

## Review Article: A Review of Melioidosis Cases in the Americas

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**Abstract.** Melioidosis is a bacterial infection caused by *Burkholderia pseudomallei*, a gram-negative saprophytic bacillus. Cases occur sporadically in the Americas with an increasing number of cases observed among people with no travel history to endemic countries. To better understand the incidence of the disease in the Americas, we reviewed the literature, including unpublished cases reported to the Centers for Disease Control and Prevention. Of 120 identified human cases, occurring between 1947 and June 2015, 95 cases (79%) were likely acquired in the Americas; the mortality rate was 39%. *Burkholderia pseudomallei* appears to be widespread in South, Central, and North America.

### INTRODUCTION

Cases of melioidosis are commonly seen in tropical and subtropical areas.<sup>1</sup> *Burkholderia pseudomallei*, formerly known as Whitmore bacillus, *Pseudomonas pseudomallei*, or *Malleomyces pseudomallei*, is the causative agent of melioidosis.<sup>2</sup> Infection most frequently occurs through contact with soil and water in endemic areas through inhalation, inoculation, or ingestion,<sup>3</sup> with increasing evidence of ingestion playing a greater role in infection than historically thought.<sup>4,5</sup> Infections may also occur after laboratory exposures when enhanced precautions such as those used in biosafety level 3 facilities are not used during testing of isolates from infected patients or animals.<sup>6–8</sup> The federal select agent program designates *B. pseudomallei* as a Tier 1 overlap select agent.<sup>9</sup> Melioidosis is not nationally notifiable in the United States.<sup>10,11</sup> Thus, Centers for Disease Control and Prevention (CDC) receives reports on cases of melioidosis from state health departments, medical facilities, microbiologic laboratories, and research facilities on a voluntary basis.

Cases have been reported in both humans and animals.<sup>3</sup> Melioidosis infections in sheep, goats, swine, cattle, primates, horses, dogs, cats, and wildlife species are well documented.<sup>12–20</sup> Although human-to-human transmission is rare, one reported patient most likely acquired the infection through sexual transmission.<sup>21</sup> In addition, testing of soil samples or water in Peru,<sup>22</sup> Brazil,<sup>22–24</sup> Haiti,<sup>22</sup> Venezuela,<sup>25</sup> Ecuador,<sup>25</sup> and Puerto Rico<sup>26</sup> has revealed the presence of *B. pseudomallei* in the environment in these locations. In one study, *B. pseudomallei* was recovered from environmental specimens (soap, floor, and shower hose) in a burn unit of a hospital in Belo Horizonte, Brazil.<sup>27</sup>

A prior review of melioidosis cases in the Americas described 105 cases with an association (residence when diagnosed, travel history, or country of birth) to the Americas.<sup>28</sup> Two of the cases (one case reported from Oklahoma in 1976 and the other reported from Georgia in 1979) have since been reclassified as infections with the closely related bacteria *Burkholderia oklahomensis*.<sup>29</sup> An additional 84 cases reported in that series occurred in soldiers/veterans with a history of service in Vietnam. Another review reported more than 340 cases among U.S. soldiers with service to Vietnam.<sup>30,31</sup>

Our review focuses on *B. pseudomallei* infections acquired in the Americas.

### MATERIALS AND METHODS

**Search strategy.** We conducted a literature review of human cases diagnosed with melioidosis with residence, travel history, or country of birth associated with the Americas, including the United States and its territories. In addition, we reviewed all case reports voluntarily submitted by states to the CDC between January 2008 and December 2013.

We first conducted a search of seven databases from their inception to October 2013: PubMed of the National Library of Medicine (1996), Web of Science (1980), Excerpta Medica Databases (1974), Global Health (1910), Latin American and Caribbean Health Sciences Literature (1982), and Google Scholar (2004). Keywords used included combinations of “melioidosis,” “*Burkholderia pseudomallei*,” “Western Hemisphere,” “America,” and “Caribbean.”

