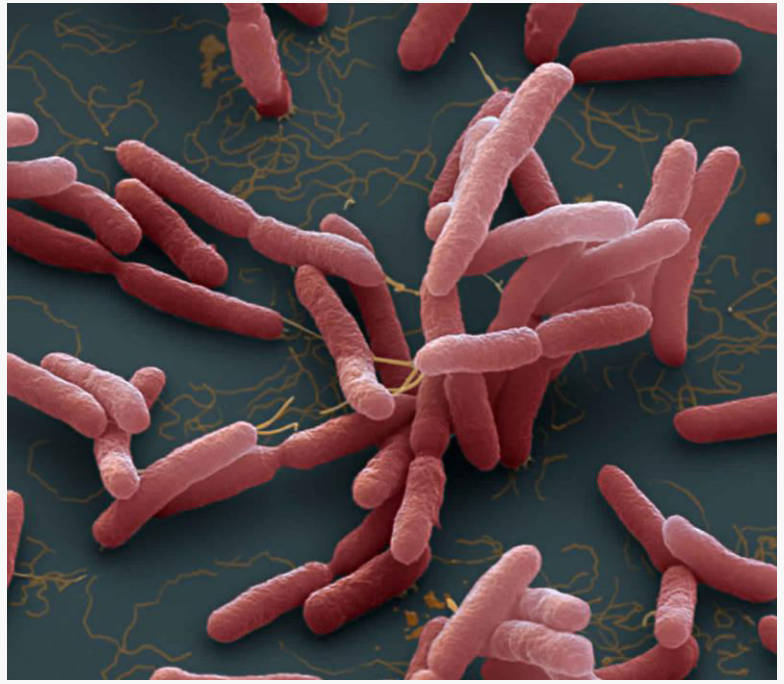
MELIOIDOSIS



?A Neglected Tropical Disease in India

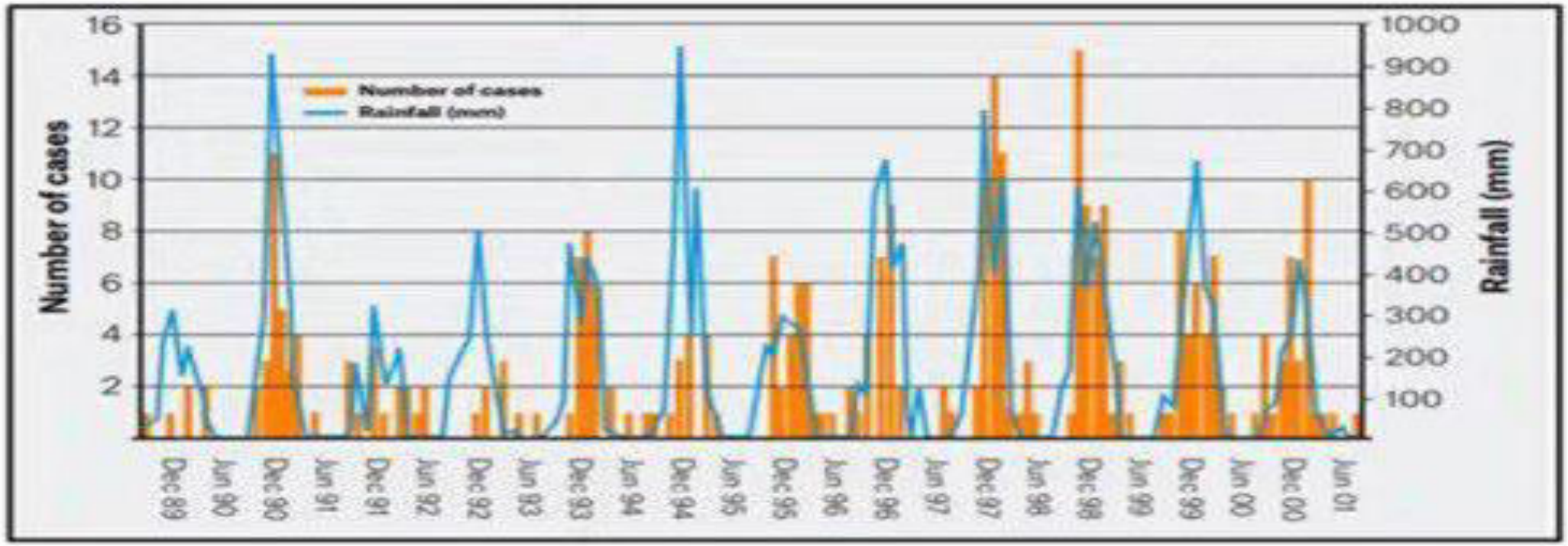
- Melioidosis, caused by ***Burkholderia pseudomallei***
- Other names :-
  - ***Whitmore's disease***
  - ***Great mimicker***
  - ***Vietnam time-bomb disease***
  - ***Paddy field disease***

Burkholderia pseudomallei

- Gram-negative environmental bacterium
- causes melioidosis in both humans and animals

- **Habitat:** found predominantly in the rhizosphere, moist soil, and both surface water and groundwater

- While the organism is most abundant in soil depths exceeding 10 cm from the surface, the rainy season can cause the organism to move closer to the surface and multiply.
- This Gram-negative bacterium can survive extreme conditions, such as in distilled (without nutrients) water (for ≥16 years), nutrient-depleted soil or desert environments



- **Melioidosis is rarely contagious**

- **Melioidosis has zoonotic potential, but it has been rarely reported.**

- **Both human and animals acquire the diseases directly from the environment**

Epidemiology

- Predominantly disease of rice farmers
- Endemic in tropics and subtropics
  - Southeast Asia, Australia, The Middle East, India, China, Caribbean

Geographical distribution

- The incidence of recognized cases is highest in
  - ✓ North- east Thailand and Northern Australia

- but melioidosis is also known to occur in numerous countries across
  - ✓ South and East Asia, in Central America,
  - ✓ Ecuador, and Brazil, and
  - ✓ in several countries in Africa.

Published in final edited form as:
Nat Microbiol. 2016 January 1; 1(1): . doi:10.1038/nmicrobiol.2015.8.

Predicted global distribution of *Burkholderia pseudomallei* and burden of melioidosis

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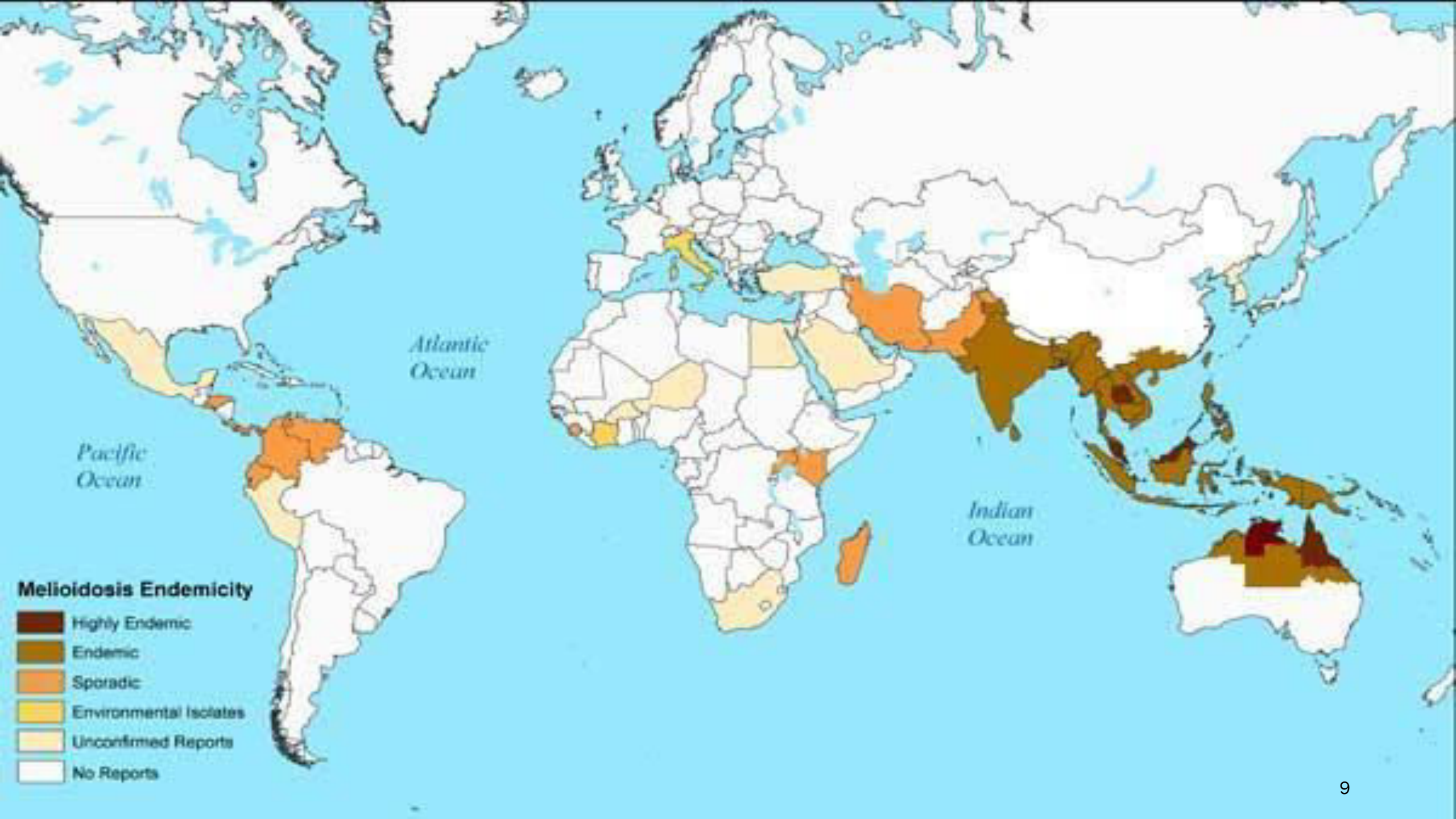
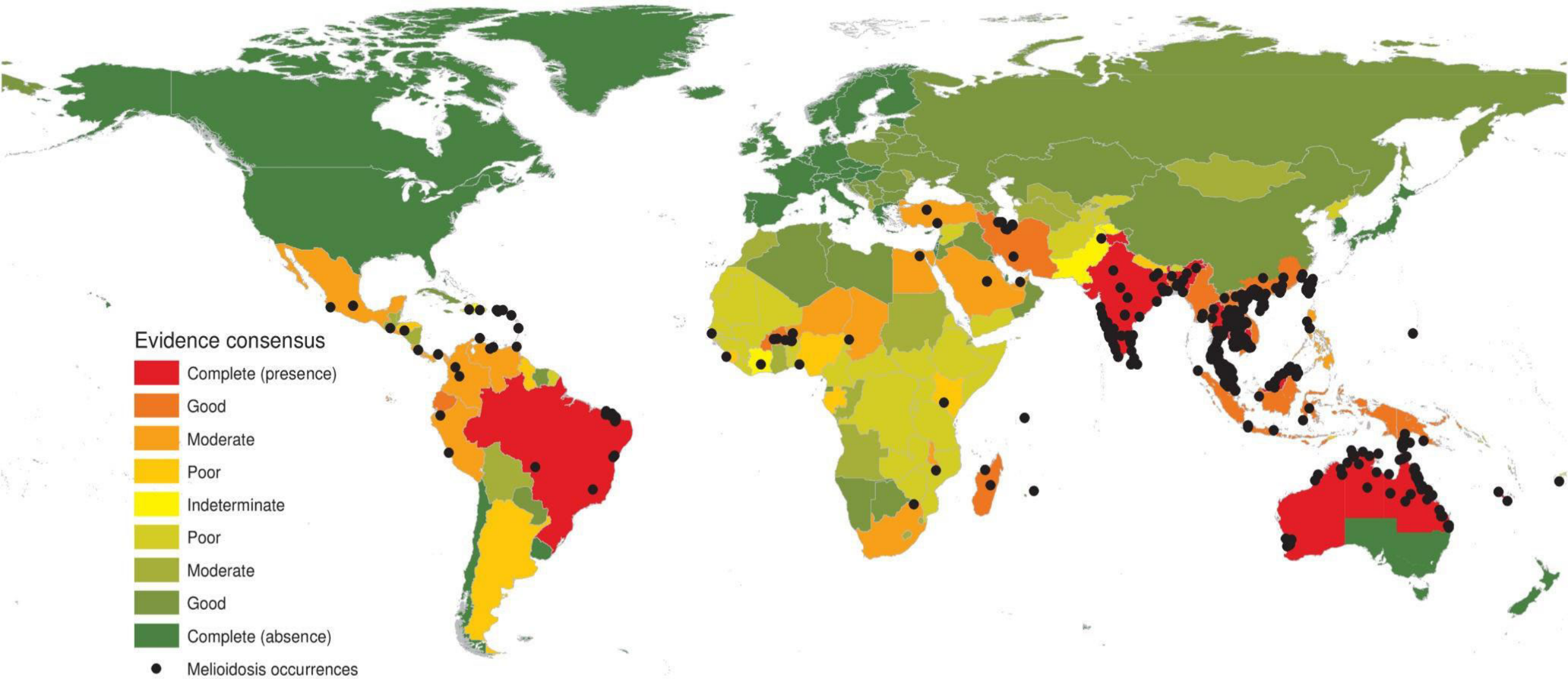
Abstract

