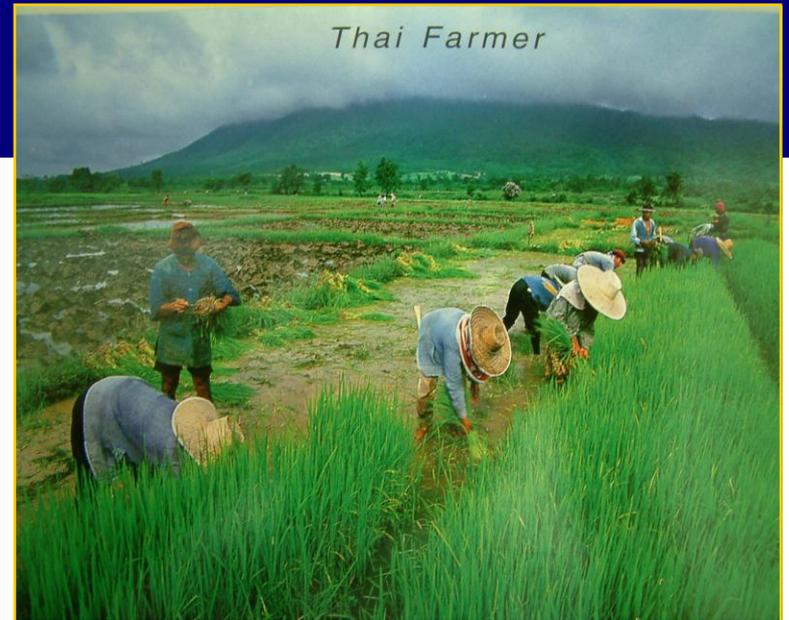


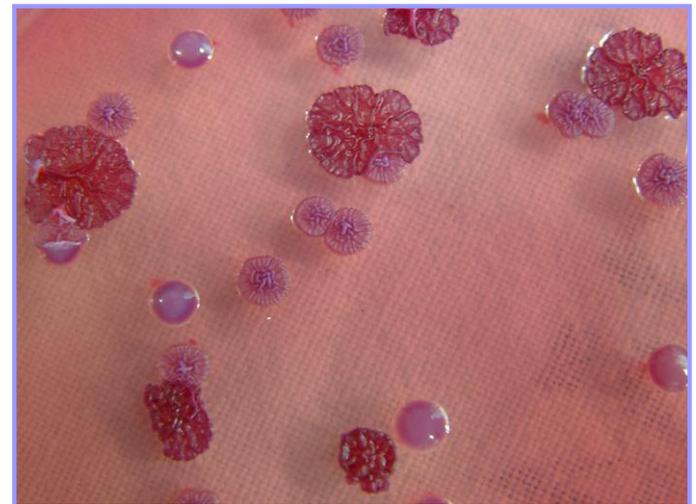
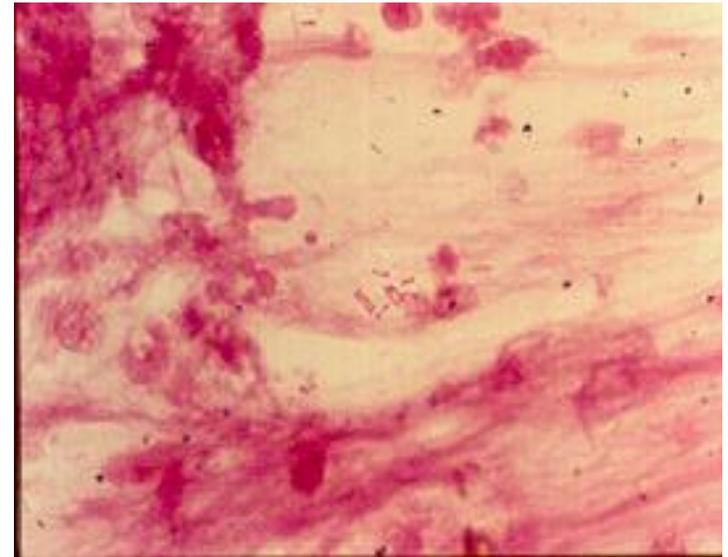
Melioidosis

