Melioidosis in India and Bangladesh: A review of case reports

Meghan Tipre[1✉], Paul Vijay Kingsley[2], Tamika Smith[1], Mark Leader[1], Nalini Sathiakumar[1]

[1]Department of Epidemiology, School of Public Health, University of Alabama, Birmingham, AL 35294–0022, USA
[2]Pantai Hospital Ipoh, Ipoh 31400, Malaysia

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ABSTRACT

Objective: To conduct an epidemiological and clinical review of published case reports of melioidosis from India and Bangladesh. **Methods:** Data from published case reports were abstracted and summarized. We further compared the clinical epidemiology of the melioidosis cases in India with case series from highly endemic areas in Northern Australia and Southeast Asia to elucidate any differences in presentations and risk factors between the regions. **Results:** We identified a total of 99 cases published between 1953 and June 2016, originating from India (n=85) or Bangladesh (n=14). Cases were predominantly male and ranged in age from 1 month to 90 years. Diabetes mellitus was the most common risk factor reported (58%). About 28% of the cases had history of exposure via high-risk occupations or exposure to contaminated water. The overall case fatality rate (CFR) was 26%. Factors influencing mortality included the occurrence of septic shock (CFR, 80%), environmental exposure (CFR, 39%), primary presentation of pneumonia (CFR, 38%), misdiagnosed and/or mistreated cases (CFR, 33%) or the presence of a risk factor (CFR, 29%). Because of the small number of cases in Bangladesh, pattern of clinical epidemiology is limited to India. Soft tissue abscess (37%) was the most common clinical presentation reported from India followed by pneumonia (24%) and osteomyelitis/septic arthritis (18%). Neurological melioidosis (n=10, 12%) presented as pyemic lesions of the brain or meninges. A few cases of prostatic abscess (n=4) in men and parotid abscess (n=4) were also noted. The above patterns were consistent with case series from Southeast Asia and Northern Australia for the most part, in terms of risk factors associated with infection and factors influencing mortality. Differences included clinical presentation of pneumonia which was notably lower than that reported in Southeast Asia and Northern Australia; a higher proportion of neurological and parotid abscess presentation; and a lower CFR compared to that reported in case series in Southeast Asia. About 39% of the cases were misdiagnosed and/or mistreated, suggesting underreporting and under estimation of the true disease burden. **Conclusions:** The concentration of melioidosis cases in southern and eastern states in India and in Bangladesh, which share climatic conditions and rice farming activities with known endemic areas in Southeast Asia, suggests an endemicity of melioidosis in this region. Thus, increased awareness among healthcare personnel, particularly among clinicians and nurses practicing in rural areas, and improved surveillance through case registries is essential to guide early diagnosis and prompt treatment.

1. Introduction

Melioidosis, also known as 'Whitmore's Disease,' is an infectious disease caused by a bacterium, *Burkholderia pseudomallei* (*B. pseudomallei*, previously known as *Pseudomonas pseudomallei*). *B. pseudomallei* is found in soil and water, and can infect human or animals. Melioidosis presents as a febrile illness with protean manifestations ranging from chronic localized infections to acute fulminant septicemia with dissemination to multiple organs characterized by abscesses[1]; the disease has a high case fatality rate (CFR) ranging from 16% to 44% in known endemic regions[2].

✉First and corresponding author: Meghan Tipre, BDS, DrPH, Department of Epidemiology, School of Public Health, University of Alabama at Birmingham, 1665 University Blvd. RPHB 523, Birmingham, AL 35294-0022, USA.
Tel: 832-665-5150
Fax: 205-975-7058
E-mail: meghan24@uab.edu

Several risk factors are associated with melioidosis including immunosuppressive conditions such as diabetes and other diseases, and certain drug treatments, one or more of which are found in 60%–90% of cases[2–4]. Diabetes mellitus is the most common risk factor and increases the relative risk of melioidosis to 20-fold[2,5].

Melioidosis is known to be endemic in Southeast Asia and Northern Australia. The recent update on the global distribution of melioidosis has expanded these endemic areas to include the Indian subcontinent[6]. However, there is no systematic reporting of melioidosis in most of the South Asian countries including India, except Sri Lanka which began an active surveillance program in 2014[7]. Therefore, we conducted a detailed review of published case reports of melioidosis from India and Bangladesh to obtain an insight into the epidemiology and clinical spectrum of melioidosis in these countries. We further compared the clinical epidemiology of the cases with case series from highly endemic areas in Southeast Asia and Northern Australia to elucidate any differences in clinical presentations and risk factors.

2. Methodology

For this review, we identified published case reports of melioidosis originating from India and Bangladesh by searching literature resources including PUBMED, MEDLINE, COCHRANE Reviews, Google Scholar, World Health Organization's Global Health Library and reference lists from the earliest case of melioidosis published until June 2016. Seventy-two papers qualified for this review. We did not attempt to include any unpublished data on case reports that may be available in these countries.