Burkholderia pseudomallei, a highly pathogenic bacterium that causes melioidosis, is commonly found in soil in Southeast Asia and Northern Australia[1,2]. Melioidosis can be difficult to diagnose due to its diverse clinical manifestations and the inadequacy of conventional bacterial identification methods[3]. The bacterium is intrinsically resistant to a wide range of antimicrobials, and treatment with ineffective antimicrobials may result in case fatality rates (CFRs) exceeding 70%[4,5]. The importation of infected animals has, in the past, spread melioidosis to non-endemic areas[6,7]. The global distribution of *B. pseudomallei* and burden of melioidosis, however, remain poorly understood. Here, **we map documented human and animal cases, and the presence of environmental *B. pseudomallei*, and combine this in a formal modelling framework[8-10] to estimate the global burden of melioidosis. We estimate there to be 165,000 (95% credible interval 68,000-412,000) human melioidosis cases per year worldwide, of which 89,000 (36,000-227,000) die**. Our estimates suggest that melioidosis is severely underreported in the 45 countries in which it is known to be endemic and that melioidosis is likely endemic in a further 34 countries which have never reported the disease. The large numbers of estimated cases and fatalities emphasise that the disease warrants renewed attention from public health officials and policy makers.

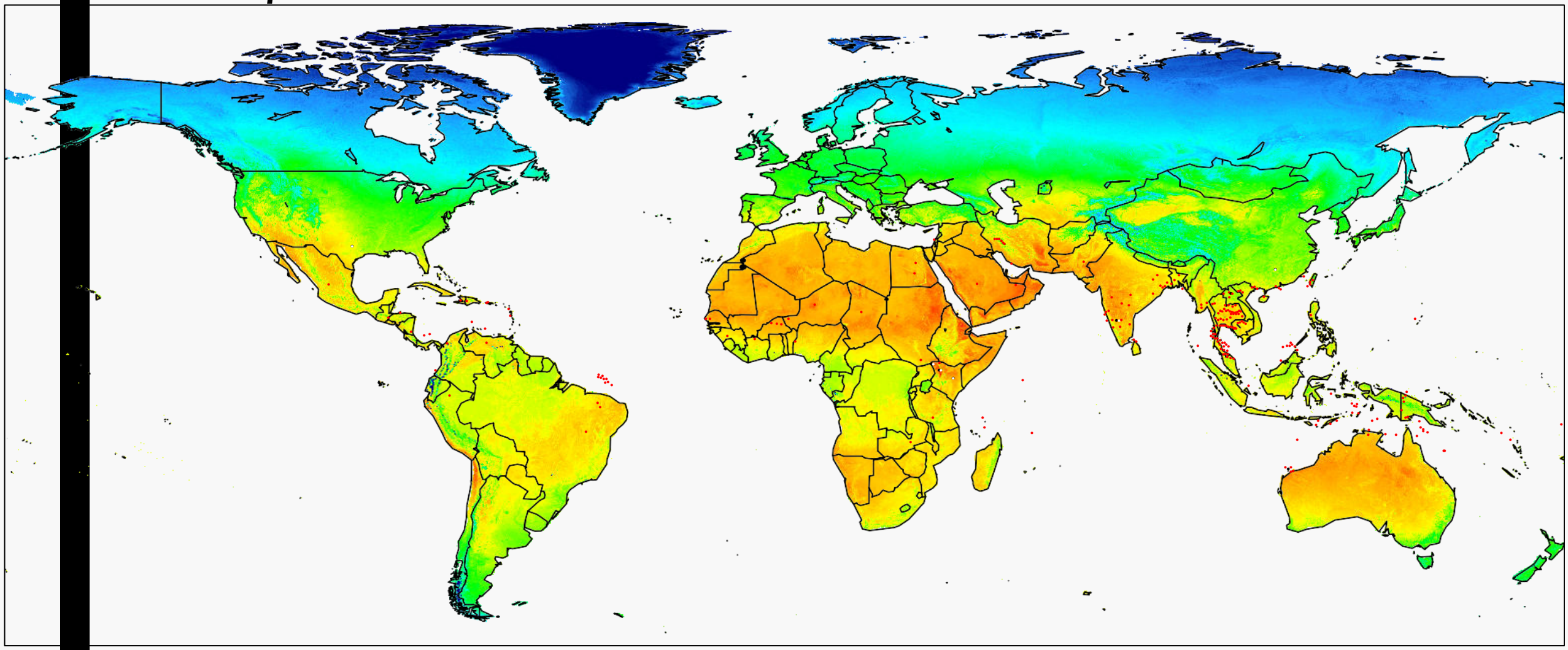

Atlantic Ocean
Pacific Ocean
Indian Ocean
Melioidosis Endemicity
Highly Endemic
Endemic
Sporadic
Environmental Isolates
Unconfirmed Reports
No Reports

Global evidence consensus and geographic locations of occurrence data from 1910 to 2014

Country coloring is based on evidence-based consensus with green representing a complete consensus on absence of *B. pseudomallei* and red a complete consensus on presence of *B. pseudomallei*. Black dots represent geo-located records of melioidosis cases or presence of *B. pseudomallei*.



Using environmental factors to predict global distribution of *B. pseudomallei*



Methods was published in Bhatt et al, Nature (2013) Apr 25; 496(7446): 504-7

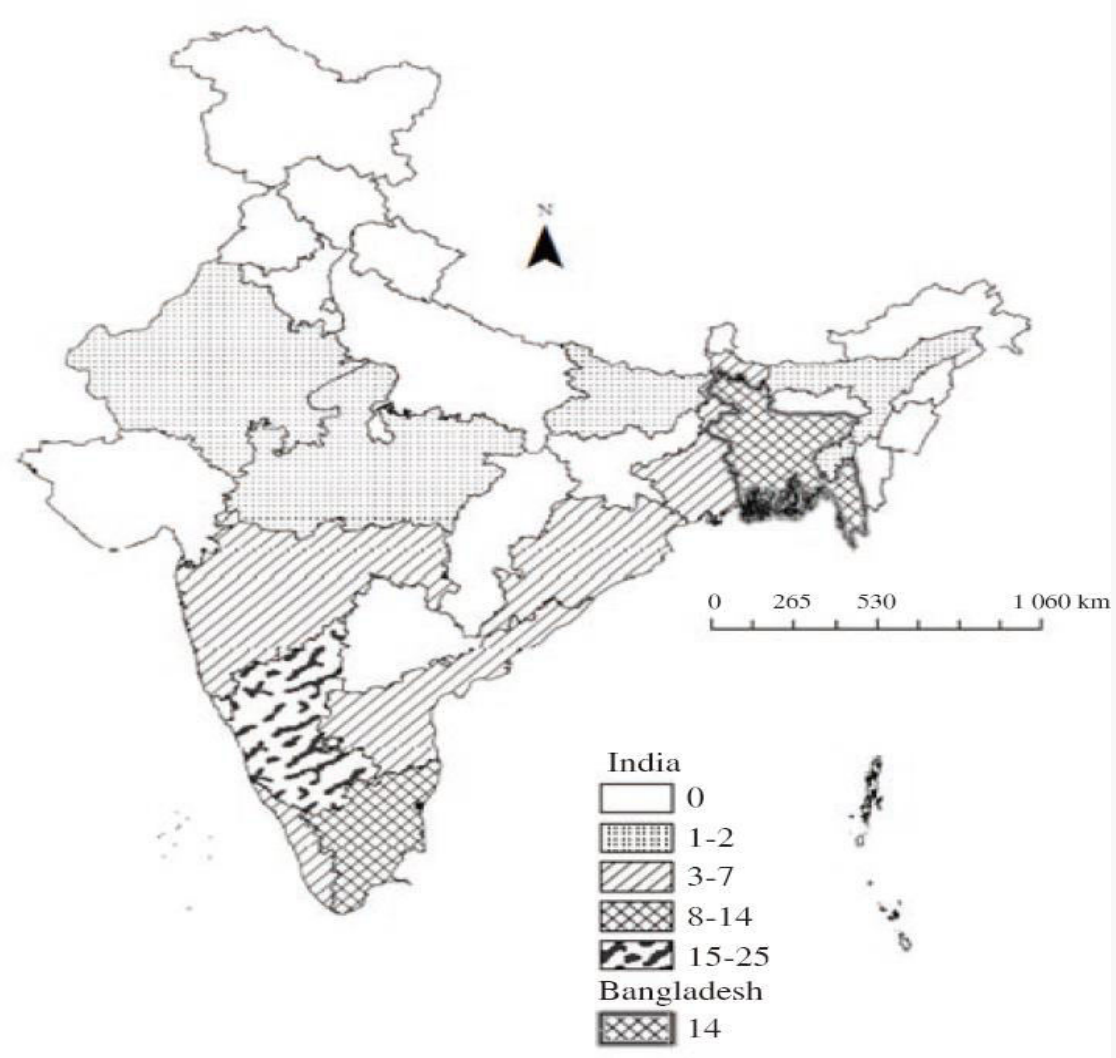
Melioidosis in India

- True burden of melioidosis in India remains poorly understood

- A 2016 modelling study has predicted a
  - ✓ Global annual incidence of **~165,000 cases** worldwide with an estimated case fatality of **89,000 (54%)**.
  - ✓ In this study predicted annual incidence for **India ~52,500 cases**.
  - ✓ However, **only ~1,300 cases were reported** per year worldwide since 2010, which is <1% of the estimated annual incidence

- This study highlights that underdiagnosis and under-reporting of melioidosis are a major issue

- A total of 96 culture-confirmed cases of melioidosis were reported from India between 1953 and June 2016.
- 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.



HOW MELIDIOSIS IS SPREAD

- Humans are believed to acquire the infection by
- ***contact with contaminated soil especially through skin abrasions***
- ***inhalation of dust,***
- ***ingestion of contaminated water***

- Melioidosis can also spread from person to person by contact with the body fluids of an infected person , but reported rarely

Transmission

- ✓ ***Percutaneous inoculation (Predominant mode)***
- ✓ ***Inhalation***
- ✓ ***Ingestion***
- ✓ ***Occasionally aspiration***
- • ***Person to person transmission is extremely unusual***
- • ***Mother infant transmission during breastfeeding – B.pseudomallei mastitis***

Risk factors

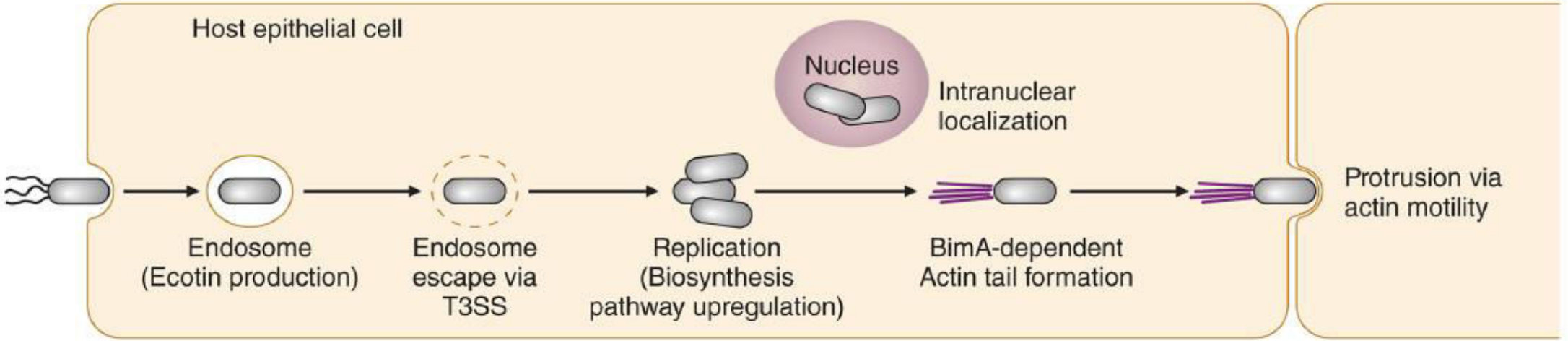
- ✓ Diabetes
- ✓ Hazardous alcohol use
- ✓ Chronic kidney disease , Urolithiasis
- ✓ Chronic lung disease , Cystic fibrosis .
- ✓ Thalassemia
- ✓ Malignancy, steroids, and other immunosuppressive therapy.
- ✓ Rheumatic heart disease and/or congestive cardiac failure.
- ✓ Pulmonary hemosiderosis, chronic granulomatous disease and tuberculosis.