Burkholderia pseudomallei

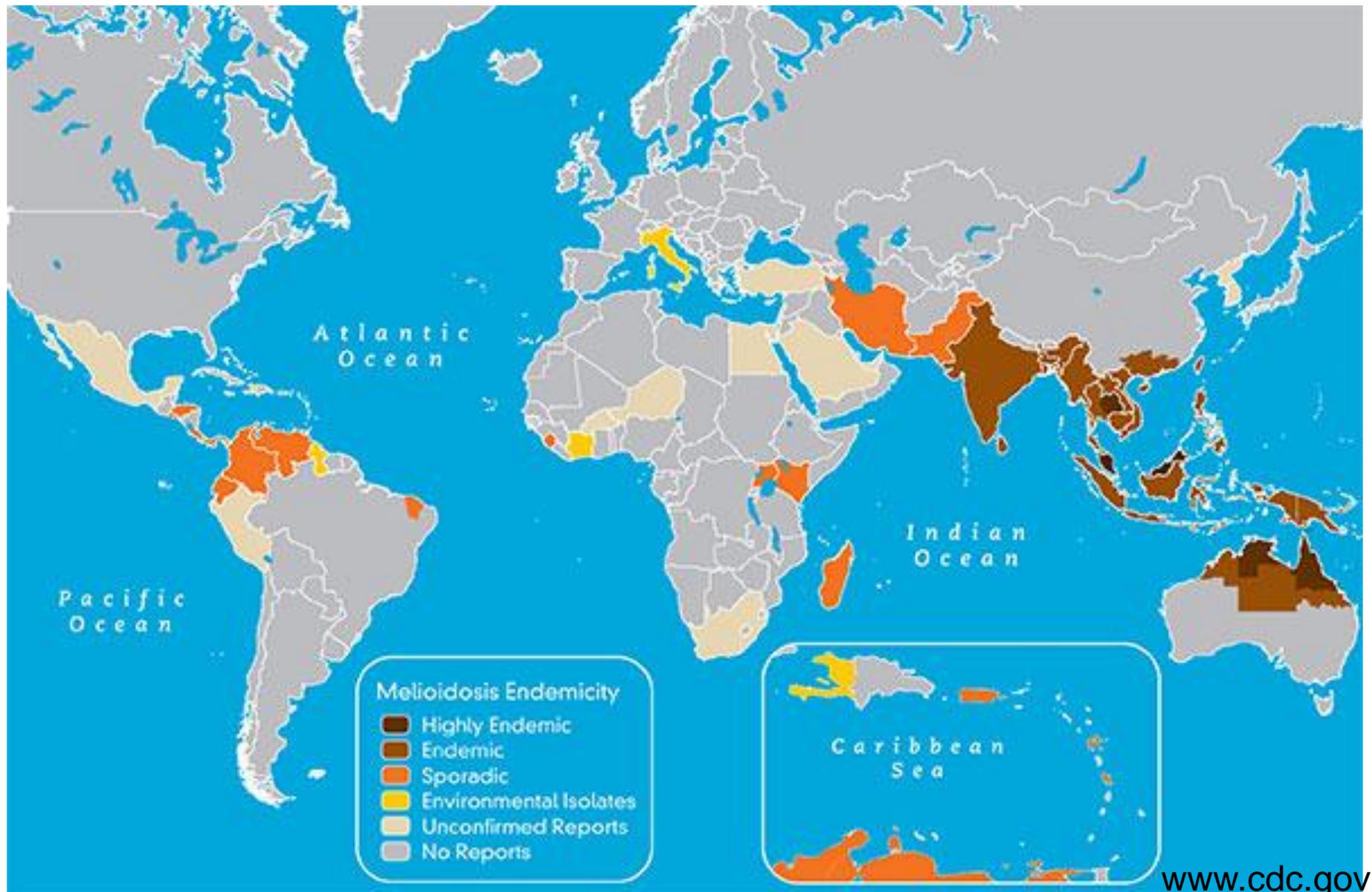


Burkholderia pseudomallei

- Gram-negative bacilli (safety-pin appearance)
- Saprophytes in soil and water
- Endemic in some parts of Southeast Asia and Northern Australia
- 20% of community-acquired septicaemia in Ubon Ratchathani (Northeast Thailand)
- ~ 40% overall mortality



Epidemiology



AN ACCOUNT OF THE DISCOVERY OF A
HITHERTO UNDESCRIBED INFECTIVE
DISEASE OCCURRING AMONG THE
POPULATION OF RANGOON.

BY A. WHITMORE,

CAPTAIN, I.R.S.,

AND

C. S. KRISHNASWAMI,

ASSISTANT SURGEON,

Pathological Laboratory, Rangoon.

ABOUT 1½ year ago a few cases of human glanders infection were discovered in Rangoon, and the opportunity was taken for a much-needed effort to lessen the incidence of this disease among the gharry ponies of the town. It was owing to our interest in this question of the occurrence of glanders in man that our eyes were opened to the fact that there was an infective



In April 1911, at this site, in the Pathology Laboratory of the Rangoon General Hospital, the disease **melioidosis** was first recognised by Captain A. Whitmore and Assistant Surgeon C.S.Krishnaswamy of the Indian Army Medical Service



History

- 1911 First recorded case in the world (Whitmore & Krishnaswami): Glander-like illness, *Bacillus whitmori*
- 1917 More than 100 cases reported from Rangoon (Krishnaswami): *Bacillus pseudomallei*
- 1932 Stanton and Fletcher named 'melioidosis' [Greek] 'melis' = a distemper of asses, 'eidos' = resemblance
- 1950-75 Vietnam war: Vietnam time-bomb, *Pseudomonas pseudomallei*
- 1974-85 Over 800 cases reported in Thailand
- 1992 *Burkholderia pseudomallei*



Burkholderia pseudomallei

Aerobic, non-spore forming, environmental saprophyte found in wet soils in South and East Asia and Northern Australasia.