Acute infections were defined as those presenting symptoms for less than 2 months and within 2 months of inoculation[8]. Chronic infections were defined as those presenting with symptoms for 2 or more months with infection acquired in the recent or remote past[8]. Cases were further categorized as those with or without septic shock; and those with or without bacteremia. Bacteremia was defined as those with positive blood culture for *B. pseudomallei*. Clinical presentations were classified into the following primary diagnostic groups: (i) pneumonia–including associated complications such as pleural effusion, lung abscess; (ii) soft tissue infections–infections of non-skeletal tissue surrounding or supporting organs and other structures including subcutaneous tissue, muscle, lymph nodes, blood vessels and soft tissue organs namely the liver or spleen; (iii) osteomyelitis/septic arthritis–infection of bones, joints, ligaments, or cartilage; (iv) neurological–brain and spinal cord including meninges and the peripheral nervous system; (v) genitourinary–infection of the urinary and genital systems including the kidneys; (vi) skin; and (vii) no evident focus[4].

3. Results

We identified a total of 99 culture-confirmed cases published between 1953 and June 2016 originating from India (*n*=85)[9–64] or Bangladesh (*n*=14)[65–72]. Spatial mapping of cases showed

that most were concentrated in southern states in India, while fewer were spread across the eastern coastal states extending up to Bangladesh (Figure 1). Cases, India and Bangladesh combined, were predominantly male and the age range was wide (1 month to 90 years). Diabetes mellitus was the most common risk factor reported (57/99, 58%). A history of exposure either by engaging in high-risk occupations or exposure to contaminated water was reported in 28% (28/99)of the cases. Soft tissue abscess was the most commonly reported primary clinical presentation followed by pneumonia and osteomyelitis/septic arthritis; these three presentations constituted 78% of all cases. Internal abscesses were noted mostly in the lung, liver, spleen, brain, and subcutaneous tissue. About 60% of cases had a secondary focus of infection. The overall CFR was 26% (26/99); factors influencing mortality included the occurrence of septic shock [CFR, 80%(12/15)], history of environmental exposure [CFR, 39%(11/28)], primary presentations of pneumonia [CFR, 38%(9/24)], misdiagnosed/mistreated cases [CFR, 33%(13/39)], and the presence of a risk factor [CFR, 29%(22/77)]. About 1/3 of cases (39/99, 39%) were misdiagnosed and mistreated for other conditions, notably tuberculosis, enteric fever or septicemia. Below, cases in India are discussed followed by cases in Bangladesh.
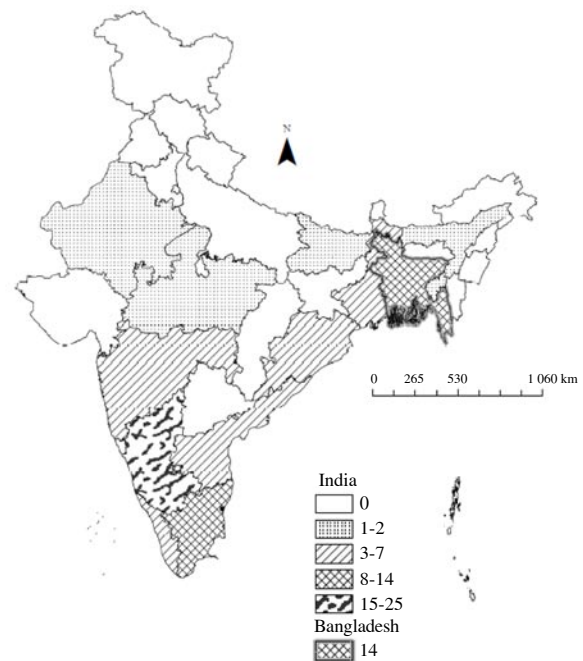
Figure 1. Spatial distribution of culture-confirmed melioidosis cases in India and Bangladesh.

3.1. India

3.1.1. Spatial distribution

A total of 85 culture-confirmed cases of melioidosis were reported from India between 1953 and June 2016. Figure 1 indicates the different states in India from where the cases were reported. Majority of the cases were concentrated in the southern states including Karnataka (*n*=22) and Tamil Nadu (*n*=17). Other major states included Andhra Pradesh and West Bengal, reporting seven cases each.

3.1.2. Demographic characteristics

Cases' ages ranged from 1 month to 71 years of age [(41±17) years, mean±SD] including 10 children; cases were predominantly male (76%) (Table 1). Information on occupation was not reported for 44 cases; 19%(14/74) of cases were engaged in agriculture one of whom was a female. The overall CFR was 27%; no remarkable differences in CFRs were noted by age or gender.