In June 2015, we conducted a broader search of case reports, meta-analyses, reviews, scientific integrity reviews, and systematic reviews from the same databases using combinations of keywords such as “*Burkholderia pseudomallei*,” “*Pseudomonas pseudomallei*,” “Whitmore bacillus,” “melioidosis,” and “*Malleomyces pseudomallei*.” There were no geographic limiters, language, gender, age, or dates applied to this second search strategy. Our search strategies resulted in a total of 1,937 articles. An additional 15 articles were identified through hand searching, citations from other articles, and correspondence with subject matter experts. After deduplication, the remaining 884 articles were evaluated for relevancy. Final selection of articles was based on the following criteria: description or review of a case or cases diagnosed in the Americas, or with travel history in the Americas, or residence in the Americas. A total of 61 articles (from 1945 to 2015) met our inclusion criteria (Figure 1). Although the majority of selected articles were published in English, four articles were published in French, two in Portuguese, and one in Spanish. Articles in French were translated by author Tina J. Benoit. Abstracts and case summaries published in Portuguese were already translated into English by the journal. A summary of a case published in Spanish was also already translated into English by the journal. Summaries of two cases published in Spanish were translated to English by a CDC Spanish speaker senior epidemiologist. All

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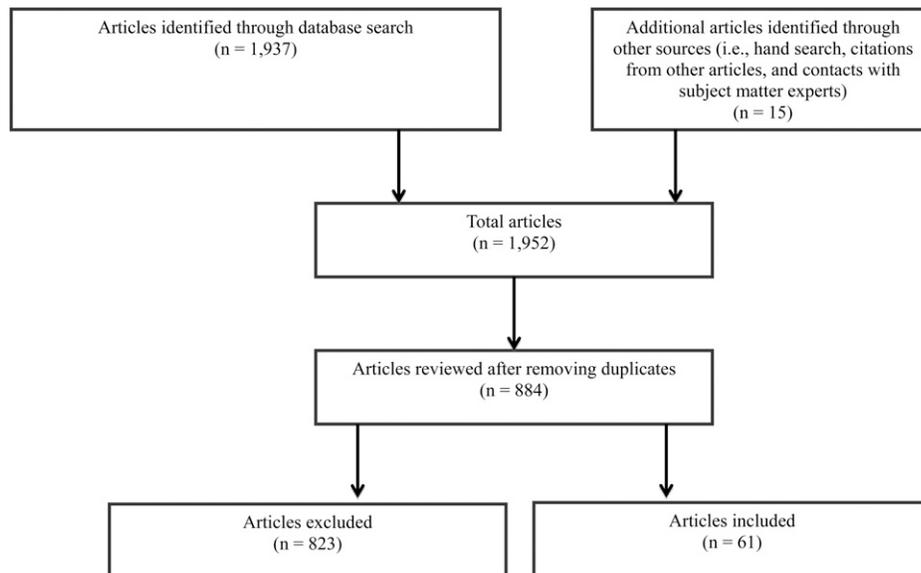


FIGURE 1. Flow chart of complex literature review of melioidosis cases in the Americas.

confirmed and probable cases were included in this review. Confirmed cases were defined as having a positive culture or isolation of *B. pseudomallei* from any clinical specimen. Probable cases were defined as having a positive result for *B. pseudomallei* polymerase chain reaction or a 4-fold rise in *B. pseudomallei* antibody titer (indirect hemagglutination assay [IHA]) between acute and convalescent samples taken 2 weeks apart. A library of all relevant references (including articles identified through other sources) was built using EndNote X6 software ([www.EndNote.com](http://www.EndNote.com)) for bibliographic management.

**Data abstraction.** The following data were abstracted from each article when available: year of diagnosis, gender, age, race, occupation, country of diagnosis, diagnostic laboratory results, travel history and/or country of birth of the patient, signs and symptoms, preexisting medical conditions, risk factors, possible exposures, treatment, and patient outcomes. The year of diagnosis was documented as the year of publication of the article if such information was not reported in the article. For cases series, the year of diagnosis was documented as unknown in the online Supplemental Appendix 1.

**Data analysis, map, and graphs.** The IBM Statistical Package for Social Sciences (SPSS) version 19 for Windows (Armonk, NY) was used for data analysis. ArcGIS ArcMAP version 10.2.1 (ESRI, Redlands, CA) was used to generate the map (Figure 2).

**Classification of countries in the Americas.** The U.S. Central Intelligence Agency 2004 *World Factbook* was used as a reference guide in classifying countries into North, Central, and South America.<sup>32</sup>

## RESULTS

Of 120 cases reviewed (Supplemental Appendix 1), 95 cases (79%) were believed to have had acquired the infection in the Americas (Table 1, Figure 2). The remaining 25 cases (Table 2) were either born in or had travel history to melioidosis-endemic countries.

