-143. https://doi.org/10.3201/eid2401.161449

[42] Rolim, D.B., Lima, R.X.R., Ribeiro, A.K.C., Colares, R.M., Lima, L.D.Q., Rodríguez-Morales, A.J., *et al.* (2018) Melioidosis in South America. *Tropical Medicine and Infectious Disease*, **3**, Article No. 60. https://doi.org/10.3390/tropicalmed3020060

[43] San Martin, P.F.M., Chua, J.C., Bautista, R.L.P., Nailes, J.M., Panaligan, M.M. and Dance, D.A.B. (2018) Melioidosis in the Philippines. *Tropical Medicine and Infectious Disease*, **3**, Article No. 99. https://doi.org/10.3390/tropicalmed3030099

[44] Sanchez-Villamil, J.I. and Torres, A.G. (2018) Melioidosis in Mexico, Central America, and the Caribbean. *Tropical Medicine and Infectious Disease*, **3**, Article

No. 24. https://doi.org/10.3390/tropicalmed3010024

[45] Smith, S., Stewart, J.D., Tacon, C., Archer, N. and Hanson, J. (2017) Children with Melioidosis in Far North Queensland Are Commonly Bacteraemic and Have a High Case Fatality Rate. *Communicable Diseases Intelligence Quarterly Report*, **41**, E318-E321.

[46] Stephens, D.P., Thomas, J.H., Ward, L.M. and Currie, B.J. (2016) Melioidosis Causing Critical Illness: A Review of 24 Years of Experience from the Royal Darwin Hospital ICU. *Critical Care Medicine*, **44**, 1500-1505. https://doi.org/10.1097/CCM.0000000000001668

[47] Stewart, J.D., Smith, S., Binotto, E., McBride, W.J., Currie, B.J. and Hanson J. (2017) The Epidemiology and Clinical Features of Melioidosis in Far North Queensland: Implications for Patient Management. *PLoS Neglected Tropical Diseases*, **11**, e0005411. https://doi.org/10.1371/journal.pntd.0005411

[48] Suttisunhakul, V., Hip, P., Ouch, P., Ly, P., Supaprom, C., Rachmat, A., *et al*. (2018) Retrospective Analysis of Fever and Sepsis Patients from Cambodia Reveals Serological Evidence of Melioidosis. *American Journal of Tropical Medicine & Hygiene*, **98**, 1039-1045. https://doi.org/10.4269/ajtmh.17-0885

[49] Tang, R.Y., Lim, S.H., Lam, J.E., Salim, N., Toh, S.S.E. and Chan, Y.W. (2019) A 5-Year Retrospective Study of Melioidosis Cases Treated in a District Specialist Hospital. *Medical Journal of Malaysia*, **74**, 472-476.

[50] Tang, Y., Deng, J., Zhang, J., Zhong, X., Qiu, Y., Zhang, H., *et al*. (2018) Epidemiological and Clinical Features of Melioidosis: A Report of Seven Cases from Southern Inland China. *American Journal of Tropical Medicine & Hygiene*, **98**, 1296-1399. https://doi.org/10.4269/ajtmh.17-0128

[51] Tauran, P.M., Wahyunie, S., Saad, F., Dahesihdewi, A., Graciella, M., Muhammad, M, *et al*. (2018) Emergence of Melioidosis in Indonesia and Today's Challenges. *Tropical Medicine and Infectious Disease*, **3**, Article No. 32. https://doi.org/10.3390/tropicalmed3010032

[52] Tipre, M., Kingsley, P., Smith, T., Leader, M. and Sathiakumar N. (2018) Melioidosis in India and Bangladesh: A Review of Case Reports. *Asian Pacific Journal of Tropical Medicine*, **11**, 320-329. https://doi.org/10.4103/1995-7645.233179

[53] Trinh, T., Hoang, T., Tran, D., Trinh, V., Göhler, A., Nguyen, T., *et al*. (2018) A Simple Laboratory Algorithm for Diagnosis of Melioidosis in Resource-Constrained Areas: A study from North-Central Vietnam. *Clinical Microbiology and Infection*, **24**, 84.e1-84.e4. https://doi.org/10.1016/j.cmi.2017.07.029

[54] Win, M.M., Ashley, E.A., Zin, K.N., Aung, M.T., Swe, M.M.M., Ling, C.L., *et al*. (2018) Melioidosis in Myanmar. *Tropical Medicine and Infectious Disease*, **3**, Article No. 28. https://doi.org/10.3390/tropicalmed3010028

[55] Yazid, M.B., Fauzi, M.H., Hasan, H., Noh, A.Y. and Deris, Z.Z. (2017) An 11-Year Analysis of Emergency Presentations of Melioidosis in Northeastern Malaysia. *Journal of Immigrant & Minority Health*, **19**, 774-777. https://doi.org/10.1007/s10903-016-0429-8