Table 1

Distribution of confirmed melioidosis cases by selected demographic characteristics and occupation and country.

Characteristics	India		Bangladesh	
	Total	Deaths [n(%)][*□]	Total	Deaths [n(%)][†□]
All	85	23(27)	14	3(21)
Age (years)				
≤18	11	3(30)	1	1(100)
19–55	60	17(28)	9	1(11)
>55	14	3(21)	4	1(25)
Mean±SD	41±17		53±20	
Median	45(35–54)		49(41–59)	
Range	0.1–71.0		0.6–90.0	
Gender				
Male	65	18(28)	11	2(18)
Female	20	5(25)	3	1(33)
Occupation[‡]				
Agriculture	14	3(21)	1	1(100)
Service sector	7	1(14)	1	1(100)
Construction	3	1(33)	0	0(0)
Mining	1	1(100)	0	0(0)
Business	3	1(33)	1	0(0)
Carpenter	1	0(0)	0	0(0)
Homemaker	1	0(0)	1	0(0)
Not reported[□]	44	13(30)	10	1(13)

[*]Outcome unknown (n=3); [†]Outcome unknown (n=5); [‡]Excludes children (India: n=11; Bangladesh: n=1); [□]The percentages are based across each category.

3.1.3. Risk factors

Table 2 presents the various risk factors including comorbid conditions and environmental exposures, and the associated CFRs. Type 2 diabetes was reported in 45 cases (53%) with a CFR of 27%; data on history of diabetes was missing for 25% of the cases. Other risk factors included history of tuberculosis (n=5), alcoholism (n=5), chronic liver disease (n=4), and chronic renal disease (n=2). About 29% (n= 25) had a history of environmental exposure through accidental drowning, employment in rice farming, mining or construction, with a CFR of 40%. Of the 25 cases with environmental exposure, 7 cases reported a history of accidental exposure to contaminated water with a CFR of 71%, compared to a CFR of 28% among those with environmental exposure from farming, mining or construction (P=0.03). Such episodes included near drowning (n=2), contact with stagnant water (n=1), bathing in contaminated water 15 d prior to infection (n=1), participating in relief operations following a cyclonic storm (n=1), 2-week vacation in Malaysia (n=1) and open defecation and cleaning with contaminated water (n=1). About 12 cases presented with no history of any risk factor, while information regarding any risk factor was missing for 6 cases.

Table 2

Risk factors, exposure history and associated deaths in cases.

Risk factors	India (n=85)		Bangladesh (n=14)	
	Cases [n(%)][*]	CFR [n(%)][*□]	Cases [n(%)][*]	CFR [n(%)][†□]
Any risk factor	66(78)	20(30)	11(79)	2(18)
No risk factor	12(14)	2(17)	-	-
Missing	7(8)	1(14)	3(21)	-
Environmental exposure	25(29)	10(40)	3(21)	1(33)
Comorbid conditions				
Diabetes	45(53)	12(27)	12(86)	2(17)
Tuberculosis	5(6)	1(20)	2(14)	1(50)
Pre-term birth	2(2)	1(50)	-	-
Chronic liver disease	4(5)	1(25)	-	-
Chronic renal disease	2(2)	-	-	-
Splenectomy	1(1)	1(100)	-	-
Marasmic kwashiorkor	1(1)	-	-	-
Hypertension	1(1)	-	-	-
Pesticide poisoning	1(1)	1(100)	-	-
Goiter	-	-	1(7)	-
Alcoholism	5(6)	1(20)	-	-

[*]Outcome unknown (n=3); [†]Outcome unknown (n=5); [□]The percentages are based across each category.

3.1.4. Clinical presentation

Of the total of 85 cases, 71(84%) presented as acute infections and 13(15%) as chronic infections; information on duration of disease

Table 3

Deaths based on primary diagnostic groups and bacteremic status, India (%)[□].

Item	Total	Bacteremia	Non-bacteremia	Not reported
Total	27(23/85)	35(12/34)	22(4/18)	21(7/33)
Septic shock	75(9/12)	63(5/8)	100(2/2)	100(2/2)
Soft tissue abscess	67(4/6)	50(2/4)	100(1/1)	100(1/1)
Pneumonia	80(4/5)	75(3/4)	-	100(1/1)
Osteomyelitis/septic arthritis	100(1/1)	-	100(1/1)	-
Septic shock not present or not reported	19(14/73)	27(7/26)	13(2/16)	16(5/31)
Soft tissue abscess	8(2/25)	29(2/7)	0(0/7)	0(0/11)
Pneumonia	20(3/15)	29(2/7)	20(1/5)	0(0/3)
Osteomyelitis/septic arthritis	14(2/14)	17(1/6)	-	13(1/8)
Neurological	40(4/10)	0(0/1)	33(1/3)	50(3/6)
Genitourinary	100(1/1)	100(1/1)	-	-
Cutaneous	0(0/1)	0(0/1)	-	-
No specific focus	29(2/7)	33(1/3)	0(0/1)	33(1/3)

[□]The percentages are based across each category.