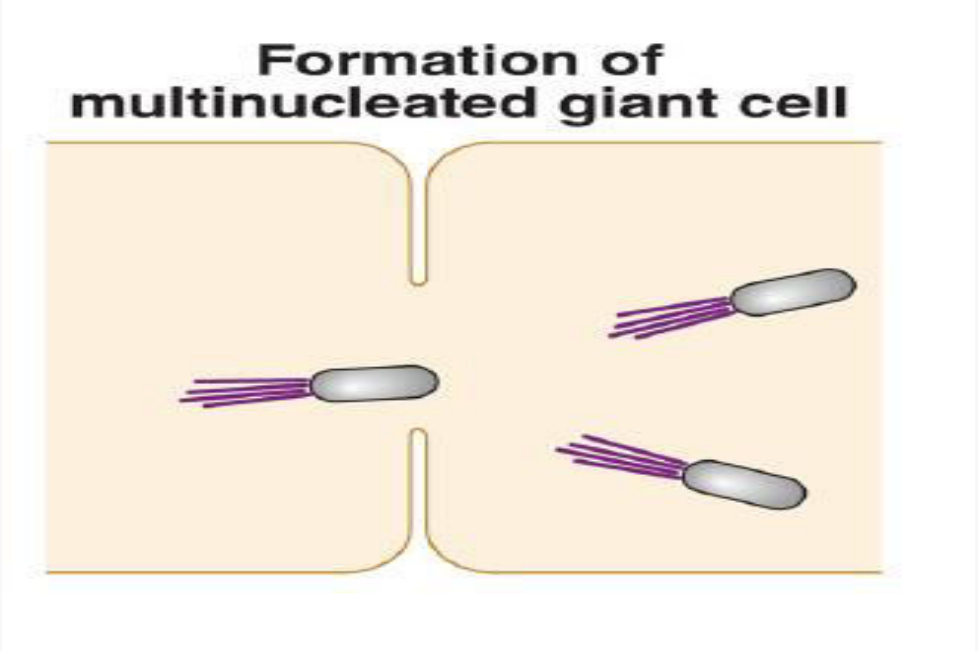
VIRULENCE AND PATHOPHYSIOLOGY

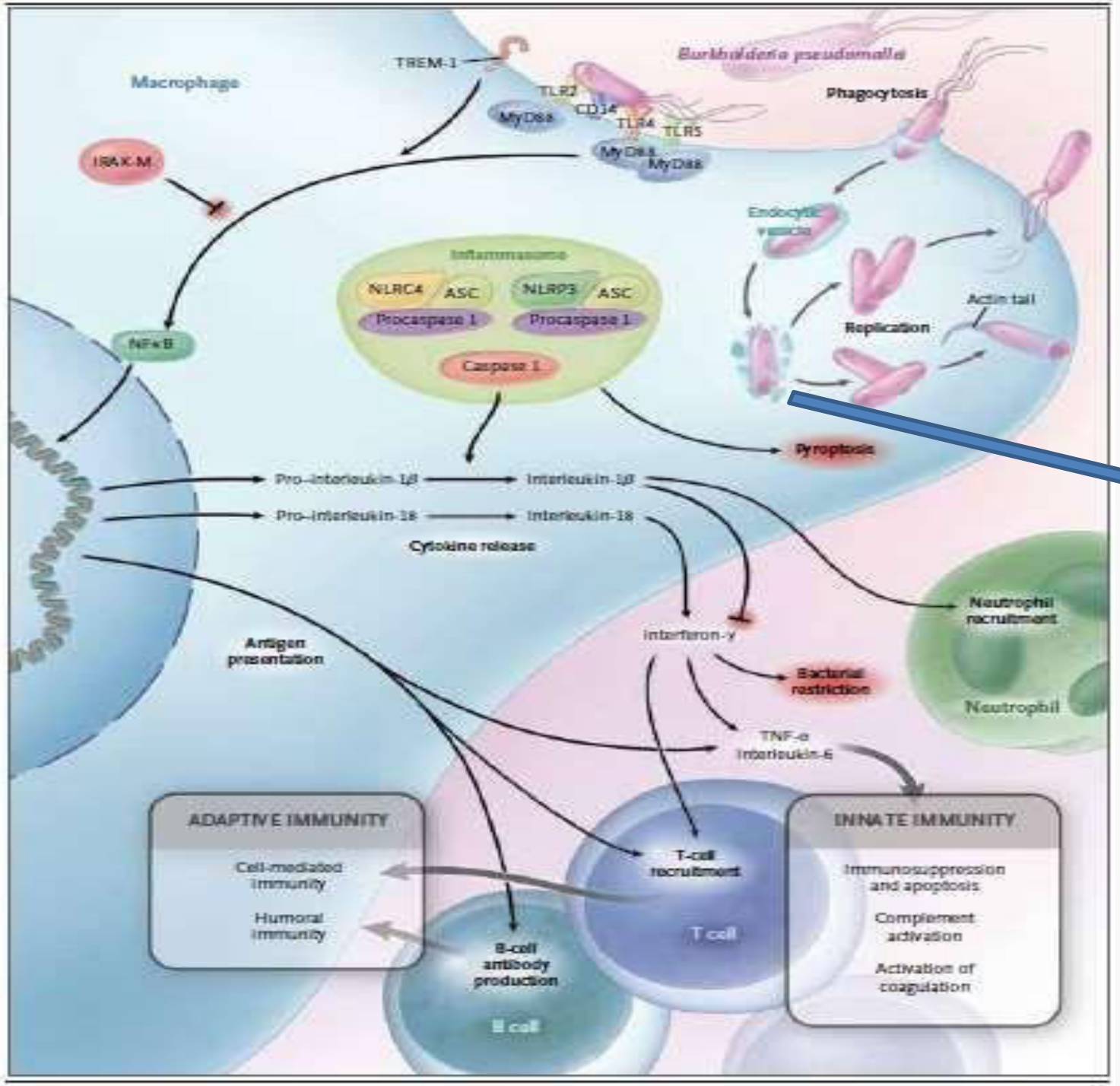
- **B. *pseudomallei*** is capable of surviving hostile environmental conditions, including prolonged
  - nutrient deficiency (of durations of up to 10 years),
  - mild antiseptic and detergent solutions,
  - acidic environments (pH 4.5 for up to 70 days) , and
  - a wide temperature range (24 to 32°C) and
  - dehydration (soil water content of <10% for up to 70 days) but not exposure to UV light.

- **VIRULENCE FACTORS** :-
  - Flagella
  - Pili
  - Capsular polysaccharide
  - Lipopolysaccharide
  - Multiple secretion systems, the Type III secretion system (T3SS), T2SS, and T5SS,,T6SS

Internalization and intracellular survival



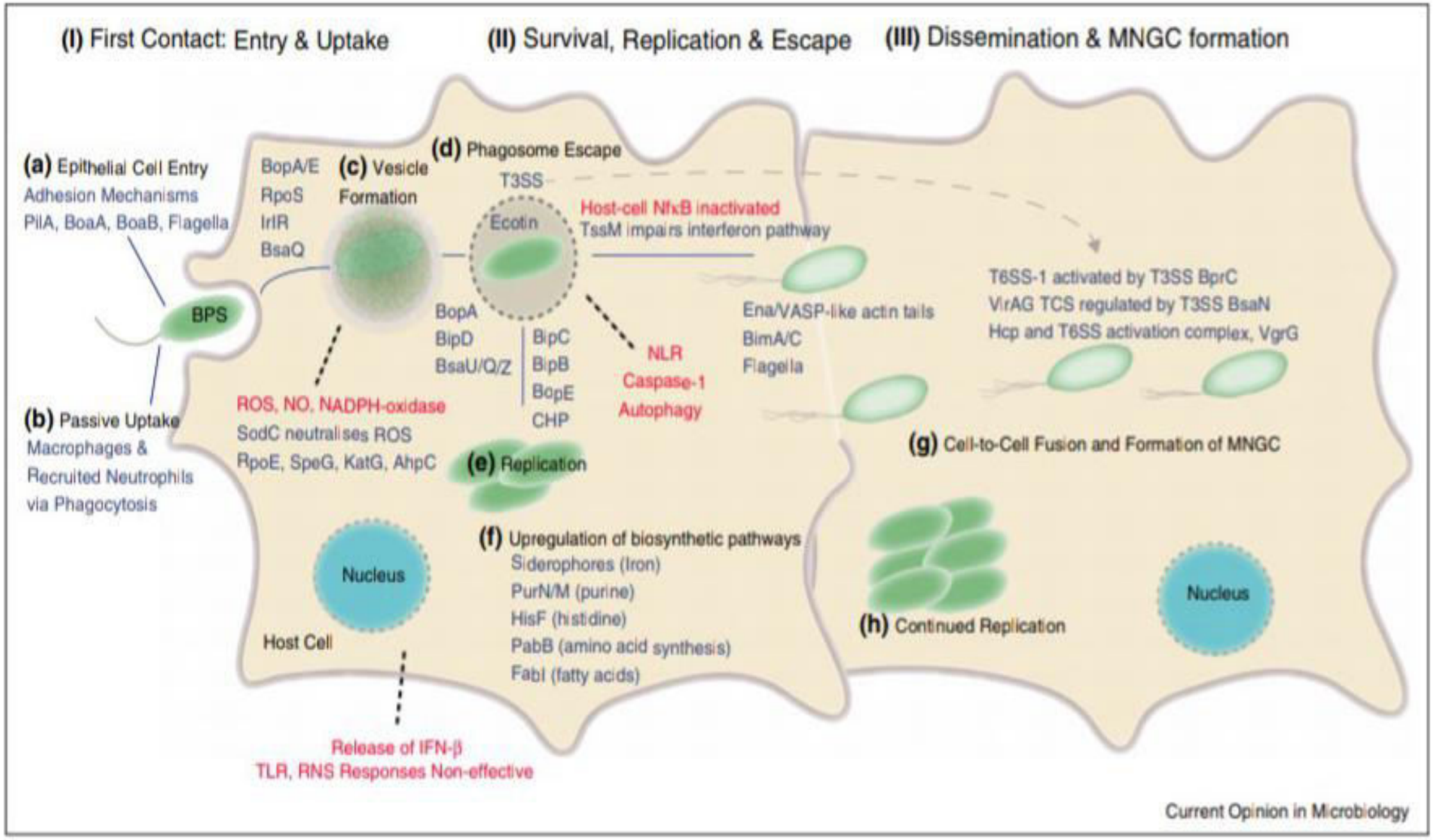




Immunopathogenesis

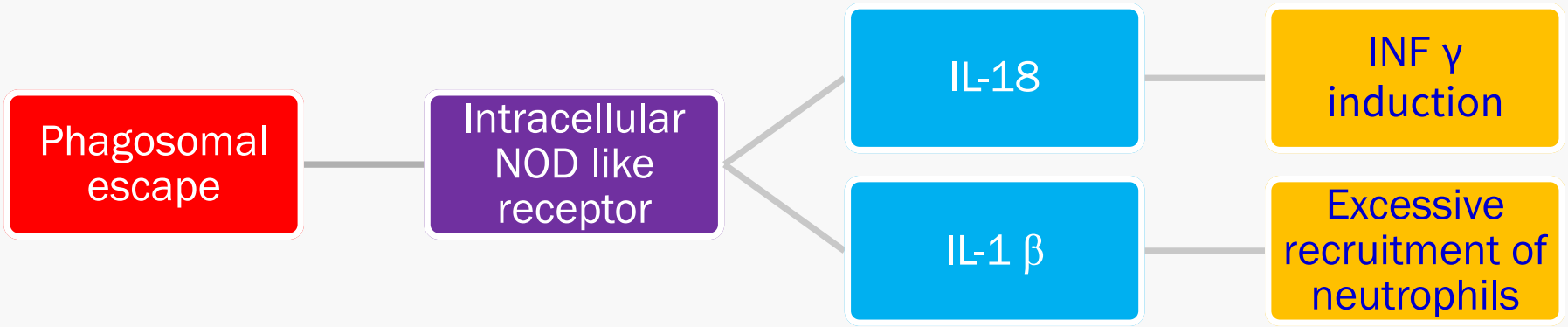
Data from in vitro and animal studies
intracellular- invasion, survival and replication in both phago & Nonphagocytic cells