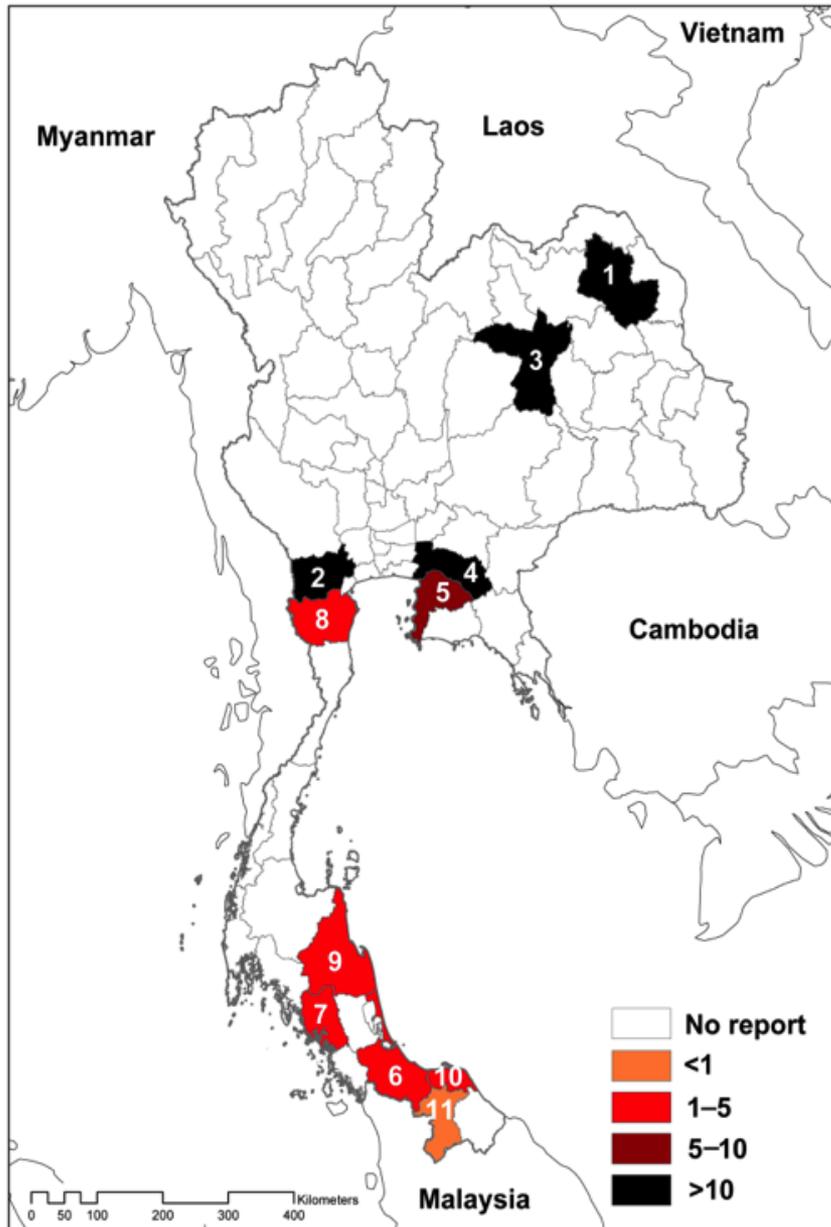


Melioidosis, a “distemper of asses”, causes infections in mammals and birds



Animal Melioidosis

Epidemiology of melioidosis in animals



- The highest incidence was in goats, followed by incidence in pigs and cattle.
- The incidence rate of goat melioidosis was high in the northeast where endemic region.
- Pasteurization of goat milk before consumption in Thailand is recommended.

Melioidosis in Northeast Thailand



CLINICAL EPIDEMIOLOGY IN THAILAND

- Affects all ages; peak incidence in fifth decade.
- Underlying predisposition to infection (particularly diabetes mellitus and chronic renal failure) in most cases.
- The majority of cases are primary infections.

Chaowakul et al. J Infect Dis 1989;159:890-9

Suputtamongkol et al. Int J Epidemiol 1994;23:1082-9.

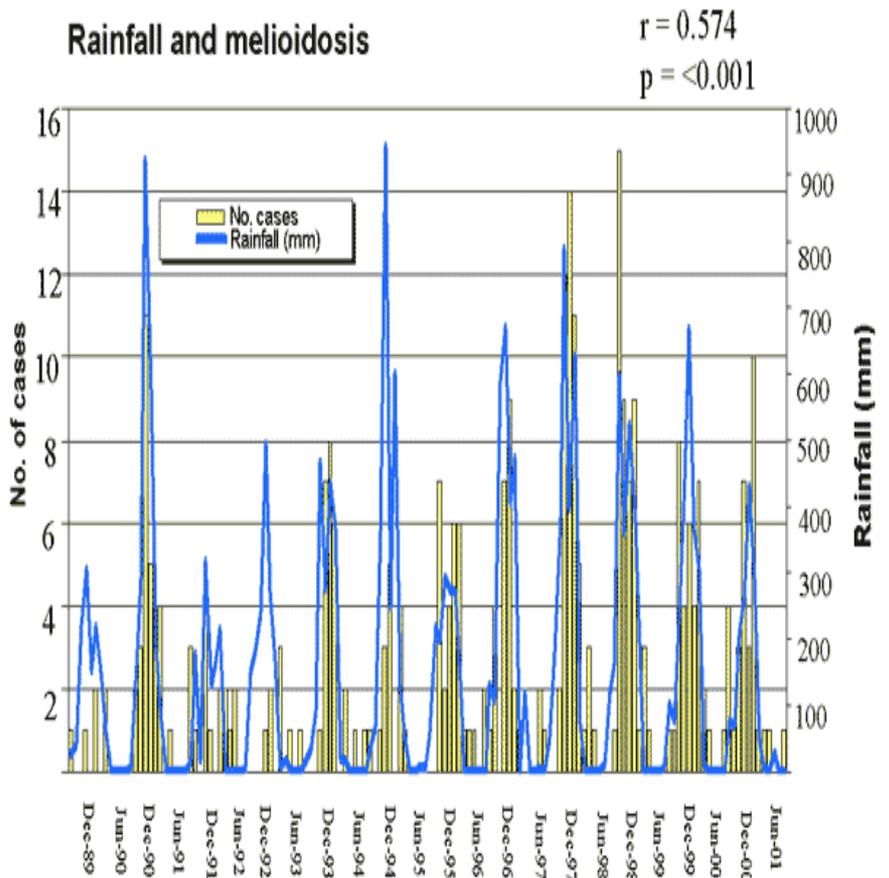
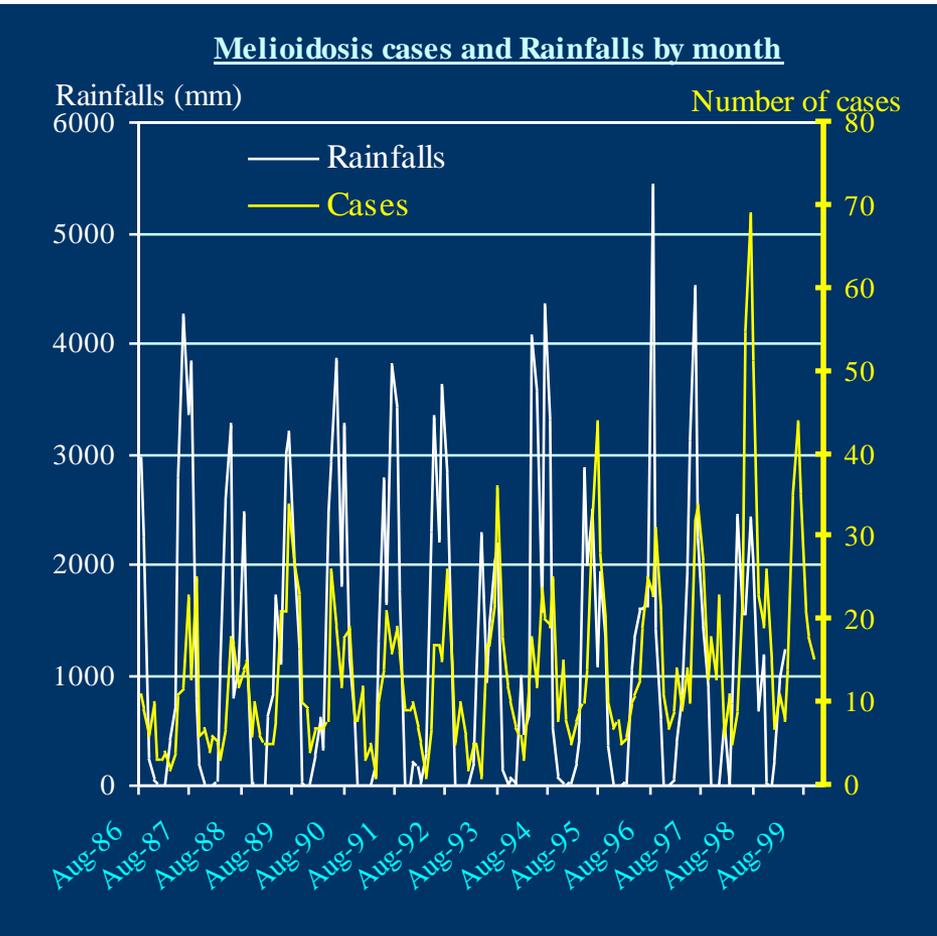
CLINICAL EPIDEMIOLOGY IN THAILAND