Table 4

Secondary clinical foci for major primary diagnostic groups.

Primary clinical presentation	India			Bangladesh		
	Total	Secondary foci [n(%)]	Common secondary foci (n)	Total	Secondary foci [n(%)]	Common secondary foci (n)
All cases	85	53(62)		14*	6(40)	
Pneumonia	20	18(90)	Liver (4); Spleen (5); Subcutaneous (2); Brain (3); Kidney (1); Other muscle abscess (1); Pericarditis (1)	4	1(25)	Liver (1); Spleen (1); Kidney (1)
Osteomyelitis/septic arthritis	15	8(53)	Lung (5); Spleen (3);Subcutaneous (1); Brain (3); Lymphadenitis (2); Prostrate (1); Other muscle abscess (1)	4	3(75)	Lung (1); Spleen (1); Prostate (2); Gall bladder (1)
Soft tissue abscess	31	16(52)	Lung (8); Liver (3); Spleen (4); Subcutaneous (10); Brain (2); Prostate (1); Kidney (1); Lymphadenitis (2); Other muscle abscess (5); Mediastinal mass (1); Para-intestinal abscess (3); Heart (1); Psoas abscess (1)	4	2(50)	Lung (1); Liver (1); Spleen (1); Subcutaneous (1); Urinary bladder (1)
Neurological	10	4(40)	Lung (1); Liver (1); Subcutaneous (1); Lymphadenitis (1); Urinary bladder (1)			
Genitourinary	1		Prostate (1)			-
Cutaneous	1					-
No specific focus	7	7(100)	Lung (2); Liver (3);Spleen (1); Prostate (1); Kidney (1); Gall bladder (1)			

*Primary clinical presentation information is missing for two cases.

onset was not available for one case. The most common clinical presentation was soft tissue abscess (n=31; 36%) followed by pneumonia (n=20; 24%), osteomyelitis and/or septic arthritis (n=15; 18%) and neurological (n=10; 12%); all other primary diagnostic groups were less frequent: genitourinary (n=1); and cutaneous infections (n=1) (Table 3). A specific focus was not found in seven cases at the time of presentation. Septic shock was reported in 12 cases with a CFR of 75%. In comparison, the CFR among cases without septic shock was 19%. Bacteremia was reported in 34 cases with a CFR of 35% (n=12) and was most frequently observed in primary presentations of pneumonia (n=11) and soft tissue abscesses (n=11). The mortality was higher among cases presenting with pneumonia (45%) compared to those with soft tissue abscess (36%); however, the difference was not statistically significant (P=0.80) (Table 3). Among those whose blood culture tested negative (n=18), the CFR was 22%. Bacteremic status was not reported for 33 patients.

Ten cases (12%) presented with involvement of the central nervous system, manifesting as brain abscess, meningitis or osteomyelitis of cranial bones. The CFR was 40%. The age range was 35–65 years, and two of them were women. Presenting symptoms included headache, drowsiness, episodes of seizures, altered sensorium, increased intracranial pressure and high-grade fever. Four cases were found to have brain abscesses and two of these cases had signs of meningitis; one case presented with pyogenic meningitis and a C6 vertebrae fracture and died before any specific treatment was initiated. In two of the cases, computerized tomography and or magnetic resonance imaging of the brain showed parietal abscesses and in the third case, the dura was observed to be breached and the pus seen tracking into brain parenchyma forming cerebral abscesses. Osteomyelitis of the skull bones was observed in two cases based on imaging of the brain.

3.1.5. Secondary foci of infection

About 62% (n=53) of cases had secondary foci of infection besides the primary presentation (Table 4). With the exception of cutaneous and genitourinary presentations, all other primary diagnostic groups had one or more secondary foci of infection. Secondary foci frequently involved the abdominal visceral organs including lung (n=16), spleen (n= 13) or liver (n=11). Brain was involved in 8 cases where the primary presentation was either pneumonia or other soft tissue abscesses involving liver, spleen or parotid gland or cranial osteomyelitis.

The frequency of involvement of internal organs is presented in Table 5. Lung (n=36, 42%), liver (n=18, 21%), brain (n=18, 21%) and spleen (15, 18%) were most often affected as part of disseminated or localized infection with an acute or chronic onset. Other internal organs included subcutaneous (n=14, 16%), muscle abscess other than psoas (n=7), lymph nodes (n=5), prostate (n=4), parotid gland (n=4), kidney (n=3), para-intestinal area (n=3), and one each in the psoas, gall bladder, urinary bladder, mediastinal cavity, pericardium and heart.