Escaping endocytic vesicles and Breakout into cytoplasm & replicate
OR
infect other cells through actin based membrane protrusions which help in spreading infection


(I) First Contact: Entry & Uptake
(II) Survival, Replication & Escape
(III) Dissemination & MNGC formation
(a) Epithelial Cell Entry
Adhesion Mechanisms
PilA, BoaA, BoaB, Flagella
BPS
(b) Passive Uptake
Macrophages &
Recruited Neutrophils
via Phagocytosis
BopA/E
RpoS
IrlR
BsaQ
(c) Vesicle
Formation
ROS, NO, NADPH-oxidase
SodC neutralises ROS
RpoE, SpeG, KatG, AhpC
(d) Phagosome Escape
T3SS
Ecotin
BopA
BipD
BsaU/Q/Z
BipC
BipB
BopE
CHP
Host-cell NfκB inactivated
TssM impairs interferon pathway
NLR
Caspase-1
Autophagy
Ena/VASP-like actin tails
BimA/C
Flagella
T6SS-1 activated by T3SS BprC
VirAG TCS regulated by T3SS BsaN
Hcp and T6SS activation complex, VgrG
(e) Replication
(f) Upregulation of biosynthetic pathways
Siderophores (Iron)
PurN/M (purine)
HisF (histidine)
PabB (amino acid synthesis)
FabI (fatty acids)
Nucleus
Host Cell
Release of IFN-β
TLR, RNS Responses Non-effective
(g) Cell-to-Cell Fusion and Formation of MNGC
(h) Continued Replication
Nucleus
Current Opinion in Microbiology

Host immune response

- Pattern recognition receptors, mainly the toll-like receptors (TLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs), are the first to detect pathogen invasion and serve as the link between the innate and adaptive immune response
- TLRs recognize pathogen associated molecular patterns (PAMPs) mediates an inflammatory response via MyD88



- **INFLAMMATORY RESPONSE**
  - **Intial pro-inflammatory response – protective**
  - **Dysregulated cytokine mediated immune response – fatal**
  - **Elevated IL-6 , IL-12, IL-15, IL-18, TNF & INF-γ – correlated with fatal outcome**
  - **Anti inflammatory cytokines IL-10, IL-4, IL-1 upregulated in septic melioidosis and non-survivors**

Time course of infection

- **INCUBATION PERIOD :-**

- **1 to 21 days (mean 9 days)**
- **Rapid onset (within 24 hours) :- presumed aspiration, heavy environmental exposure**
- **Factors influencing incubation period :-**
    a. **Inoculating dose**
    b. **Mode of transmission**
    c. **Host risk factors**
    d. **Variable properties of the isolate**

- Most B. pseudomallei are Asymptomatic
- If symptomatic
  - **Acute infection**
    - 89% of symptomatic individuals present with acute illness
  - **Chronic infection**
    - Mimics pneumonia, tuberculosis, non healing ulcer or abscess
  - **Latent infection with reactivation**

Clinical manifestations

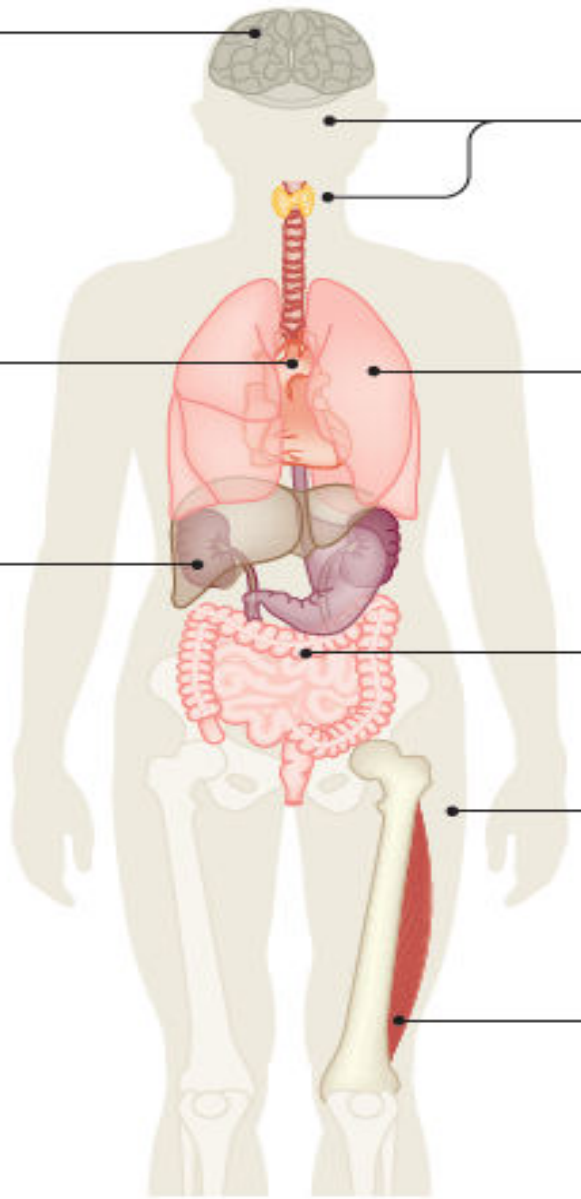
- **Most B.pseudomallei infections are sub-clinical.**
- **Most common clinical manifestations**
  - **Pneumonia (adults) with or without septicemia**
  - **Localised skin infection (children)**
- **Bacteremic spread of the organism can result in clinical manifestations involving virtually any site.**

Central nervous system (1–5%)
- Encephalomyelitis
- Brain abscess

Cardiovascular system (40–60%)
- Bacteraemia (40–60%; bacteria without evident focus 10%)
- Pericarditis
- Mycotic aneurysm

Urinary tract system (14–28%)
- Acute pyelonephritis
- Kidney abscess
- Prostatic abscess (20% of males in Austrailia)

Other
- Mastitis
- Mediastinal mass
- Corneal ulcer
- Epididymo-orchitis
- Scrotal abscess



Head and neck (0–30%)
- Parotid abscess (30% of children in Thailand)
- Neck abscess
- Lymphadenitis

Respiratory system (40–60%)
- Pneumonia (40–60%)
- Pulmonary abscess
- Pleuritis

Gastrointestinal system (10–33%)
- Liver abscess
- Splenic abscess
- Para-intestinal mass

Skin and soft tissue (13–24%)
- Skin ulcer
- Soft tissue abscess

Musculoskeletal system (4–14%)
- Septic arthritis
- Myositis
- Osteomyelitis

PULMONARY MELIOIDOSIS

- Fever
- Cough
  - Productive /non productive
  - Haemoptysis is rare in acute disease but may be present in up to 31% of patients with chronic disease
- **Acute fulminant pneumonia** with septicaemia which commonly requires mechanical ventilation and intensive care, mortality exceeding 80%

- Chest radiograph
  - **Acute:** localised patch or bilateral diffuse patchy alveolar infiltration or multiple nodular lesions which may coalesce, cavitate and form abscesses.
  - **Chronic**: mimic pulmonary tuberculosis
- Rarely pleural effusion, empyema, pyopericardium and hilar lymphadenopathy

Pneumonia

- ***Acute presentation***
  - High fever, cough, sputum, chills, rigors, and respiratory distress with or without shock

- ***Subacute or chronic presentation***
  - Cough, Purulent sputum production, hemoptysis, and night sweats, (which make suspicious of tuberculosis)

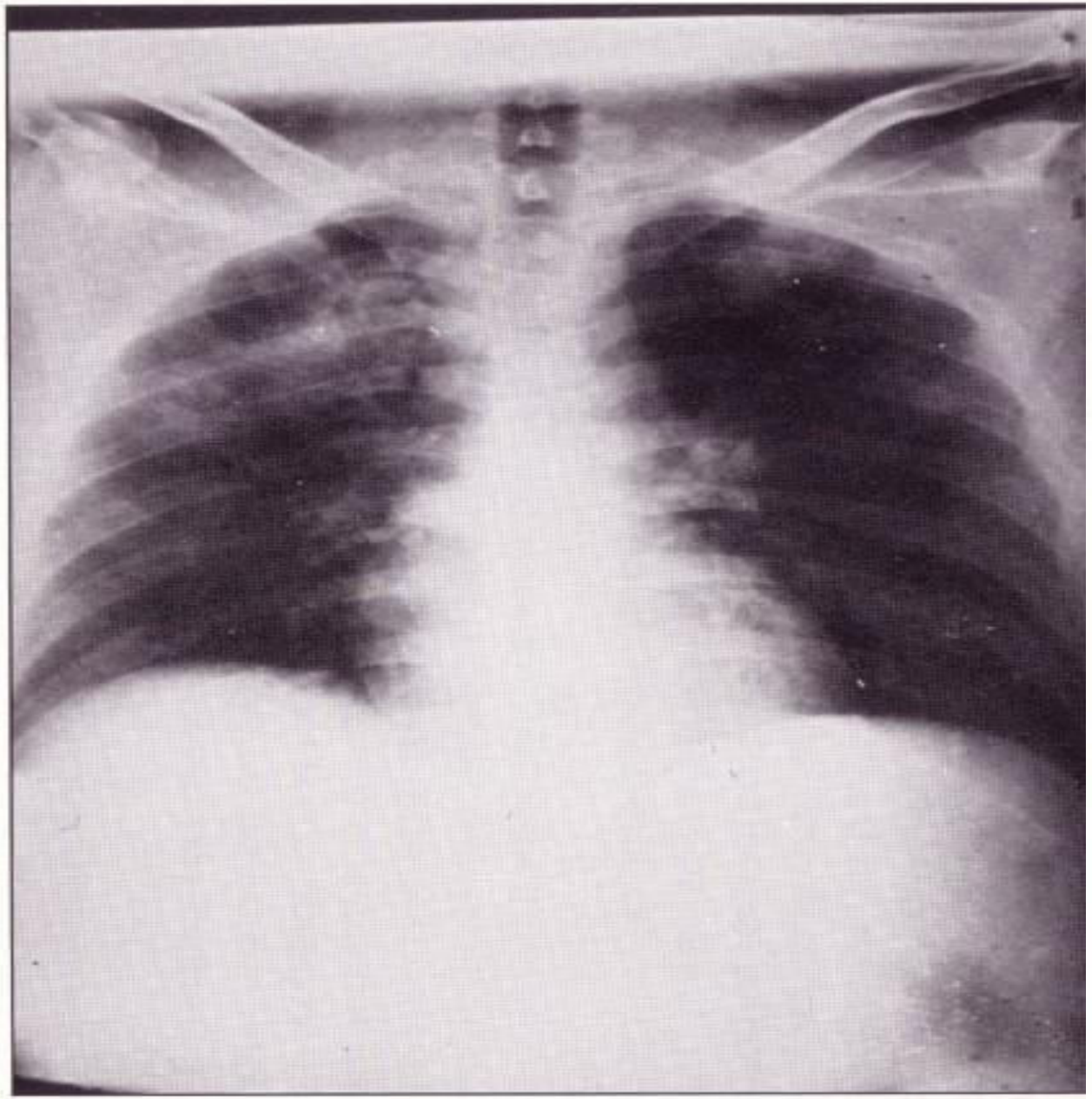


FIGURE 53.—Typical X-ray of cavitary melioidosis. Note t
resemblance to tuberculosis. (Courtesy, Col. John J. Deller, J
MC.)

