## **Emergence of Melioidosis in Indonesia**

- Melioidosis is a community-acquired infectious disease caused by Burkholderia pseudomallei which lacks a specific clinical presentation.
- The current diagnostic gold standard for B. pseudomallei is culture but it can be misidentified as a culture contaminant or as another species.<sup>1</sup>
- The crude case fatality rate ranges from 14% to 40%, and could be as high as 80% if effective antimicrobial drugs are not given.<sup>2</sup>
- Melioidosis is known to be highly endemic in parts of southeast Asia and northern Australia.<sup>3</sup>
- Both human and animal melioidosis cases exported from Indonesia have been frequently observed in many countries.<sup>4-8</sup>
- Here, we report three cases of culture-confirmed melioidosis presenting at Wahidin Hospital, South Sulawesi, Indonesia, between 2013 and 2014.
- The gold standard for diagnosis is Culture; organism commonly misidentified as contamination or Pseudomonas spp.
- Clinical sample : Blood, respiratory secretion, urine, pus and fluid
- Laboratory diagnosis of melioidosis:
  - Gram-negative bacillus, oxidase positive
  - Dry and wrinkle colonies and sweetish earthy odor
  - Resistance to gentamicin and colistin and susceptibility to co-amoxiclav is characteristic



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Year presented(ref)	Locations	Age/ Gender, Nationality	Clinical characteristics	Diagnostic method (bacterial identification method)	Outcome
1929 <sup>°</sup>	Cikande, Java	50/M,Indonesian	Chronic painless nodules in the left thigh with fistula discharging greenish yellow pus	Culture of pus (biochemistry, phenotypic and virulence in animal model))	Died
1934 <sup>10</sup>	Jakarta, Java	38/M,Indonesian	Severe sepsis with pulmonary, splenic and prostatic abscesses (postmortem)	Severe sepsis with pulmonary, splenic and prostatic abscesses (postmortem) Culture of pus (biochemistry, phenotypic and virulence in animal model)	
1935 <sup>11</sup>	Surabaya, Java	25/F,Indonesian	Abscess in the right gluteal region	Abscess in the right gluteal region Culture of pus (biochemistry, phenotypic and virulence in animal model)	
1936 <sup>12</sup>	Bogor, Java	60/M,Indonesian	Skin lesion with ulcers on right lower leg after trauma	Ilcers on right lower leg after Culture of pus (biochemistry and phenotypic)	
1937 <sup>12</sup>	Jakarta, Java	55/M,Indonesian	Abscess left foot, originated from small trauma while farming	Culture of pus (biochemistry and phenotypic)	Fully recovered
1950 <sup>13</sup>	Surabaya, Java	28/F,European	Pain in the lower abdomen and then high fever	Culture of abscess from the right ovary (biochemistry and phenotypic)	Fully recovered
2005 <sup>14</sup>	Banda Aceh, Sumatra	15/F;18 mo/M;10/F;13/F (4 tsunami survivors)	Pneumonia	Culture of sputum (API20NE)	Fully recovered (n=1) or reported as improving (n=3)
2011-2013 <sup>15</sup>	Malang, Java	51 Patients	Unknown	Culture of sputum, blood, pus and urine (VITEK2)	Unknown
2013(Case 1)	Luwu Timur, Sulawesi	41/M,Indonesian	High grade fever, chill, headache and shortness of breath	Culture of blood (VITEK2)	Died
2013(Case 2)	Makassar, Sulawesi	45/F,IndonesianSkin ulcer on neck, fever, vomiting, abdominal pain, headache, diarrhea, poor appetite and weight lossCulture of blood (VITEK2)		Died	
2014(Case 3)	Makassar, Sulawesi	26/M,Indonesian	Purulent discharge from incised wound behind the left ear lobe, painless and no fever	Culture of Pus (VITEK2)	Lost to follow-up

Age		41 years old			
Sex		Male			
Occup	ation	An excavator operator in Tambak Yoso village, Kalaena District, East Luwu Regency.			
History	y	He was referred from I La Galigo Hospital, East Luwu Regency to Wahidin Hospital in August 2013	Five days of fever, chill, shortness of breath, headache and confusion	No underlying diseases	
• On Ad	mission (day-1)	Physical examination : fever (39.8°C), icteric sclera, hepatomegaly, abdominal tenderness, and calf tenderness			
Labora	atory test:	Leukopenia (2,700/µL), thrombocytopenia (37,000/µL), hyperglycemia (350 mg/dL), hyperbilirubinemia (total bilirubin 4.4 mg/dL and direct bilirubin 3.9 mg/dL) and hypercreatinemia (4.5 mg/dL).			
		Rapid diagnostic tests for leptospirosis, de	pirosis, dengue infection, and malaria : negative.		
Presur	Presumptive diagnosis         Weil's disease and type 2 diabetes mellitus				
Therap	ру	intravenous ceftriaxone and subcutaneous insulin			
He died because of septic shock (day 2)					
Blood	Blood culture B. pseudomallei (day 5)				