Table 5

Internal organs abscesses among cases according to country.

Site	India (n=85)		Bangladesh (n=14)	
	n	%	n	%
Lung	36	42	6	43
Liver	18	21	2	14
Spleen	15	18	3	21
Sub-cutaneous	14	16	1	7
Brain	18	21		
Other muscle abscess†	7	8		
Lymphadenitis	5	6		
Prostate*	4	5	3	21
Parotid	4	5		
Para-intestinal	3	4		
Kidney	3	4	1	7
Psoas abscess	1	1		
Urinary bladder	1	1	1	7
Gall bladder	1	1	1	7
Mediastinal mass	1	1		
Pericarditis/myocarditis	1	1		
Heart	1	1		

*Percentage calculated for men; †Other than psoas abscess.

3.1.6. Treatment and misdiagnosis

Of the total 85 cases, 70 cases were treated with intensive phase regimen followed by eradication phase regimen. Of the 70, 66 cases were treated by the first line of drugs that included intravenous (IV) ceftazidime, meropenem or imipenem. Four cases were treated by the second line agents that included IV amoxicillin–clavulanate, IV meropenem, with oral trimethoprim. The CFR among those treated with first or second line of drugs was 7%. Fifteen cases did not receive the appropriate treatment regimen; 13 of these 15 patients died (CFR, 87%). The lack of treatment was either due to a misdiagnosis or because the patient died before treatment could be initiated.

A total of 38 cases were misdiagnosed and treated initially for other causes; the CFR among these patients was 34% (13/38) compared to 21% (10/47) among those diagnosed accurately for melioidosis (P=0.18). The most common cause of misdiagnosis was tuberculosis (n=18). Other causes included pneumonia, enteric fever, pyogenic infections, septicemia, respiratory infections, pseudomyxoma peritonei, complicated malaria, dengue fever, acute rheumatic fever, urinary tract infection, diabetic ketoacidosis, pyelonephritis, or lymphoproliferative disorders.

3.1.7. Comparison of clinical epidemiology with other case series.

The median age of cases in the present review was comparable with the median age in Sri Lankan and Malaysian series; however, it was slightly lower than the Australian and the Thailand series (Table 6). Male preponderance was similar to Sri Lanka but higher than that noted from the Malaysia, Thailand, and Australian case series. Environmental exposure, reported in 29% of cases, was lowest compared to all other series. All the three series including Sri Lanka, Thailand and Australia reported twice as many cases with environmental exposure (78%–81%)[4,73-76]. About 78% of the Sri Lankan cases were predominantly reported from rural areas with rice farming[73]; 75% of the Australian group was considered to have exposure through recreational activities[4]; and 84% of the Thai study group were farmers in an endemic area[74]. The proportion of cases with diabetes (53%) is close to the lower range of that reported in case series from Southeast Asia (60%–75%)[73,74,76], while Australia reports only 39% of the cases with history of diabetes[4].

Table 6

Comparisons of selected results from the present case review and of previously published case reviews of from India, Sri Lanka, Malaysia and Northern Australia.

Characteristics	Present review (*n*=85) India	Corea EM, 2016[96] (*n*=32) Sri Lanka	Zueter *et al.*, 2016[76] (*n*=158) Malaysia	Currie *et al.*, 2010[4] (*n*=540) Australia	Suputtamong-kol *et al.*,1999[74]; Cheng & Curie, 2005[3]; (*n*=204[a]; 686[b]), Thailand
Geographic area	India (all states)	Sri Lanka (15/25 districts in 8/9 provinces	Kubang Kerian, Kelantan	Top End, Australia	Northeastern Thailand[a,b]
Data source	Published cases	National surveillance	A hospital laboratory	Prospective study	4-hospital case-control study[a]; 6 hospitals[b]
Time period	1953–2016	2006–2014	2001–2015	1989–2009	1997[a]; vary between 1978–1985[b]
Inclusion criteria	Confirmed cases	Culture+ve cases	Confirmed cases	Culture+ve cases	Culture+ve cases
Demographic					
Age, median (years)	45	41–50	46[*]	55	58[a]
Male:female ratio	3.3:1	4:1	2.8:1	2.2:1	1.6:1[a]
Risk factor					
Environment exposure %	29	78	-	81	81[a]
Diabetes mellitus %	53	63	75	39	60[a]
No risk factor %	14.1	5.7	16.0	20.0	36.0[a]
Primary dx groups					
Pulmonary %	23	31	41	51	45[b]
Soft tissue abscess/skin %	37	63	28	16	34
Bone and joint %	18	19	13	4	5[b]
Genitourinary %	1.2	-	3.2	14.0	7.0[b]
Neurologic %	11.8	3.1	5.7	2.6	3.0[b]
No clinical focus %	8.2	6.3	22.0	11.0	-[b]
Primary or secondary					
Liver abscess %	21	28	12	3	7[b]
Splenic abscess %	17.6	13.0	9.5	5.0	2.0[b]
Prostate abscess %[†]	4.7	-	2.6	20.0	0.3[b]
Parotid abscess %	4.7	-	2.5[‡]	-	2.0[b]
Mycotic pseudoaneurysm %	1.2	-	-	<1.0	-[b]
Pericardial effusion %	1.2	3.1	-	<1.0	3.0[b]
Bacteremia %	40	56	77	55	58[b]
Septic shock %	14	56	34	21	-[b]
Mortality %	27	28	33	14	38–61[b]