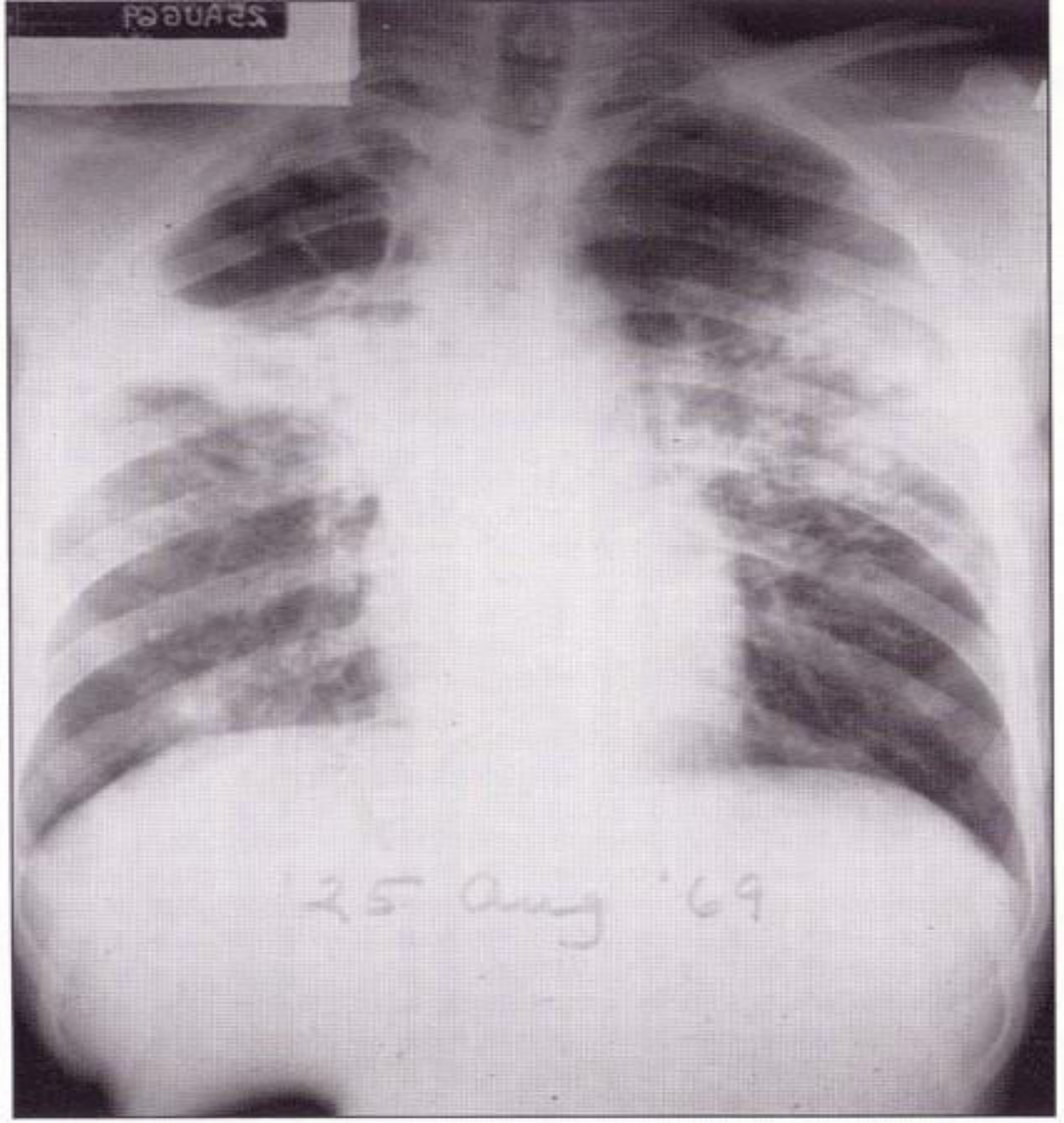
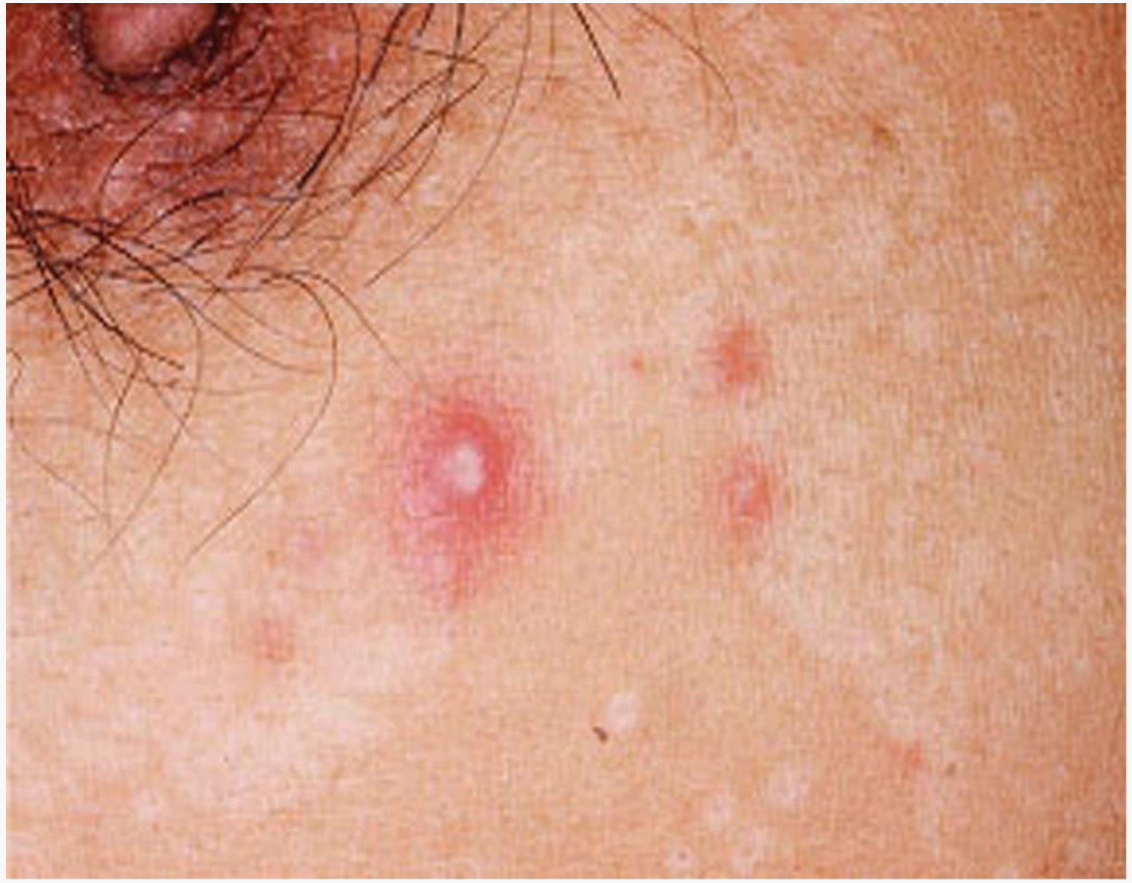
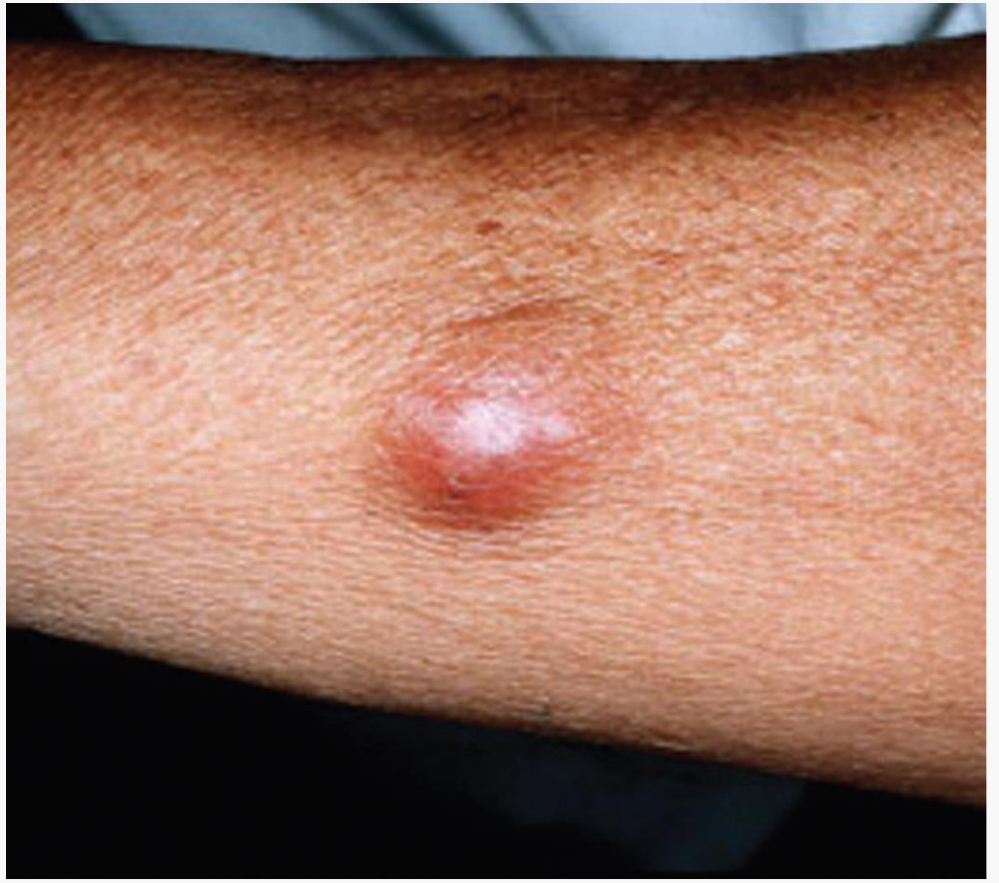


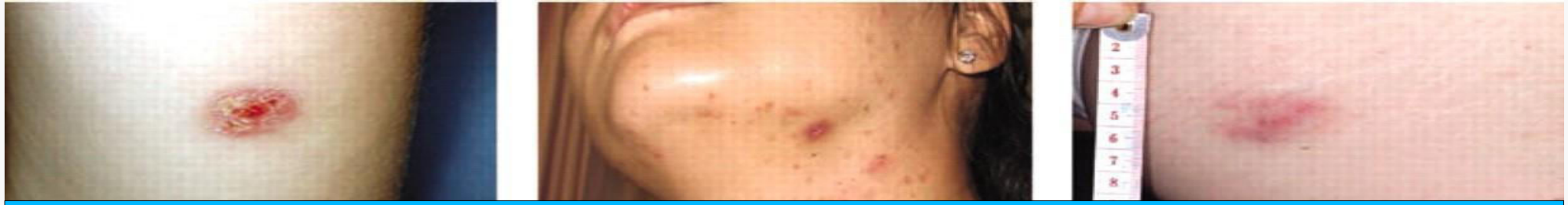
FIGURE 58.—Initial X-ray in a case of pulmonary melioidosis, untreated on 25 August 1969. (Courtesy, Col. John J. Deller, Jr., MC.)

- **Skin ulcers and abscess**
- **Bacteremia and sepsis**
- **Genitourinary melioidosis :-**
  - ✓ **Suprapubic pain, dysuria, difficultly passing urine, or acute urinary retention**
  - ✓ **Diarrhoea frequently accompanies these symptoms**
  - ✓ **A tender , boggy prostate may be found on rectal examination**
- **Septic arthritis or osteomyelitis**

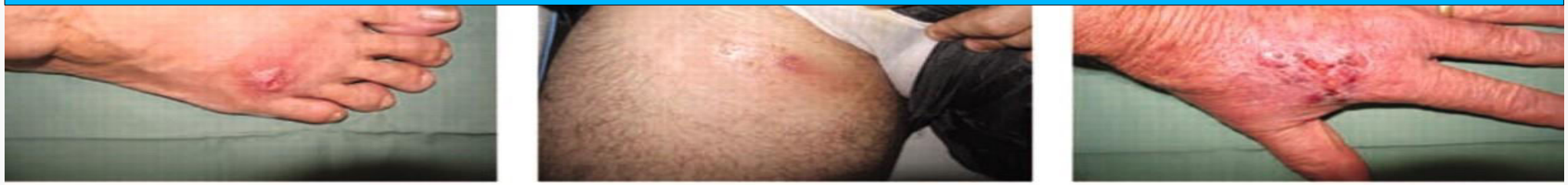




- Skin and soft tissue involvement in two patients with melioidosis. Skin pustules and subcutaneous abscess occurring as secondary foci of infection associated with disseminated infection