- A rainy season disease.
- Occurs mainly in the North-East of the country where the organism is abundant in wet soil.
- Affects predominantly rice-farmers and their families.



Suputtamongkol et al. Int J Epidemiol 1994;23:1082-9.

Comparison of Melioidosis Cases and Rainfalls: Ubon Ratchathani and Darwin



Currie BJ. *Emerg Infect Dis* 2003.



MELIOIDOSIS

- Commonest cause of septicaemia during the rainy season
- Commonest cause of septicaemia in patients with diabetes, renal disease, or immunosuppression

Chaowakul et al. J Infect Dis 1989; 159: 890-9

B. pseudomallei is commonly isolated from clinical specimens in **NE**, **East**, **West** and **South** Thailand

- In 2008, there were 2,557 culture-confirmed melioidosis cases in **NE** Thailand ¹
- There are regular report of melioidosis in **South** of Thailand ²
- Between 2006-10, there were 8, 50, 76 and 151 culture-confirmed melioidosis in 4 provinces in **West** and **East** Thailand ³
- In 1999, there was a report of 100 and 127 culture-confirmed melioidosis patients in **North** and **Central** Thailand ²

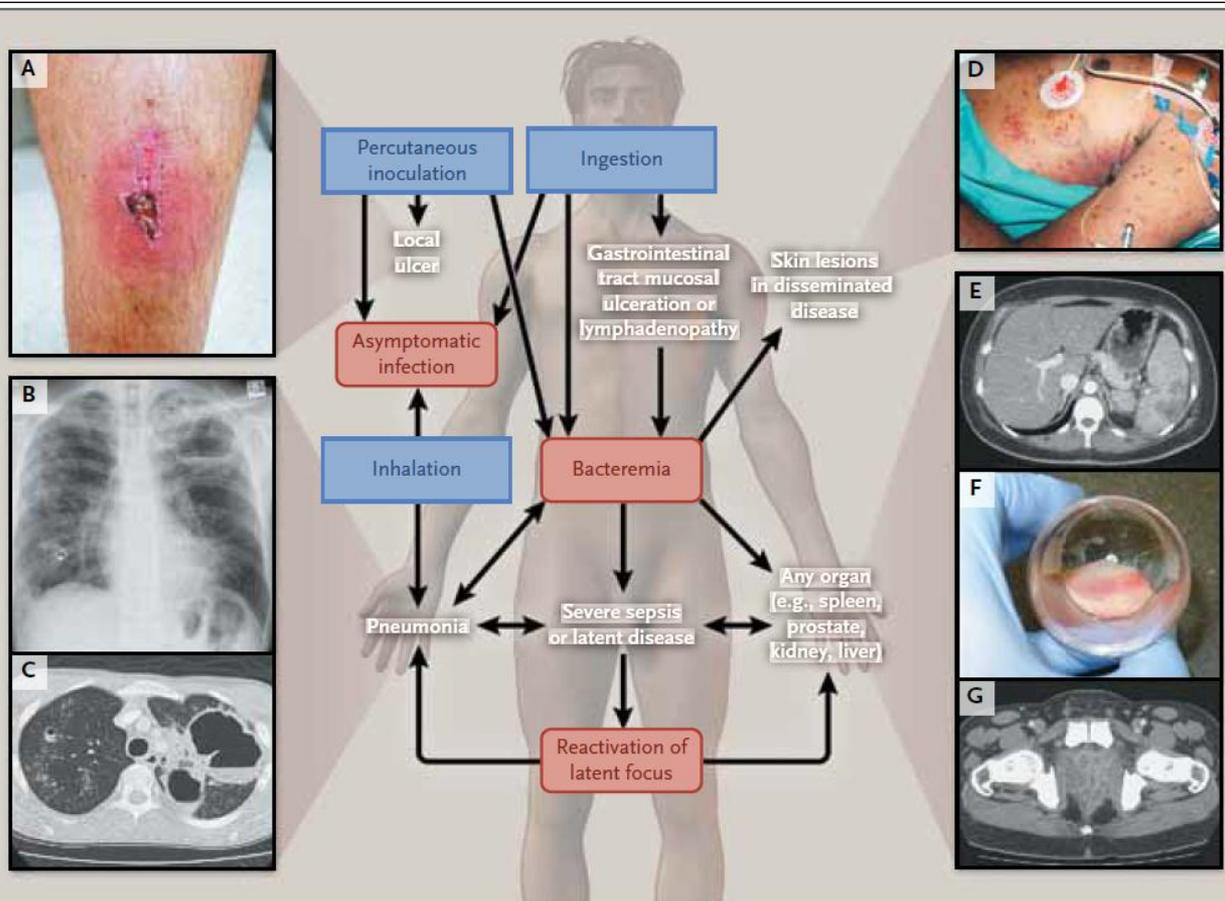
(1) Wongratanacheewin (IS-02), World Melioidosis Congress 2013