Age	45 years old				
Sex	Female				
Occupation	A housewife in Makassar				
History	She was referred from Daya Regional Hospital, Makassar to Wahidin Hospital in	Three months of swelling on the right side of the neck	During the past month : the mass became bigger, ruptured, and produced thick, white pus.	Fever, abdominal pain, vomiting, diarrhea, poor appetite, and lost 5 kgs	Diabetes mellitus and hypertension for 3 years.
On Admission (day-1)	Physical examination : febrile (38.1°C), discharge of pus from neck abscess				
Laboratory test:	Hyperglycemia (310 mg/dL). Sputum acid-fast bacilli smears were negative				
	Complete blood count, renal and function tests, and liver function tests were normal				
	Chest radiography : cardiomegaly with pulmonary edema and signs of pulmonary hypertension				
Diagnosis	Suspected tuberculo	ous lymphadenitis and	type 2 diabetes mellitu	JS	
Therapy	intravenous ceftriaxone, subcutaneous insulin, and oral meloxicam and metronidazole				
Day 4	dyspnea				
Cardiologist diagnosis	Chronic heart failure due to coronary artery disease				
		She died due to card	liogenic shock (day	6)	
Pus culture	B. pseudomallei (day 7)				

A	\ge	26 years old
S	iex 🛛	Male
C	Occupation	An employee of a state-owned enterprise

This is the first report of indigenous melioidosis cases in Sulawesi.

1. Clinical manifestations are consistent with common clinical presentations of melioidosis:

1.a. Case 1 and 2 : severe sepsis with multiple organ failure

- 1.b. Case 3 : localized subcutaneous abscesses that fail to improve after treatment with antimicrobials ineffective against B. pseudomallei.
- 2. Identification B. pseudomallei by VITEK2 is generally reliable<sup>1</sup>, although no further confirmatory tests1 because the isolates were not stored.
- Previous reports of indigenous melioidosis from Indonesia were from Sumatra and Java.
- Considering that melioidosis is endemic in east Malaysia and Papua New Guinea, it is likely that indigenous melioidosis cases also occur unrecognized and unreported in the contiguous parts of Indonesia, Kalimantan and Papua, respectively.<sup>3</sup>
- Our findings strongly support the suggestion that melioidosis is endemic throughout Indonesia but is currently under-recognized.<sup>3</sup>
- Burkholderia pseudomallei isolates from all the three cases were identified by VITEK2 Compact (installed at Wahidin Hospital in December 2012).
- Before 2012, B. pseudomallei was likely misidentified or discarded as a contaminant.<sup>1</sup>
- Guidance on how to diagnose melioidosis and identify B. pseudomallei, even without the use of automated machines such as VITEK, was recently published.
- None of the isolates were tested for antimicrobial susceptibility because this was not included in the laboratory's standard operating procedures (SOPs) for this organism.
- Burkholderia pseudomallei can also cause laboratory-acquired infection, and appropriate safety precautions for suspected isolates is required.<sup>1</sup>
- Since the recognition of these three cases, laboratory SOPs for bacterial identification and susceptibility testing and reporting are being revised in the hospital.

History





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ENT clinic (day 1)         Physical examination:       Afebrile (36.6°C)         Hearing was normal and tympanic membrane was intact. The incised wound was painless         Theraphy:       Oral ciprofloxacin and wound dressing         ENT clinic (day 8)       Complaining of persistent discharge         Further incision and drainage was performed and the pus was sent for bacterial culture         He was lost to follow-up		medication) at a private hospital.			
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Further incision and drainage was performed and the pus was sent for bacterial culture         He was lost to follow-up         Rue culture         Rue culture	ENT clinic (day 8)	Complaining of persistent discharge			
He was lost to follow-up		Further incision and drainage was performed and the pus was sent for bacterial culture			
Pue aulture P. psoudomalloi (day 11)	He was lost to follow-up				
D. pseudomailer (day 11)	Pus culture	B. pseudomallei (day 11)			



FIGURE 1. Map of reported indigenous melioidosis cases in Indonesia. Locations of the previous case reports are indicated by red circles (Banda Aceh, Jakarta, Cikande, Bogor, Malang, and Surabaya). Locations of the current case reports are indicated by red stars (Makassar and Kalaena).