Primary(Localised) skin melioidosis



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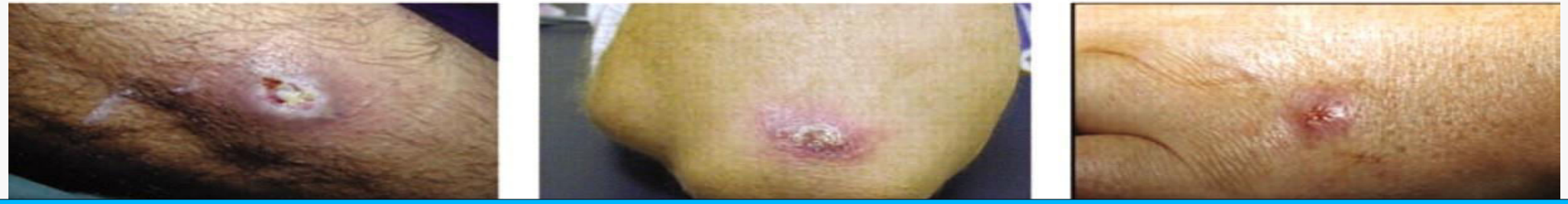
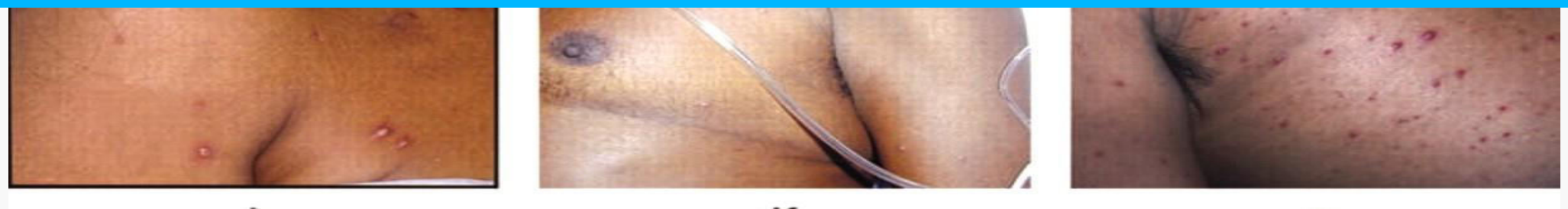


Secondary (Disseminated) skin melioidosis



- **Neurological involvement**
  - unilateral upper motor neuron limb weakness,
  - cerebellar signs,
  - cranial nerve palsies (particularly VI, VII nerve palsy and bulbar palsy), or
  - flaccid paraparesis alone
  - brain abscesses,
  - myelitis, and
  - brainstem encephalitis .

- **Other sites of involvement include**
  - lymphadenitis,
  - pericarditis,
  - adrenal gland abscess,
  - mycotic aneurysm,
  - breast abscess,
  - pancreatitis,
  - orbital cellulitis, and sinusitis.

MELIOIDOSIS IN CHILDREN

- Acute septicaemia with foci of infection in the lungs (the most frequently involved organ), liver, spleen or other organs

- Localised infection is common
  - **Unilateral suppurative parotitis** has been reported to account for 40% of localised melioidosis in Thailand
    - unilateral parotid swelling with abscess formation
      - facial nerve paralysis
      - periorbital cellulitis
      - conjunctivitis
      - purulent discharges at the opening of Stensen's duct and the ear
  - **Pharyngocervical melioidosis**: fever and sore throat with or without cervical lymphadenopathy.

Clinical Definitions of Melioidosis

TABLE 1

Criteria for the diagnosis of naturally acquired melioidosis

	Definition
Definite melioidosis	One or more clinical samples culture-positive for *B. pseudomallei*
Probable melioidosis	Evidence of one or more abscesses that would be consistent with a diagnosis of melioidosis* but culture not performed or negative for *B. pseudomallei*, or culture negative for *B. pseudomallei* on first presentation but represented to hospital within 1 month with culture-proven melioidosis
Possible melioidosis	Clinically suspected melioidosis improved after treatment with an effective antimicrobial regimen for melioidosis (ceftazidime/carbapenem drug/amoxicillin-clavulanate) or clinically suspected melioidosis but the patient died before improvement was observed
Not melioidosis	Definite alternative diagnosis for manifestations leading to suspected melioidosis or resolution of clinical features of suspected melioidosis without treatment with antimicrobial drugs with activity against *B. pseudomallei*

* Evidence of splenic and/or hepatic abscesses with appearance on ultrasound characteristic for melioidosis (Swiss cheese appearance or small dispersed abscesses) or parotid or prostatic abscess in a melioidosis-endemic region where *B. pseudomallei* is the most probable cause.

Meliodosis – Diagnosis

- Clinical features, patient from endemic area or with h/o travel
- Radiological – splenic/hepatic abscess (swiss cheese)
- Microbiological ***– Gold Standard – Culture***
  - Confirmatory even with single colony
    - Confirmation by latex agglutination
  - Serological - IHA
  - Molecular
    - ***Real-Time PCR Assay Targeting the Type III Secretion System of Burkholderia pseudomallei***

DIAGNOSIS

- Melioidosis is diagnosed by ***isolating Burkholderia pseudomallei*** from the blood, urine, sputum, or skin lesions.

- ***Detecting and measuring antibodies*** to the bacteria in the blood is another means of diagnosis

DIAGNOSIS

- **Culture** is the **gold standard** for the diagnosis of melioidosis.
- It is 100% specific, but sensitivity may be as low as 60%.
- Samples of **blood, urine, throat swab, and respiratory secretions(CSF when indicated)**should be obtained for culture from all patients, together with **pus and wound swabs** where relevant.
- ***All sample types should be taken where possible since site of culture positivity may not necessarily relate to clinical focus of infection***

LAB DIAGNOSIS

- **Ashdown media** that contains aminoglycoside to which this organism is resistant : ***non-sterile specimens***

- **Blood agar and mac conkey media**: ***sterile specimens***

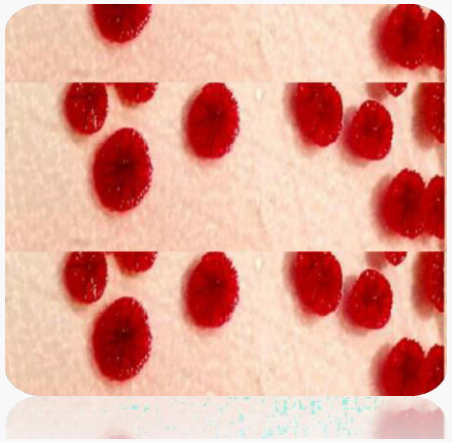
- Respiratory sample has been shown to have 100% specificity with 38% and 47% sensitivity in adult and paediatric patients, respectively

- J Clin Microbiology 2001; 39:3901-2 , J Infect Dis 1993; 167: 230-33

GROWTH ON STANDARD MEDIUM

- Grows on Standard Bacteriological media like macconkey or blood agar, colonies become rough and wrinkled on prolonged incubation

GROWTH ON ASHDOWN MEDIA



- **Ashdown's medium** is a selective culture medium for the isolation and characterisation of *Burkholderia pseudomallei*.
- the medium contains crystal violet and Gentamycin as selective agents to suppress the growth of other bacteria.
- Colonies of *B. pseudomallei* also take up neutral red which is present in the medium, Ashdown's agar needs to be incubated for a minimum of 96 hours instead of 48 hrs

selective Ashdown's medium :- Pinpoint, flat, dry. Purple. May be wrinkled

Blood agar :- Smooth , creamy colonies

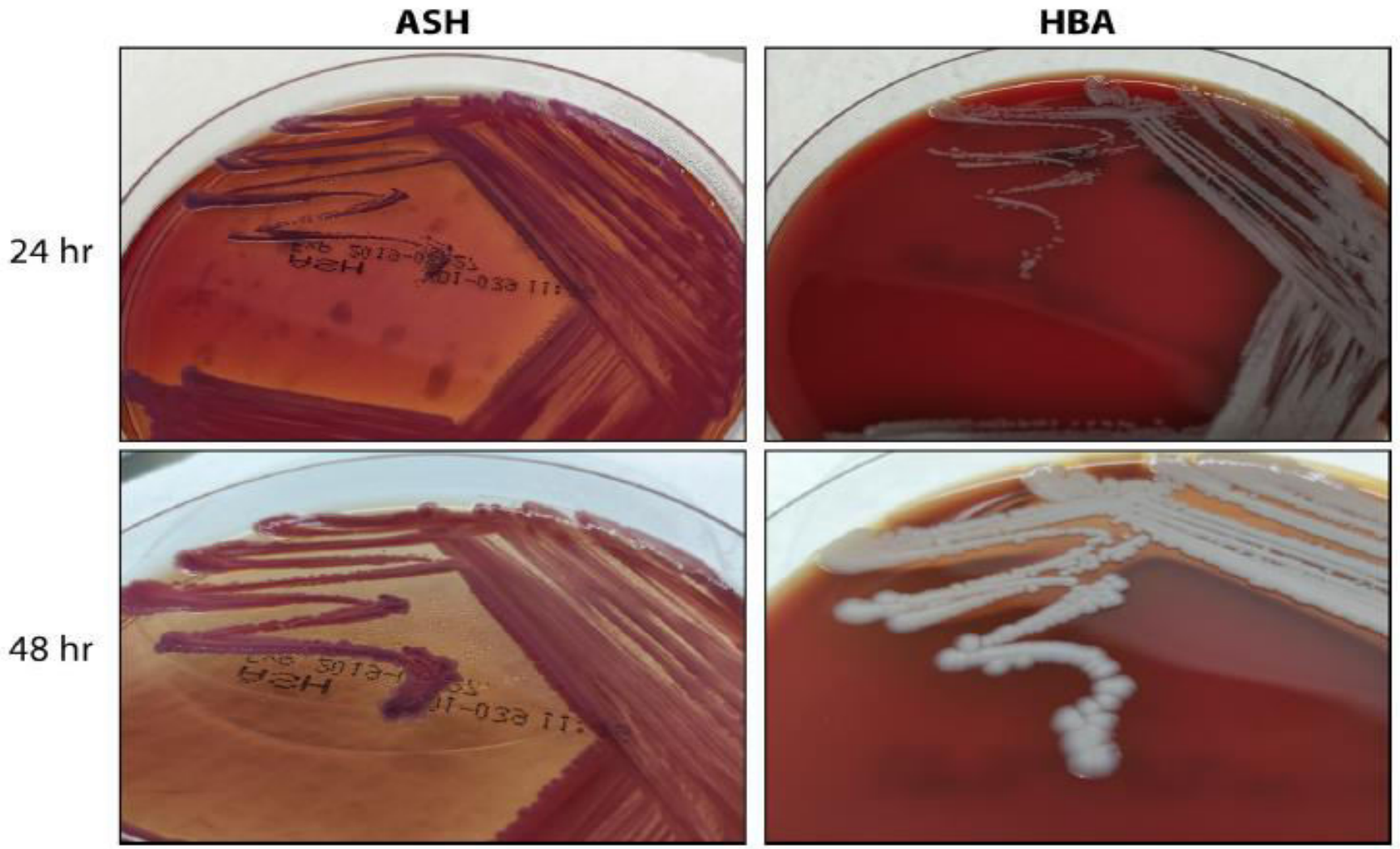
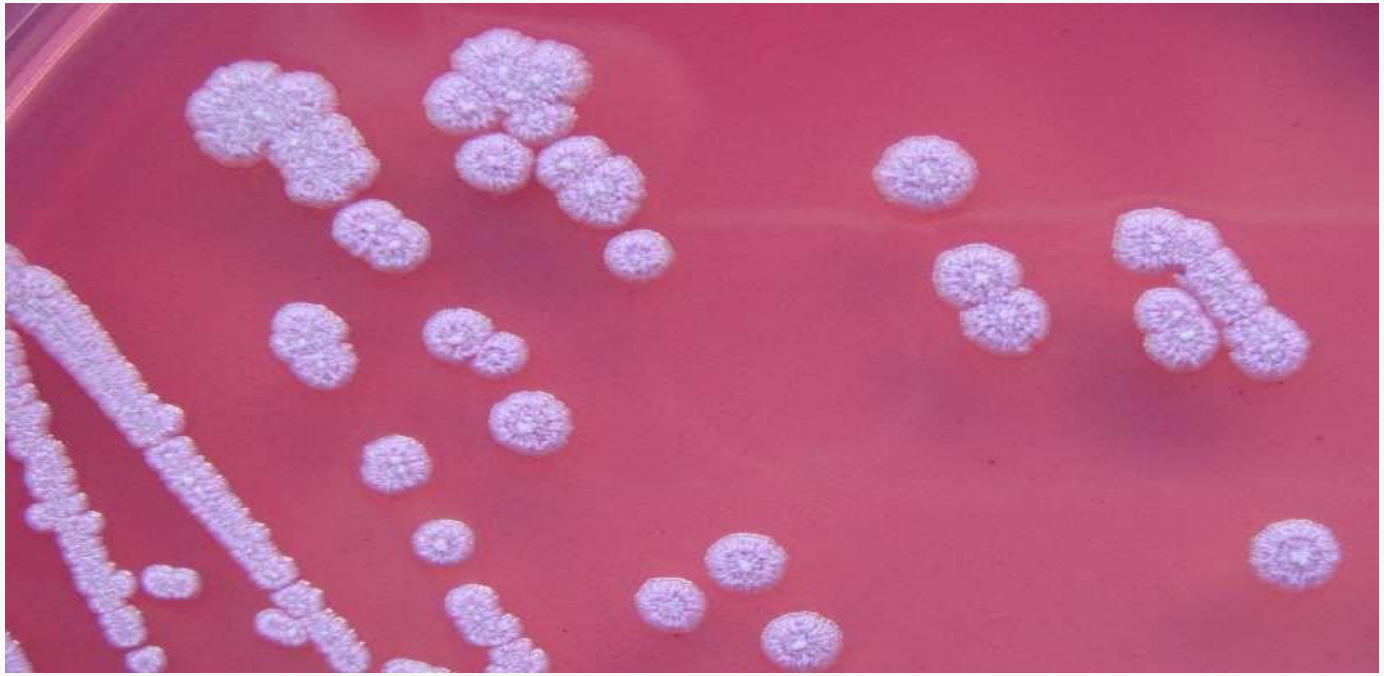