%, calculated as percentage of total number of cases; -Not recorded; [*]Estimated; [†]Computed for males; Reference [a]: Suputtamong-kol *et al.*, 1999[74]; [b]: Cheng & Curie, 2005[3].

3.2. Bangladesh

A total of 14 cases of melioidosis were reported from Bangladesh between 1988 and 2016. Cases ranged in age from 6 months to 90 years with an average of 53 years (SD, 20 years); 11 were men (Table 1). Twelve of the 14 cases had history of diabetes mellitus (Table 2). Three of the cases had contact with contaminated water or soil. Clinically, cases presented with pneumonia (n=4), osteomyelitis or septic arthritis (n=4) or soft tissue abscess (n=4); data on clinical presentation was missing in two cases (Table 4). A secondary focus of infection was reported in six cases. Lung followed by spleen and prostate gland were the most frequently affected internal organs (Table 5). Outcome was reported in only three of the 14 cases; all three cases were fatal. No other information including treatment was provided for most cases.

4. Discussion

The current review summarizes clinical findings and risk factors for melioidosis cases identified from India or Bangladesh, and it is based on case reports. In light of the paucity of systematic data on melioidosis, review of case reports aid in understanding the clinical spectrum of the disease in specific regions and may play a significant role in medical education facilitating early diagnosis and prompt treatment. Though case reports due to their intrinsic methodologic limitations are placed at the foot of the hierarchy of clinical evidence, they generate useful information towards evidence-based medicine[77]. However, as typical, unremarkable cases are less likely to be reported or published, use of case reports as scientific evidence must take into account publication bias. Disease registries overcome the limitations of case reports.

In this review, we noted that cases were concentrated in Southern India and extending along the Eastern coast to Bangladesh. Rice farming, a known risk factor associated with melioidosis[3,74,76], is a primary agricultural activity in this region. Further, climatic conditions such as rainfall and temperature in the region are similar to known endemic regions. Bangladesh and eastern states in India including West Bengal and Orissa also shares similar agricultural practices and climatic conditions as the endemic areas. However, fewer cases were reported from these areas which may be due to underreporting of cases.

Several factors may contribute to underreporting. The first factor is a low index of clinical suspicion by physicians. Secondly, melioidosis tends to be misdiagnosed due to the broad spectrum of clinical presentations as well as similarities with other diseases such as tuberculosis, enteric fever or other bacterial diseases causing pneumonia or pyogenic infections common in these regions. This is supported by the high proportion of misdiagnosed cases (38/85, 45%) noted in this review. The third factor is the lack of adequate laboratory support to confirm a diagnosis of melioidosis.

In general, B. pseudomallei from sterile samples of blood, sputum, pus or cerebrospinal fluid can be grown in blood agar or MacConkey agar. On sheep blood agar, B. pseudomallei is typically small,

smooth, cream-colored with a metallic sheen, and may develop a dry or wrinkled appearance upon incubation beyond 24–48 h which at times may take up to 5 d[78]. On MacConkey agar, colonies are lactose, non-fermenting, and colorless, and may develop a metallic sheen with a pinkish, rugose appearance after ≥48 h. In selective media such as Ashdown's, the colonies are typically pinpoint in size at 18 h and develop into purple, flat, wrinkled colonies at 48 h[78]. The Ashdown medium is used to differentiate the B. pseudolammei colonies from other Gram-negative bacteria when the samples are taken from non-sterile sites[79]. A positive oxidase and a negative indole test, an earthy putrid odor from the culture plates (although sniffing may increase the risk of laboratory exposure) and resistance to antibiotics such as polymyxins and gentamicin can provide additional confirmation. A definitive diagnosis of the bacterium should include molecular identification through some assays like TTS1 real-time PCR[80] or latex agglutination[81]. In resource limited laboratory settings in endemic areas where laboratory facilities are limited, a combination of findings from Gram's stain, culture, biochemical profile and antibiotic sensitivity pattern supported by high-level of clinical suspicion may be sufficient to make a probable diagnosis of melioidosis. This may aid in prompt and appropriate treatment.