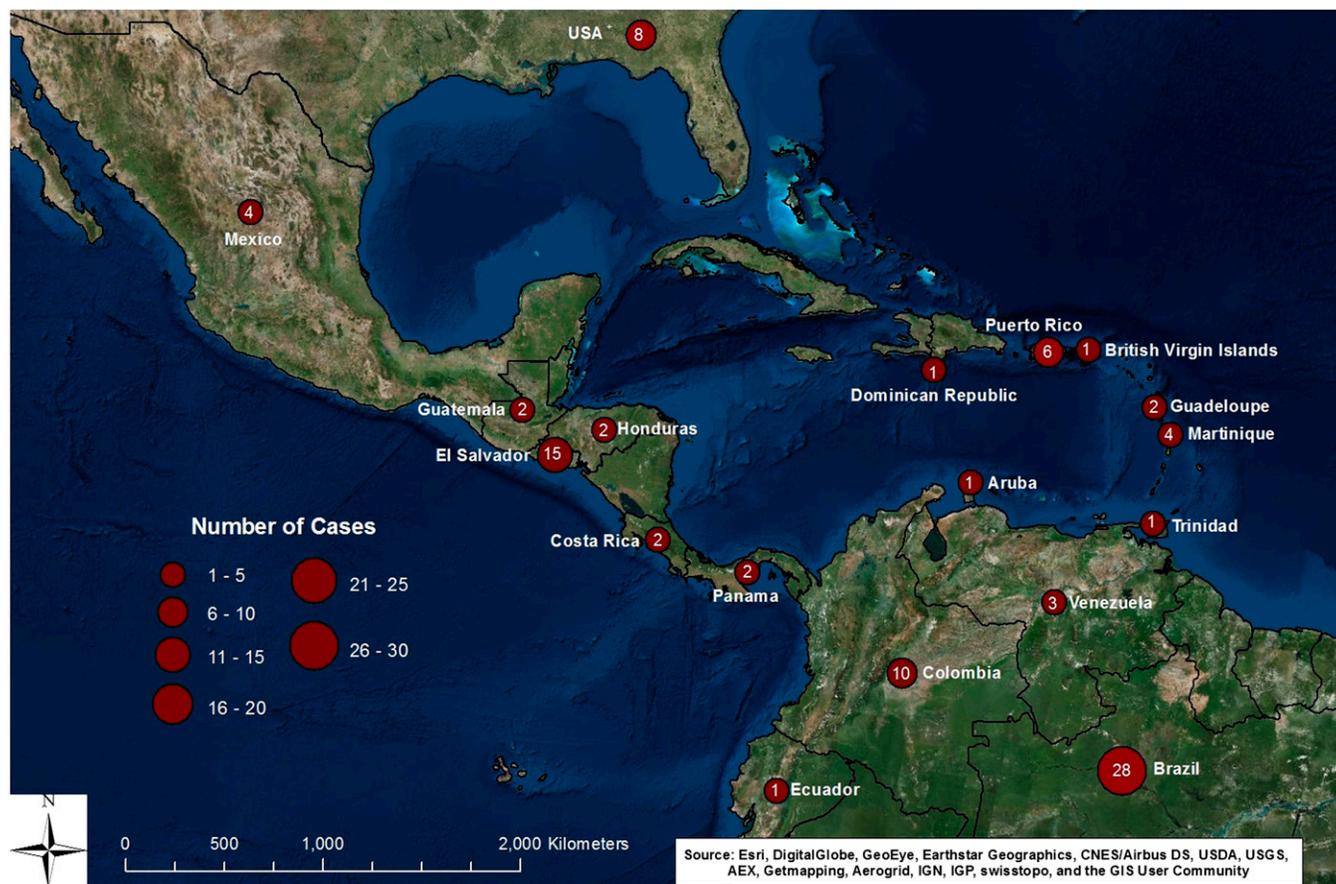
Among those cases with reported source of exposure to *B. pseudomallei* in the Americas (47 of 95 cases), approxi-

mately 20% reported contact with soil only, 7% reported contact with water only, and 17% reported contact with both, soil and water (Table 3). This is consistent with other reports from endemic regions.

**North America.** Twelve cases were likely acquired in either the U.S. mainland (7 cases), Hawaii (1 case) or Mexico (4 cases). Two of the U.S. mainland cases potentially acquired the infection through occupational exposure. One individual worked with *B. pseudomallei* in a laboratory.<sup>6</sup> The other individual, a zoological warehouse employee, may have acquired the infection through contact with reptiles (case no. 76 in the online Supplemental Appendix 1; CDC, unpublished data), as melioidosis has been reported in iguanas sold in the United States.<sup>33</sup> An African-American infant diagnosed soon after birth likely acquired the infection in utero. The infant's father was a Vietnam veteran with unknown disease status.<sup>34</sup> A fourth individual may have acquired infection through sexual transmission. The patient's husband was a U.S. veteran with travel history to Hong Kong, Japan, Mexico, and the Philippines.<sup>21</sup> The source of infection for the other three cases from U.S. mainland,<sup>35-37</sup> one case from Hawaii,<sup>38</sup> and all four cases from Mexico (Supplemental Appendix 1) remains unknown.