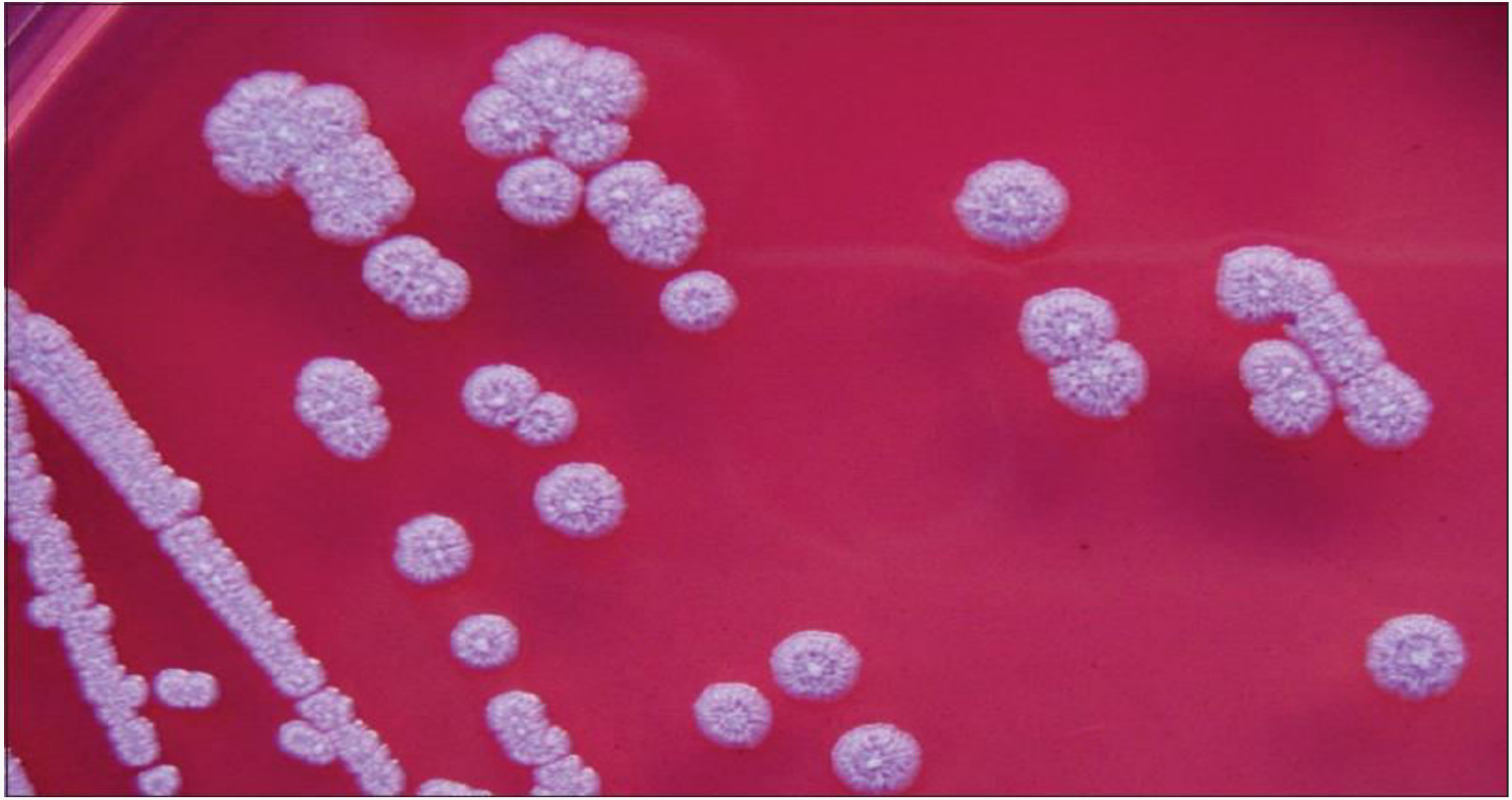
FIG 3 Colonial morphology of *B. pseudomallei*. Shown are *B. pseudomallei* cultures on ASH (left) and HBA (right) at 24 h (top) and 48 h (bottom).

Most common colony morphology of *B. pseudomallei* on Ashdown's agar - The colony appears irregular- edge, rough and pale purple.



Growing colonies of Burkholderia Pseudomallei on blood agar

Growing colonies of Burkholderia Pseudomallei on MacConkey agar



Culture confirmation-latex agglutination

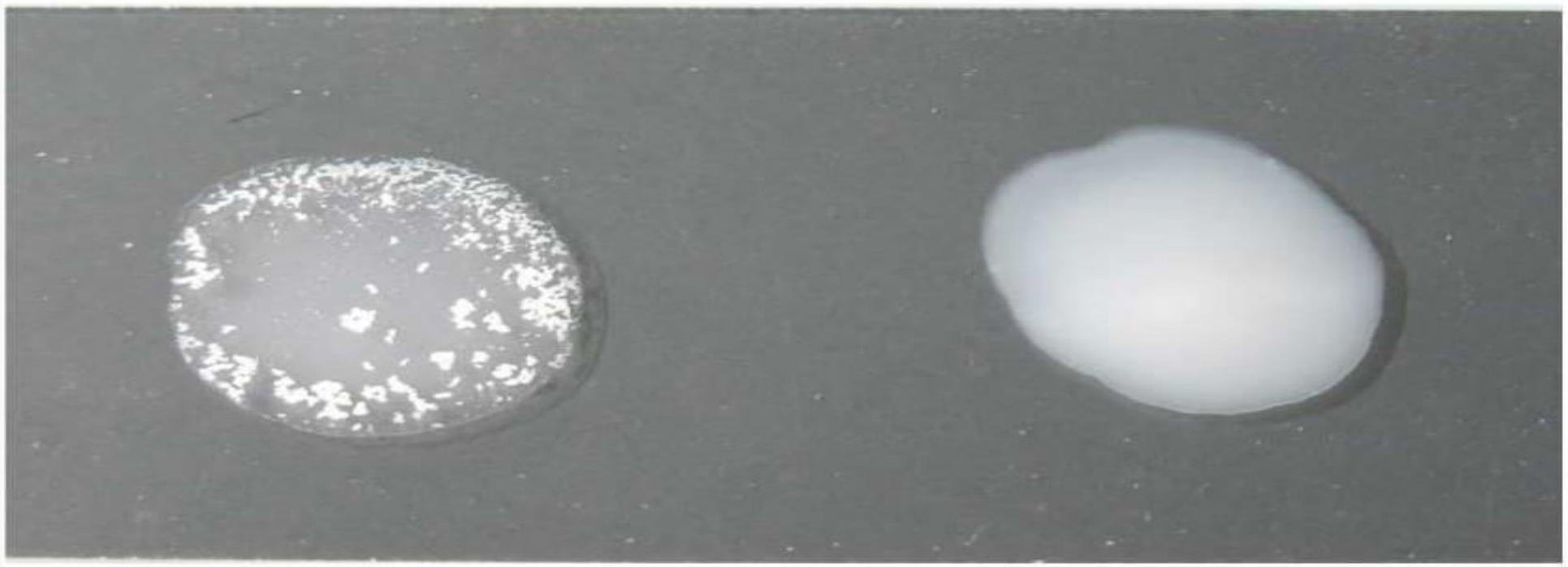


Figure 1: Positive latex agglutination test (left) after mixing 10 µl latex reagent with 10 µl positive control reagent provided and negative latex agglutination test (right) after mixing 10 µl latex reagent with 10 µl negative control reagent provided.

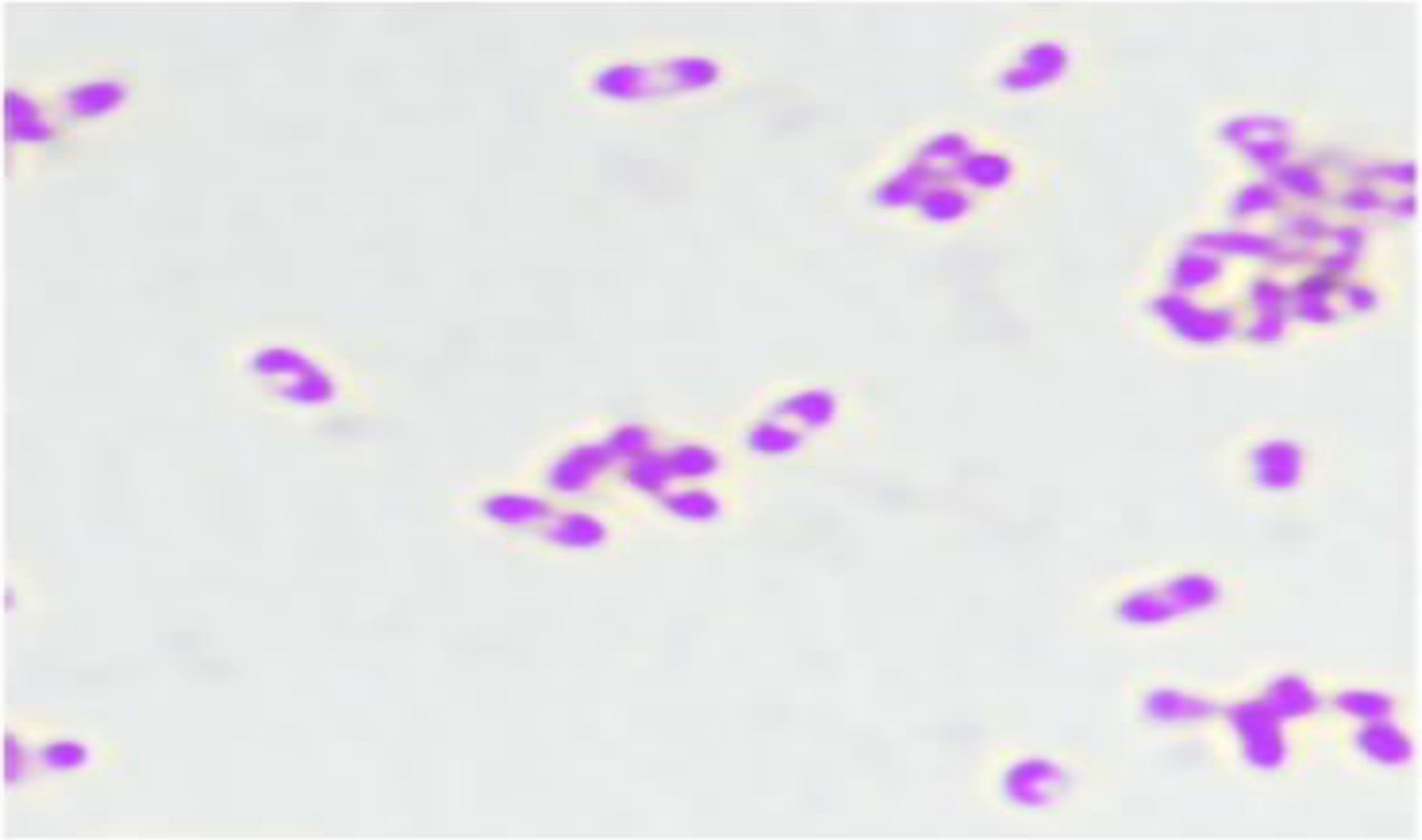


FIG 2 Gram stain demonstrating "safety pin" appearance. Magnification, ×100.