Most cases from India were reported from tertiary care hospitals which are supported by well-equipped laboratories. Patients were referred to these tertiary hospitals after unsuccessful diagnosis and treatment in primary care hospitals which are typically located in rural areas. Failure to identify the infection in the primary care settings may be due to a combination of lack of awareness and/ or required laboratory facilities to isolate the organism. It can also be noted that increased awareness among selected hospitals have increased the identification and reporting of melioidosis cases from these hospitals particularly in the state of Karnataka.

The diverse age range of cases reflects the potential of the disease to affect any age group. A preponderance of male cases may be due to social norms in India and Bangladesh where farming and related occupational sectors are dominated by men[82].

We found diabetes to be the most common risk factor for melioidosis. South Asia has collectively the world's largest pool of diabetic patients. With more than 35 million people living with diabetes[83], it has potentially the largest population at risk for the disease. Other risk factors were related to immunosuppressive conditions either due to disease or drugs. About 6% of cases reported history of alcoholism; details on frequency and amount were not available. There is good evidence that binge drinking, rather than chronic liver disease is associated with increased melioidosis risk due to suppression of host's immunity[84]. This is further supported by our finding that there was no overlap of history of alcoholism with chronic liver disease in this review.

We found a CFR of 27% which is lower than that reported in known endemic countries such as Thailand (CFR, 38%–61%) and Malaysia (CFR, 33%). Majority of cases were reported from tertiary hospitals which are well-equipped with laboratories and facilities for management of acute respiratory failure and septic shock. Thus, the observed low CFR may not reflect the true mortality of the disease.

Septic shock was the foremost predictor of mortality among all cases (CFR, 75%). This is consistent with other case series. For example, Cheng *et al.* observed a CFR of 96% in severe sepsis patients diagnosed with melioidosis in Thailand[85]. History of inhalation of contaminated water following an accidental near-drowning or swimming in contaminated water carried a high mortality rate of 71%. This is supported by similar findings in other studies from known endemic regions including Thailand and Cambodia[74,86]. A higher mortality was also reported among misdiagnosed/mistreated cases (CFR, 34%). Since the management of melioidosis is distinct and very specific to the disease, a delay in treatment has been noted to increase the mortality rate to as high as 40%–60%[87]. The treatment for melioidosis includes the administration of antimicrobials for 6–8 months. The initial intensive-phase therapy comprises of third generation antibiotics such as ceftazidime, imipenem or meropenem administered intravenously for 10–14 d followed by ambulatory eradication phase therapy of 3–6 months of oral trimethoprim/sulfamethoxazole, which is preferred over a combination of trimethoprim/sulfamethoxazole plus doxycycline on the basis of safety and tolerance by patients[88,89]. Studies have also indicated that mistreatment by other antibiotics as a result of misdiagnosis may result in multi-drug resistance[7,90].

As variations in clinical presentations have been reported by geographic region, we compared our review of cases from India with those reported in the Sri Lanka, Malaysia, Australia and Thailand case series[4,73,74,91]. Because of the small number of cases, Bangladesh is not included in this comparison. Pulmonary infection is known to be most common presentation of melioidosis ranging from 41% to 51% in case series from Malaysia, Thailand and Northern Australia[3,74,76,84]. However, in this review, soft tissue abscess (37%) was the most commonly reported primary clinical presentation followed by pneumonia (24%). A similar trend was observed in the Sri Lankan case series which reported 63% of cases with soft tissue abscess and 31% cases with pneumonia[73]. The lower percentage of pneumonia may be due to the high mortality associated with pneumonia within 24 h which may preclude accurate diagnosis; and that case reports not being a systematic compilation of cases may underrepresent the typical pattern. Our study found a 3-fold higher mortality among pneumonia cases compared to soft tissue infections.

Compared to the case series in Sri Lanka, Malaysia, Thailand and Northern Australia, a higher proportion (12%) of neurological cases were noted in our study based on 10 cases; all other series reported 2.6%–5.7% of neurological cases. The clinical presentations of neurological melioidosis were mainly pyemic, brain abscess and/or pyogenic meningitis. Zueter *et al.* reported brain abscesses in 6% in their Malaysian series[76]. In Northern Australia, a distinct syndrome of brain stem encephalomyelitis presenting with flaccid paralysis has been reported in 3% of cases. This syndrome appears to be uncommon in South Asia and Southeast Asia. A study conducted in Australia found that patients infected by the *B. pseudomallei etbimA$_{Bm}$* variant were 14 times more likely to present with neurological involvement compared with patients infected with the *bimABp*

variant (95% *CI*=4.7–44.6)[92]. To date, *B. pseudomallei etbimA$_{Bm}$* have been reported from Australia and in India[92,93] suggesting that the *etbimA$_{Bm}$* may be associated with neurological melioidosis in India. However, in the absence of molecular typing data, no firm conclusions can be made. Further, the higher occurrence of neurological melioidosis may be accounted in part by publication bias.