**Central America and the Caribbean.** Cases have been reported from every country in Central America, except Belize and Nicaragua. El Salvador, Puerto Rico, and Martinique have the highest number of cases in Central America and the Caribbean (Table 1).

Five of six cases from Puerto Rico reported exposure to environmental sources such as soil, flood water, or both, while one source of exposure was unknown. None of the six had traveled outside Puerto Rico or the U.S. mainland. Most cases (13 of 15 cases) from El Salvador were Salvadoran residents and reported never traveling outside the country. The authors also did not report the year of diagnosis for those cases. Two patients that likely acquired disease in El Salvador were U.S. residents. One patient was from a 47-year-old U.S. born male with travel history to El Salvador 3 weeks before diagnosis. The other patient was a 37-year-old



Two cases are not shown above. One case had a travel history to multiple locations such as Aruba and several other Caribbean countries. The other case had a travel history to Trinidad and Tobago.

\* Seven cases were in mainland USA and one was in Hawaii.

FIGURE 2. Distribution of melioidosis cases in the Americas.\*

Salvadoran female resident of the United States and believed to have acquired infection in El Salvador.

Two of the four patients from Martinique reported no travel history outside Martinique and thus likely acquired the infection there. A third individual, a 66-year-old Martinique resident had traveled to non-endemic areas of Africa and South America more than 40 years before diagnosis. The authors reported that the patient never lived in rural areas and that the source of infection remained unknown.<sup>39</sup> The last patient was a resident of Switzerland who became ill shortly after a 10-day visit to Martinique.<sup>40</sup>

**South America.** Thirty-seven cases from 1962 to 2015 with suspected origin in South America were reported from Brazil, Colombia, Venezuela, and Ecuador. Brazil accounted for the majority (67%) of South American cases (Table 1), with the State of Ceará in northeast Brazil accounting for 91% of cases reported in Brazil.<sup>23,41</sup> Since 2003, there have been 25 cases of melioidosis, including one family cluster, reported in Brazil. This cluster was reported among four siblings, of which three died, from a rural area of Ceará following contact with water after the rainy season.<sup>41,42</sup>

## DISCUSSION

Historically, melioidosis has been described as endemic in southeast (SE) Asia, south Asia, and northern Australia.

However, our review of the literature indicates the need to update the epidemiology of melioidosis and expand the list of countries with sporadic occurrence or that may be considered endemic. Since the last review of melioidosis in the Americas,<sup>28</sup> more than 2 dozen cases have been identified in patients with no travel history outside their native country in the Americas or in patients with travel history only within the Americas. The increasing occurrence of melioidosis in Brazil, as well as reports of the disease acquired in Central and North America suggests the disease is endemic in many countries throughout the Americas. The environmental conditions present in many of these countries, as well as environmental isolates of *B. pseudomallei*, support the possibility of endemicity in these areas.<sup>26</sup>

A bit puzzling are the three cases reported from the United States with no travel history outside the U.S. mainland.<sup>35-37</sup> One was reported as a chronic case.<sup>35</sup> In the other two<sup>36,37</sup> cases, extensive investigations took place, including detailed travel history, occupational history, and recreation and hobbies; in addition, environmental sampling around the home environment was carried out and serology was conducted on family members and pets. In both cases, no source of *B. pseudomallei* was identified and there was no serologic evidence of exposure in family members or pets. However, both patients had been hospitalized for several weeks before identification of *B. pseudomallei*, and strain types

TABLE 1

Number of cases in the Americas by classification of countries of likely exposure or acquisition, 1947–2015

	Number of cases
North America	
United States (mainland)*	7
Mexico	4
Noncontiguous United States (Hawaii)	1
Total	12
Central America and the Caribbean	
El Salvador	15
United States (Puerto Rico)	6
Martinique	4
Costa Rica	2
Guadeloupe	2
Guatemala	2
Honduras	2
Panama	2
Aruba	1
Aruba or other Caribbean countries†	1
British Virgin Islands	1
Dominican Republic	1
Trinidad	1
Trinidad or Tobago‡	1
Total	41
South America	
Brazil	28
Colombia	10
Venezuela	3
Ecuador	1
Total	42
Grand Total	95

\*Two cases with likely occupational exposure in the United States, five cases acquired elsewhere in the Americas.