(2) Chusri et al. AJTMH (2012) 87(5): 927-32

(3) Limmathurotsakul et al. EID (2012) 18(2): 325-7

(4) Vuddhakul et al. AJTMH (1999) 60(3): 458-61

Mode of transmission



- Underlying diseases
- Broad spectrum of disease
- Response to antibiotics slow
- Antibiotic treatment prolonged
- Relapse common

Figure 3. Clinical Events after Infection with *B. pseudomallei*.

Melioidosis may have a wide range of clinical manifestations, and severity varies from an acute fulminant septic illness to a chronic infection. Shown are the routes of infection (blue boxes: percutaneous inoculation, inhalation, and ingestion), the natural history of infection (red boxes: asymptomatic infection, bacteremia, or reactivation of latent focus), and the diverse disease manifestations (white text). Panel A shows cutaneous melioidosis in a healthy host. Panel B shows lung abscesses on the chest radiograph of a patient with acute melioidosis pneumonia, and Panel C shows the corresponding computed tomographic (CT) scan. Panel D shows the skin manifestations in a fatal case of disseminated melioidosis. Panel E shows splenic abscesses on an abdominal CT scan. Panel F shows aspirated pus in a patient with prostatic and periprostatic abscesses, and Panel G shows the abscesses on a CT scan from the patient.



Risk factors

- DM
- Renal disease
- Alcohol excess
- Chronic lung disease
- Thalassemia
- Immunocompromised: cancer, non-HIV
- Occupational exposure

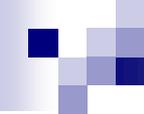
MELIOIDOSIS presentation



Incubation period 1 to 2 days
to > 60 years.

| | |
|-------------------|-----|
| Fever: | 85% |
| Acute (<7d) | 30% |
| Sub-acute (7-28d) | 48% |
| Chronic (>28d) | 22% |





Disease classification

- Localized infection
- Pulmonary infection
- Blood stream infection
- Dissiminated infection

“The Great Mimicker”

Skin and soft tissue

- Signs of dissemination
- Pustule
- Subcutaneous nodule -
-> abscess
- Ecthyma gangrenosum

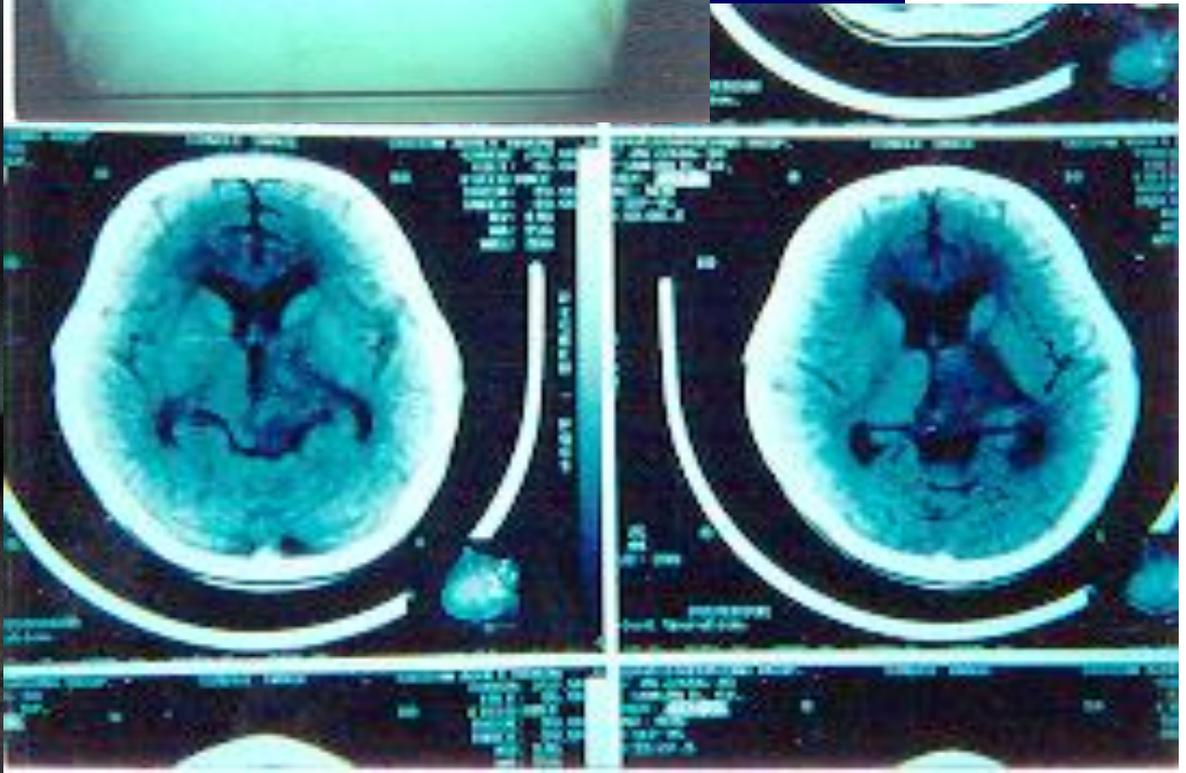
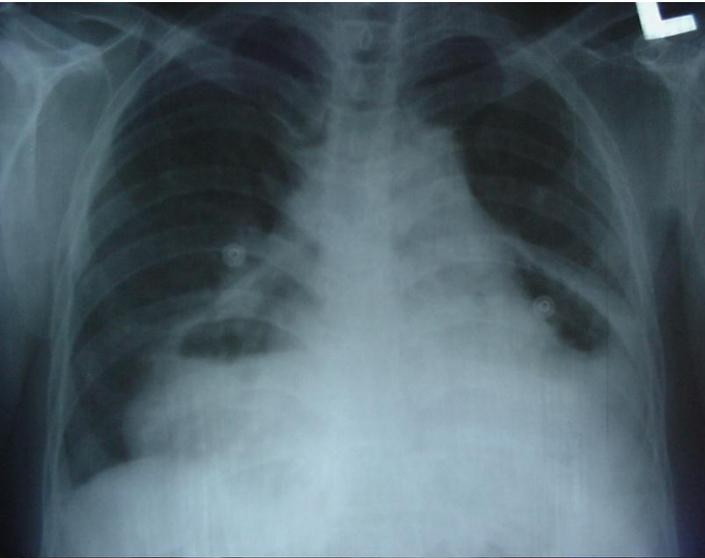