- None of the three patients reported received antimicrobials recommended for melioidosis2 because of the delayed recognition of the organism.
- Treatment guidelines for clinicians in the Wahidin hospital are being revised to consider empirical treatment with antimicrobials effective against B. pseudomallei in patients presenting with severe sepsis and hyperglycemia.<sup>1,2</sup>
- The melioidosis cases in Sulawesi reported here are likely to represent the tip of the iceberg in Indonesia.
- Training on how to identify B. pseudomallei accurately and safely in all available microbiological facilities in Indonesia should be provided.
- Consideration should be given to make melioidosis a notifiable disease in Indonesia.

## REFERENCES

- 1. Hoffmaster AR, AuCoin D, Baccam P, Baggett HC, Baird R, Bhengsri S, Blaney DD, Brett PJ, Brooks TJ, Brown KA, ChantratitaN, ChengAC, DanceDA, Decuypere S, Defenbaugh D, Gee JE, Houghton R, Jorakate P, Lertmemongkolchai G, Limmathurotsakul D, Merlin TL, Mukhopadhyay C, Norton R, Peacock SJ, Rolim DB, Simpson AJ, Steinmetz I, Stoddard RA, Stokes MM, Sue D, Tuanyok A, Whistler T, Wuthiekanun V, Walke HT, 2015. Melioidosis diagnostic workshop, 2013. Emerg Infect Dis 21: 1-9.
- 2. Lipsitz R, Garges S, Aurigemma R, Baccam P, Blaney DD, Cheng AC, Currie BJ, Dance D, Gee JE, Larsen J, Limmathurotsakul D, Morrow MG, Norton R, O'Mara E, Peacock SJ, Pesik N, Rogers LP, Schweizer HP, Steinmetz I, Tan G, Tan P, Wiersinga WJ, Wuthiekanun V, Smith TL, 2012. Workshop on treatment of and postexposure prophylaxis for Burkholderia pseudomallei and B. mallei infection, 2010. Emerg Infect Dis 18: e2.
- 3. Currie BJ, Dance DA, Cheng AC, 2008. The global distribution of Burkholderia pseudomallei and melioidosis: an update. Trans R Soc Trop Med Hyg 102 (Suppl 1): S1–S4.
- 4. Beeker A, Van de Stadt KD, Bakker K, 1999. Melioidosis. Neth J Med 54: 76-79.
- 5. Dance DA, Smith MD, Aucken HM, Pitt TL, 1999. Imported melioidosis in England and Wales. Lancet 353: 208.
- 6. Lee SW, Yi J, Joo SI, Kang YA, Yoon YS, Yim JJ, Yoo CG, Han SK, Shim YS, Kim EC, Kim YW, 2005. A case of melioidosis presenting as migrating pulmonary infiltration: the first case in Korea. J Korean Med Sci 20: 139–142.
- 7. Dance DA, King C, Aucken H, Knott CD, West PG, Pitt TL, 1992. An outbreak of melioidosis in imported primates in Britain. Vet Rec 130: 525-529.
- 8. Ritter JM, Sanchez S, Jones TL, Zaki SR, Drew CP, 2013. Neurologic melioidosis in an imported pigtail macaque (Macaca nemestrina). Vet Pathol 50: 1139-1144
- 9. de Moor CE, Soekarnen, van der Walle N, 1932. Melioidosis op Java. Geneeskd Tijdschr Ned Indie 72: 1618–1635.
- 10. Pet MA, Fossen A, 1934. Melioidosis der inwendige organen [Melioidosis of internal organs]. Geneeskd Tijdschr Ned Indie 74: 976–981
- 11. Bezemer F, 1935. Melioidosis op Celebes. Geneeskd Tijdschr Ned Indie 75: 1577-1579.
- 12. Sudibyo RMS, 1938. Twee gevallen van huidmelioidosis. Geneeskd Tijdschr Ned Indie 78: 1424–1444.
- 13. Dunlop SJ, 1952. Rapid recovery in a case of melioidosis. Doc Med Geogr Trop 4: 296-300.
- 14. Athan E, Allworth AM, Engler C, Bastian I, Cheng AC, 2005. Melioidosis in tsunami survivors. Emerg Infect Dis 11: 1638–1639.
- 15. Irmawanti-Rahayu S, Noorhamdani AS, Santoso S, 2014. Resistance pattern of Burkholderia pseudomallei from clinical isolates at Dr. Saiful Anwar General Hospital, Malang-Indonesia. J Clin Microbiol Infect Dis 1: 17-20.

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