†Patient with travel history to multiple locations such as Aruba and several Caribbean countries.

‡Patient with travel history to Trinidad and Tobago.

were consistent with SE Asian origin. The most recent case in an Ohio resident was found to be internal transcribed spacer (ITS) type CE, which is commonly seen in SE Asia and Australia but not in the Western Hemisphere.<sup>37,43,44</sup> Since melioidosis is not considered endemic to the United States (mainland),<sup>45</sup> it raises the question of whether contaminated medical supplies (intravenous supplies, medications, etc.) could have been imported from an endemic area, lead-

TABLE 2

Number of cases with likely exposures outside the Americas

Countries	Number of cases	Percent
Thailand	3	12
Vietnam	3	12
Philippines	3	12
Cambodia	2	8
India	2	8
Malaysia	2	8
Africa	1	4
China	1	4
Southeast Asia	1	4
Hong Kong, Vietnam, Japan, Mexico, or the Philippines	1	4
Indonesia	1	4
Laos or Cambodia	1	4
Laos or Thailand	1	4
Saudi Arabia or Bangladesh	1	4
Singapore, Malaysia, Burma, or Thailand	1	4
Vietnam, southeast and central Asia, Iraq, or Afghanistan	1	4
Total	25	100

TABLE 3

Distribution of exposure sources among the 47 cases in the Americas with reported risks, 1945–2015

	Frequency	Percent
Soil	19	20
Water	7	7
Soil and water	16	17
Animals	2	2
Sexual contact	1	1
In utero	1	1
Occupational exposure	1	1
Total	47	100

ing to a nosocomial acquisition of *B. pseudomallei*. However, *B. pseudomallei* could also have been introduced through plants or other commodities imported from endemic areas. Cases are more likely imported by travelers, animals, or environmentally contaminated materials from endemic countries.

The increasing number of cases seen with acquisition in the Americas since the first review of melioidosis in the Americas by Inglis and others<sup>28</sup> raises the question of why this disease is being seen with increasing frequency. Specifically, does the epidemiology of melioidosis in the Americas differ from that elsewhere, or are the increasing numbers a reflection of increased awareness of this disease? Gee and others<sup>44</sup> have noted that ITS type G is found predominantly in Western Hemisphere isolates of *B. pseudomallei*, and is rarely seen outside the Western Hemisphere. This could support the theory that melioidosis exhibits a different clinico-epidemiologic presentation in the Americas. However, our review found no evidence of any differences epidemiologically in the cases reported or with underlying clinical conditions. Mortality rates are similar to that seen elsewhere where melioidosis is endemic. We therefore feel that the increasing numbers seen are a reflection of increased awareness and identification of melioidosis among clinicians and laboratories.

This review has the major limitation of relying solely on peer-reviewed and published case reports, which sometimes lacked detailed information on source of exposure. Additional unpublished cases were mentioned during our review, and we have no doubt that many cases have gone either unpublished or unidentified because of lack of familiarity with *B. pseudomallei* by clinicians and laboratory staff. Also worth noting is that melioidosis is not a nationally reportable disease in the United States, so even cases presumptively identified at the local level may not be reported to the CDC or other public health agencies. Furthermore, many of the published case reports reviewed did not contain travel history. Finally, many of the published reports lacked information on underlying medical illness/risk factors and exposure history, limiting our ability to investigate clinico-epidemiologic patterns in more detail. With these limitations noted, this report is a more comprehensive review of melioidosis cases with presumed acquisition of infection in the Americas, providing an update to the seminal publication by Inglis and others and contributing to better understanding of the global and regional distribution of melioidosis.

Continued improvement in the accurate and timely diagnosis of melioidosis cases is crucial to understanding the incidence and epidemiology of the disease in the Americas. The early identification of *B. pseudomallei* infection and the initiation of appropriate antimicrobial treatment will also reduce

morbidity and mortality of melioidosis. Recent publications have addressed current diagnostics and future directions<sup>46</sup>; in the meantime, physicians and laboratory personnel should be sensitized to the presence of melioidosis in the Americas. In addition, areas with clusters of melioidosis, such as in the State of Ceará, may consider additional studies, such as community serosurveys to delineate endemic areas and to allow health-care systems to focus resources where they are needed to address this emerging disease.

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**Disclaimer:** The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the CDC or the U.S. Department of Health and Human Services.

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