Acute pyomyositis

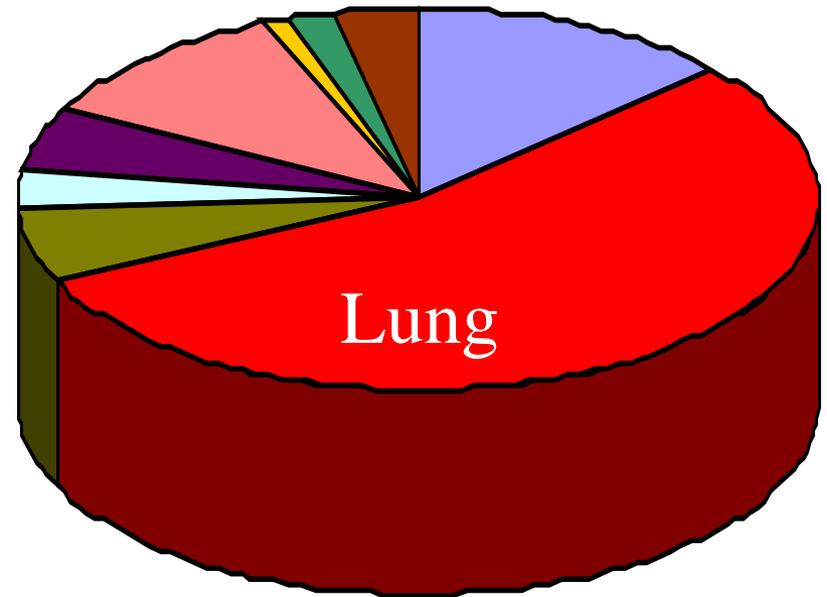
- Any sites
- Peri-articular area
- Cause of chronic ulcer
- Need specific medical treatment

Abscesses



Adults (%) (N = 1271)

| | |
|----------------------|-----------|
| Lung | 51 |
| Liver | 6 |
| Spleen | 4 |
| Urinary tract | 5 |
| Soft tissue | 10 |
| Parotid | 1 |
| Bone/ joint | 2 |
| Other | 7 |
| None | 12 |



Septic arthritis

- Acute septic arthritis as part of dissemination
- Monoarthritis to oligoarthritis
 - Shoulder jt, Knee jt
 - Elbow jt, Ankle jt
 - Sterno-clavicular jt
 - Hip jt, Wrist jt
- Inappropriate treatment
- chronic arthritis



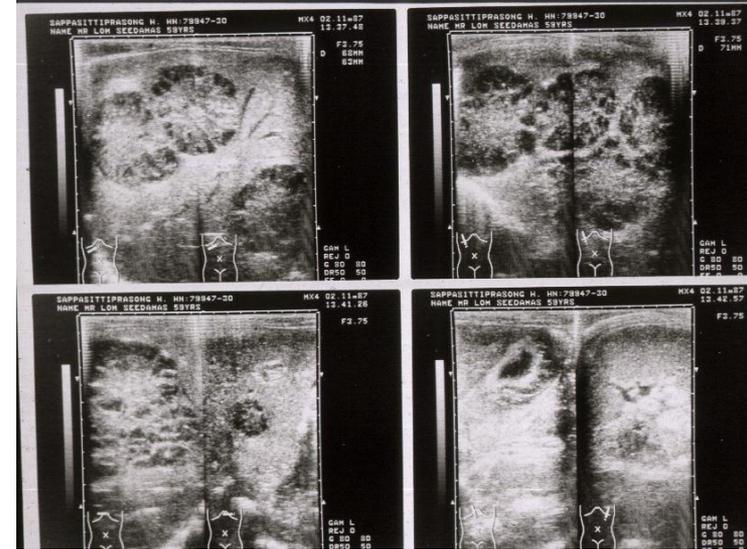
Chest radiographs (abnormal 67%)

| Abnormalities | Frequency (%) |
|-----------------------------|---------------|
| Zonal opacities | 140 (52.6%) |
| Widespread opacity | 96 (36.1%) |
| Cavitations | 25 (9.4%) |
| Diffuse interstitial shadow | 24 (9.0%) |
| Pleural effusion | 46 (17.3%) |
| Pericardial effusion | 2 (0.8%) |
| Cardiomegaly | 18 (6.8%) |
| Pneumothorax | 4 (1.5%) |



Ultrasound findings in melioidosis (N = 552)

| | |
|---------------------------|-----|
| Normal | 27% |
| Liver abscess | 27% |
| Multiple liver abscesses | 16% |
| Splenic abscess | 24% |
| Liver & spleen abscesses | 11% |
| Renal tract abnormalities | 14% |



The Ubon Ratchathani Melioidosis study group.