Prostatic abscess in melioidosis appears to have a differing regional distribution varying from a high of 20% in Northern Australia[4] to 0.3% in Thailand[3,74]. This review noted prostate abscesses in 6.2% of males occurring most commonly in association with other intra-abdominal abscesses specifically of the liver or spleen.

Likewise, parotid abscess appears to have differing regional distribution. About 2% of cases in the Thailand case series presented with parotid abscess; none were reported in the Australian case series. In this review, all of the parotid gland abscesses (*n*=4, 4.7%) occurred among females, two of whom were pediatric cases aged 3 and 12 years. Cases presented as suppurative parotitis with meningoencephalitis in one of the cases. One child had a history of tuberculosis. All cases were successfully treated. It is plausible that the higher proportion of parotid abscess in India may be due to exposure to *B. pseudomallei* through ingestion of unchlorinated drinking water[94,95]. A majority of rural population in India have limited access to chlorinated drinking water which may increase their risk of contracting melioidosis. In contrast, the high rates of chlorination of water supplies in Australia may explain the rarity of parotid abscess in the country[95].

The higher prevalence of environmental exposures in Sri Lankan, Thailand and Australian cases series (78%–81%) may possibly be due to inadequate information provided on environmental exposures in the Indian case reports[4,73–76].

Our review indicates that there is a critical need to increase education and awareness of melioidosis and its management among medical professionals especially in areas where laboratory facilities are inadequate for early diagnosis of the disease. As there is a wide range of age groups presenting with melioidosis, all clinicians from pediatricians to geriatricians should have a high index of clinical suspicion. There is a need to develop epidemiology at the community level through studies which include population seroprevalence assessment and selective environmental investigations. Seroepidemiological studies provide a valuable insight into disease exposure of a community, and clustering of susceptible individuals within specific age, occupational or geographic groups. Careful attention to the environmental microbiology of *B. pseudomallei* will provide important insight for developing risk reduction strategies identifying vulnerable populations in vulnerable environments. There is also need for improved diagnostic facilities that should be rapid, specific, simple and affordable and establishments of rapid communication between various levels of laboratories in these countries. Without improving microbiological expertise and extending its application, as well as epidemiological skills and practices, emerging and re-emerging diseases may not be recognized, identified or intercepted in their early stages. Further, studies should be carried out to assess knowledge, attitude and

practices of people employed in high-risk occupations which are risk factors for melioidosis. Surveys of physicians, laboratory technicians and medical staff should be carried out to assess knowledge of the disease especially in regions, where the infection appears to be endemic.

Overall, studies exploring the role of preventive measures, early clinical identification, and better management of severe sepsis are required to reduce the fatality from this disease. Effective surveillance can also play an important role in the early containment of the disease. Concurrently, the establishment of statewide melioidosis registries would be useful to estimate the disease incidence and trends by geographic area, and to ascertain the effectiveness of measures to reduce disease incidence. Such registries can provide health care professionals and researchers with accurate information on the clinico-epidemiologic patterns, and in tracking trends in the incidence, mortality and treatment of melioidosis. Also, using uniform criteria for reporting cases and primary diagnostic groups will increase the specificity of reporting and improve the comparability of information reported from different geographic regions.

In conclusion, melioidosis is an under-diagnosed disease in the South Asian region. Historically, Southeast Asia is known to be endemic for melioidosis; however, increasing number of cases reported from India and Bangladesh suggest that certain regions in these countries may be more endemic than earlier assumed. A distinct geographical pattern particularly indicates that Southern India (Karnataka, Tamil Nadu and Andhra Pradesh), the eastern coast of India and Bangladesh are at higher risk. These regions share similar climatic and farming conditions as those found in highly endemic areas in Southeast Asia including in Malaysia and Thailand. With regard to clinical spectrum, results of the Indian case series differed with other case series from Southeast Asia and Northern Australia indicating that soft tissue abscesses were most common clinical presentation followed by pneumonia. The reverse is seen in known endemic regions. The number of neurological manifestation was comparatively high in proportion and primarily presented as pyemic infections such as brain abscess or meningitis. Although based on small numbers, prostate abscesses in men and parotid abscess among children were noted. In terms of risk factors, our results are consistent with previous case series. Diabetes mellitus was a major risk factor. Bacteremic melioidosis had a poor prognosis and septic shock was a strong predictor of mortality. Similarly, misdiagnosis and consequently mistreatment increased the risk of mortality, underscoring the importance of laboratory diagnosis which remains the gold standard for accurate diagnosis of the diseases. Overall, this review highlights the crucial importance of increasing awareness among health care providers in these regions as the disease is treatable with early intervention.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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