[56] Zheng, X., Xia, Q., Xia, L. and Li, W. (2019) Endemic Melioidosis in Southern China: Past and Present. *Tropical Medicine and Infectious Disease*, **4**, Article No. 39. https://doi.org/10.3390/tropicalmed4010039

[57] Sim, S.H., Ong, C.E.L., Gan, Y.H., Wang, D., Koh, V.W.H., Tan, Y.K., *et al*. (2018) Melioidosis in Singapore: Clinical, Veterinary, and Environmental Perspectives. *Tropical Medicine and Infectious Disease*, **3**, Article No. 31. https://doi.org/10.3390/tropicalmed3010031

[58] Smith, S., Hanson, J. and Currie, B.J. (2018) Melioidosis: An Australian Perspective. *Tropical Medicine and Infectious Disease*, **3**, Article No. 27. https://doi.org/10.3390/tropicalmed3010027

[59] Koh, G.C., Maude, R.R., Schreiber, M.F., Limmathurotsakul, D., Wiersinga, W.J., Wuthiekanun, V., *et al*. (2011) Glyburide Is Anti-Inflammatory and Associated with Reduced Mortality in Melioidosis. *Clinical Infectious Diseases*, **52**, 717-725. https://doi.org/10.1093/cid/ciq192

[60] Currie, B.J., Ward, L. and Cheng, A.C. (2010) The Epidemiology and Clinical Spectrum of Melioidosis: 540 Cases from the 20 Year Darwin Prospective Study. *PLoS Neglected Tropical Diseases*, **4**, e900. https://doi.org/10.1371/journal.pntd.0000900

[61] Sanderson, C. and Currie, BJ. (2014) Melioidosis: A Pediatric Disease. *The Pediatric Infectious Disease Journal*, **33**, 770-771. https://doi.org/10.1097/INF.0000000000000358

[62] Cheng, A.C., Wuthiekanun, V., Limmathurotsakul, D., Chierakul, W. and Peacock, S.J. (2008) Intensity of Exposure and Incidence of Melioidosis in Thai Children. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **102**, S37-S39. https://doi.org/10.1016/S0035-9203(08)70010-5

[63] Dance, D., Davis, T., Wattanagoon, Y., Chaowagul, W., Saiphan, P., Looareesuwan, S., *et al*. (1989) Acute Suppurative Parotitis Caused by *Pseudomonas pseudomallei* in Children. *Journal of Infectious Diseases*, **159**, 654-660. https://doi.org/10.1093/infdis/159.4.654

[64] Limmathurotsakul, D. and Peacock, S.J. (2011) Melioidosis: A Clinical Overview. *British Medical Bulletin*, **99**, 125-139. https://doi.org/10.1093/bmb/ldr007

[65] Stoesser, N., Pocock, J., Moore, C.E., Soeng, S., Chhat, H.P., Sar, P., *et al*. (2012) Pediatric Suppurative Parotitis in Cambodia 2007-2011. *The Pediatric Infectious Disease Journal*, **31**, 865-868. https://doi.org/10.1097/INF.0b013e318258873b

[66] Lumbiganon, P. and Viengnondha, S. (1995) Clinical Manifestations of Melioidosis in Children. *The Pediatric Infectious Disease Journal*, **14**, 136-139. https://doi.org/10.1097/00006454-199502000-00010

[67] Mukhopadhyay, C., Eshwara, V.K., Kini, P. and Bhat, V. (2015) Pediatric Melioidosis in Southern India. *Indian Pediatrics*, **52**, 711-712.

[68] Birnie, E., Virk, H.S., Savelkoel, J., Spijker, R., Bertherat, E., Dance, D.A.B., *et al*. (2019) Global Burden of Melioidosis in 2015: A Systematic Review and Data Synthesis. *Lancet Infectious Diseases*, **19**, 892-902. https://doi.org/10.1016/S1473-3099(19)30157-4

[69] Limmathurotsakul, D., Kanoksil, M., Wuthiekanun, V., Kitphati, R., de Stavola, B., Day, N.P., *et al*. (2013) Activities of Daily Living Associated with Acquisition of Melioidosis in Northeast Thailand: A Matched Case-Control Study. *PLoS Neglected Tropical Diseases*, **7**, e2072. https://doi.org/10.1371/journal.pntd.0002072

[70] Birnie, E, Savelkoel, J., Reubsaet, F., Roelofs, J.J.T.H., Soetekouw, R., Kolkman, S., *et al*. (2019) Melioidosis in Travelers: An Analysis of Dutch Melioidosis Registry Data 1985-2018. *Travel Medicine and Infectious Disease*, **32**, Article ID: 101461. https://doi.org/10.1016/j.tmaid.2019.07.017

## List of Abbreviations

CICML: Centre d'Infectiologie Christophe Mérieux du Laos;
CFR: Case Fatality Rate;
DALY: Disability-Adjusted Life Year;
LOMWRU: Lao-Oxford-Mahosot Hospital-Wellcome Trust Research Unit;
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta Analyses;
WHO: World Health Organisation.