SUPPURATIVE PAROTITIS

- 28% of melioidosis in childhood.
- Unique presentation
- Useful epidemiological marker of the infection.
- Usually no underlying predisposing factor.



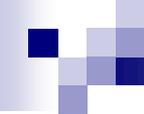
Dance et al. J Infect Dis 1989; 159:654-60.

- Prognosis excellent with prompt incision, drainage, and antibiotics.
- May erode facial nerve or external auditory meatus.
- Relapse very unusual



Melioidosis

- Risk factors for melioidosis are associated with dysfunction of white blood cells
- Intracellular pathogen able to survive and multiply inside phagocytes
- Intrinsically resistant to most narrow and expanded-spectrum cephalosporins and the aminoglycosides.
- High relapse rate (>10%)



Laboratory diagnosis

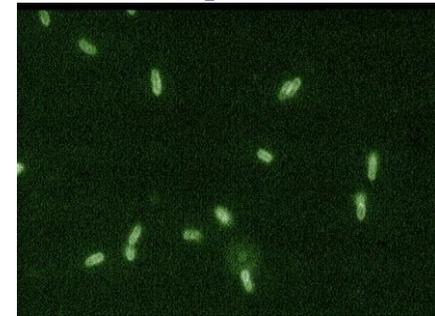
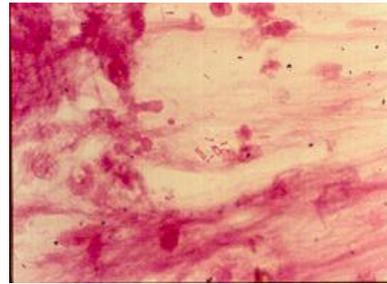
1. **Isolation and identification**
2. **Serology diagnosis**
3. **Molecular techniques**



Isolation and identification of *B.pseudomallei*

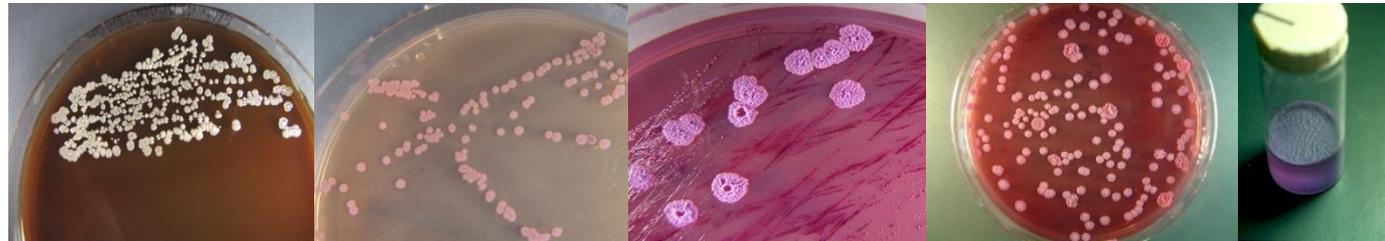
Clinical samples

1. Blood
2. Respiratory secretion
3. Urine
4. Pus and fluid



1. Gram stain and direct Immunofluorescence microscopy

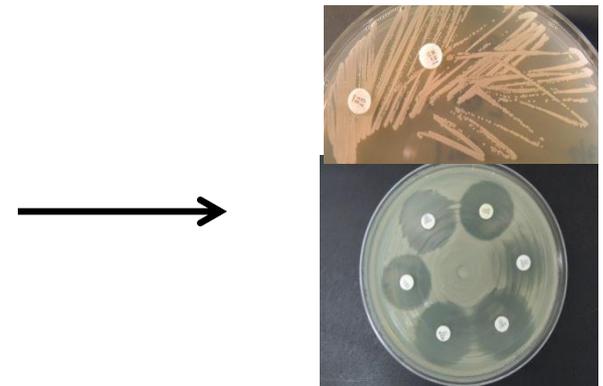
2. Culture on agar plates; BA, Mac, ASH and selective broth



3. Identification method



4. Susceptibility testing



2. Serology diagnosis

2.1 Antigen detection

- ❑ **Latex agglutination (LA) test**
- ❑ Direct immunofluorescent (IF) assay
- ❑ Enzyme-linked immunosorbent assay (ELISAs)

2.2 Antibody detection

- ❑ **Indirect hemagglutination test (IHA)**
- ❑ Enzyme-linked immunosorbent assay (ELISAs)
- ❑ Rapid IgG (or IgM) immunochromogenic test

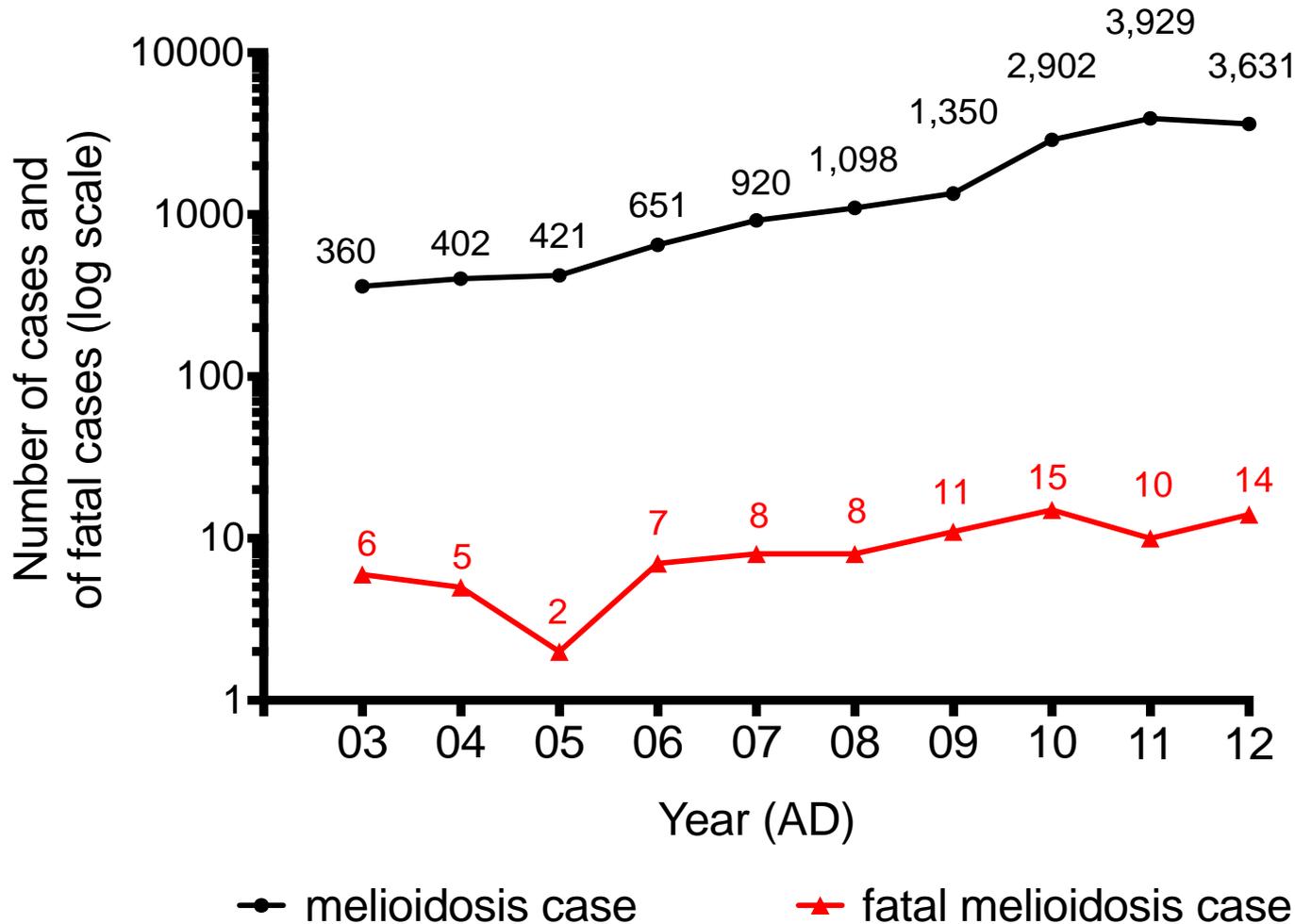
Melioidosis Case Classification (defined by MoPH, Thailand, 2001)

- Suspected case: None
- Probable case: Clinical criteria plus one IHA \geq 1:160
- Confirmed case: Clinical criteria plus bacterial culture positive for *B. pseudomallei* or IHA four-fold rising

Clinical criteria

- High fever with localized infection, septicaemia, or septic shock without culture positive for other pathogenic organisms

Official Data for Total Number of Melioidosis in Thailand, Bureau of Epidemiology, MoPH



Impossible!
How come?

Current Diagnostic Approach in Thailand (In general, countrywide)

- Use clinical criteria (which is neither sensitive nor specific)
- Start treatment if melioidosis is suspected by the clinical criteria
- Order lab test for IHA
- Order blood culture with or without culture of other clinical specimens
- No selective media for *B. pseudomallei* is used
- No latex agglutination is used
- Diagnose melioidosis based on clinical criteria, IHA or culture

Conclusion - IHA

- IHA is available in nearly every hospital in Thailand
- A lot of melioidosis cases in Thailand are (falsely) diagnosed by IHA \geq 1:160 or four-fold rise of IHA
- **We found that standardization of IHA is problematic, and some community hospitals gave a number of false positive results**
- Most doctors in Thailand believe that IHA is a good diagnostic test without knowing its problem of poor sensitivity and specificity

Recommended Diagnostic Approach in Thailand (Used in Research Facilities / Settings [1])

- Use **empirical treatment** regimen to cover *B. pseudomallei* (e.g. Cloxacillin + Ceftazidime) in areas where melioidosis is present for all sepsis and severe sepsis patients (unless definite diagnosis of other diseases is made e.g. malaria, measles, ..)
- Ignore IHA
- Order blood, urine and throat swab **culture**
- Order pus and sputum **culture** if available
- Confirm laboratory that “**selective media for *B. ps*”** and “**latex agglutination**” are used
- Order **Ultrasound for abdomen** (or CT scan if possible)

Recommended Diagnostic Approach in Thailand (Used in Research Facilities / Settings [2])

- Re-evaluate patients daily, search for abscesses and collect more clinical specimens for culture if available
- **Definite melioidosis** = culture +ve
(report only this group to MoPH)
- **Probable melioidosis** = abscesses that is consistent with melioidosis but culture was not done or negative, **or** culture negative for *B. ps* and represent within 1 month with culture-proven melioidosis
- **Possible melioidosis** = clinically suspected melioidosis and improved after treatment with an effective antimicrobial regimen for melioidosis **or** died before improvement was observed

Treatment

■ Initial treatment

- Ceftazidime (50 mg/kg, up to 2 g) IV every 8 hr
- Meropenem (25 mg/kg, up to 1 g) IV every 8 hr
- Imipenem (25 mg/kg, up to 1 g) IV every 6 hr

■ Eradication treatment

- TMP/SMX every 12 hr +/- doxycycline every 12 hr

The type of infection and the course of treatment will impact long-term outcome. Treatment generally starts with intravenous antimicrobial therapy for 10-14 days, followed by 3-6 months of oral antimicrobial therapy.

CURRENT RECOMMENDATIONS

- Oral treatment should only be substituted when there is evidence of clinical improvement.
- The total duration of antibiotic treatment should usually be 20 weeks.
- Patients need life-long follow-up.



Prevention

- Avoid direct exposure to wet season soil, dust clouds, heavy rain and surface water
- Wear protective gears
- Drink boiled or bottled water only
- Avoid travel to endemic area for high-risk patients
- Health care workers: standard contact precaution



**THANK YOU FOR YOUR
ATTENTION**