Antimicrobial Susceptibility Testing and Antimicrobial Resistance

- *B. pseudomallei* is intrinsically **resistant** to most antimicrobial agents, including
  - penicillin, ampicillin,
  - first- and second-generation cephalosporins,
  - the aminoglycosides gentamicin, tobramycin, and streptomycin, and
  - Polymyxin and colistin
- **Sensitive** to Ceftazidime and meropenem , co-trimoxazole (TMP-SMX), doxycycline, and amoxicillin-clavulanic acid

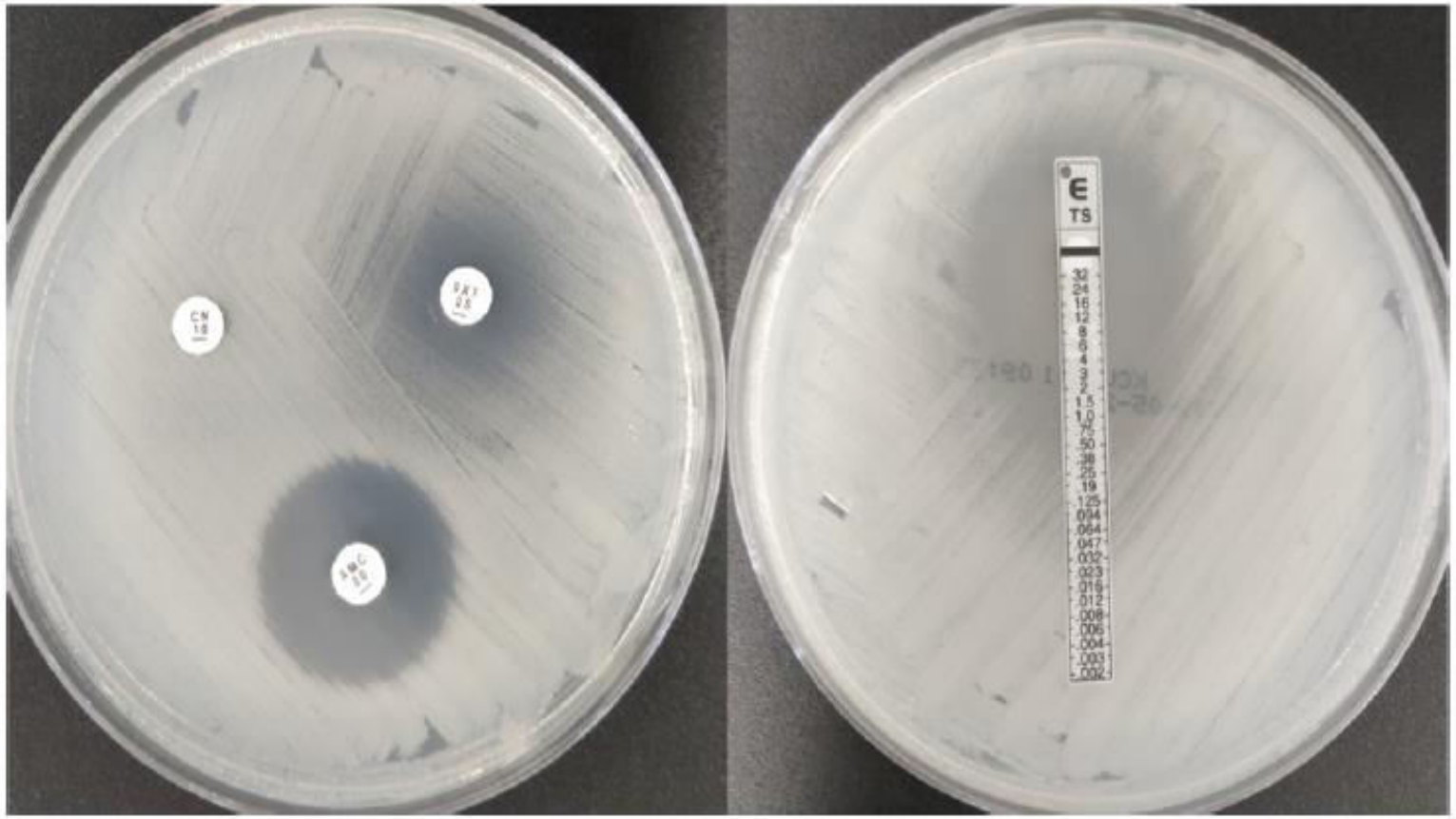
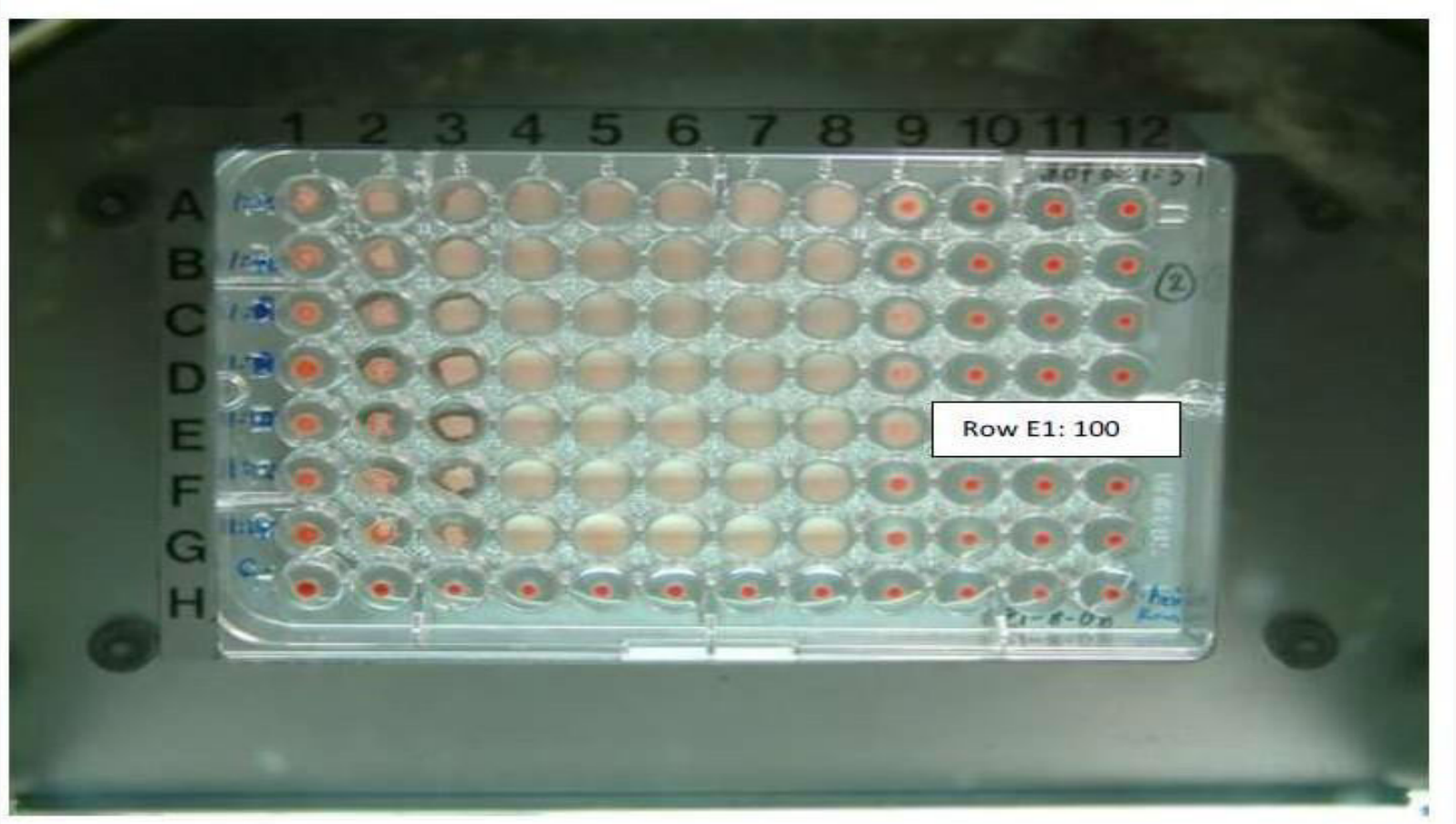


FIG 5 Susceptibility characteristics of *B. pseudomallei*. AMC, amoxicillin-clavulanate; CN, gentamicin; SXT and TS, trimethoprim-sulfamethoxazole. Double zone of susceptibility were seen with SXT.

SERODIAGNOSTIC TESTS

- Serodiagnostic tests should be considered for the investigation of persons with suspected melioidosis who are culture- negative, but should be interpreted with caution.
  - A rising antibody titre to *B. pseudomallei* in paired serum samples taken 2 weeks or more apart. Or
  - single high antibody titre at presentation.
- The most commonly used serodiagnostic method is the **indirect haemagglutination assay (IHA).**
- Several new enzyme-linked immunosorbent assays (ELISAs) targeting specific antigens, such as **hemolysin co-regulated protein 1 (Hcp1)** and **Opolysaccharide (OPS),** are being used

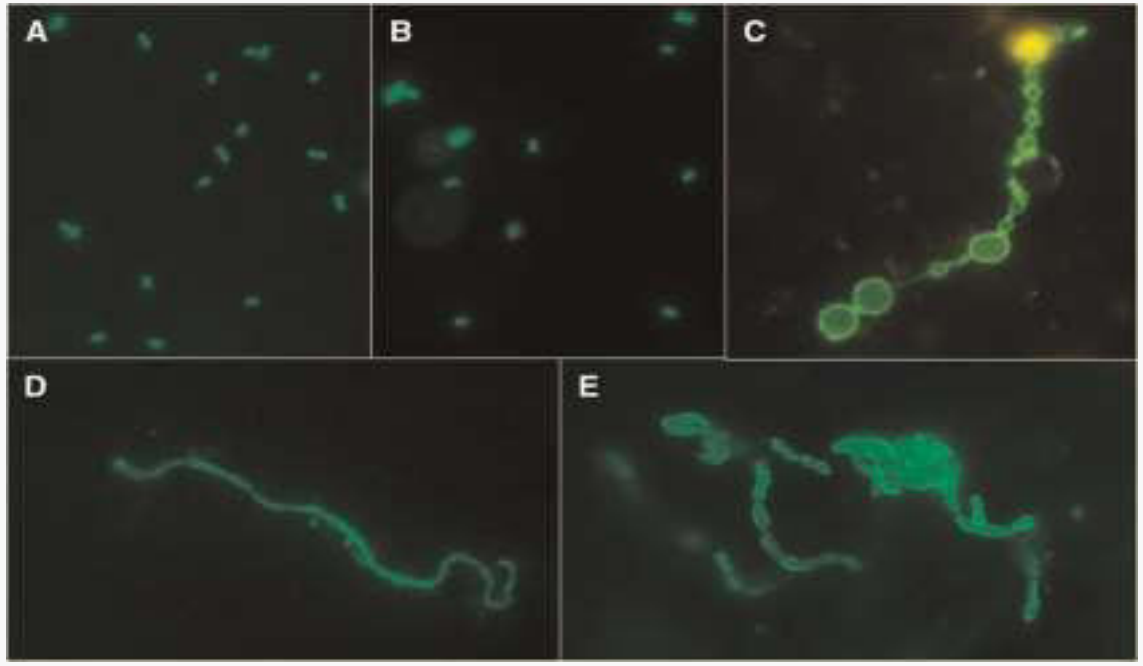
IHA - Indirect haemagglutination



Other techniques

- A variety of other antigen and DNA-detection techniques have been used to increase the diagnostic yield
- ***Rapid immunofluorescence microscopy*** of pus, sputum, and urine has been useful in Thailand
- ***Lateral flow immunoassays***
- ***Polymerase chain reaction (PCR)*** for direct detection from clinical samples ***Real-Time PCR Assay Targeting the Type III Secretion System of Burkholderia pseudomallei***
- ***Gene sequencing*** ***(*** 16s Rrna , groEL gene sequences***)***
- MALDI-TOF MS (Matrix-Assisted Laser Desorption/Ionization-Time Of Flight***) mass spectrometry***

Monoclonal antibody specific to B. pseudomallei (Mab-IFA)



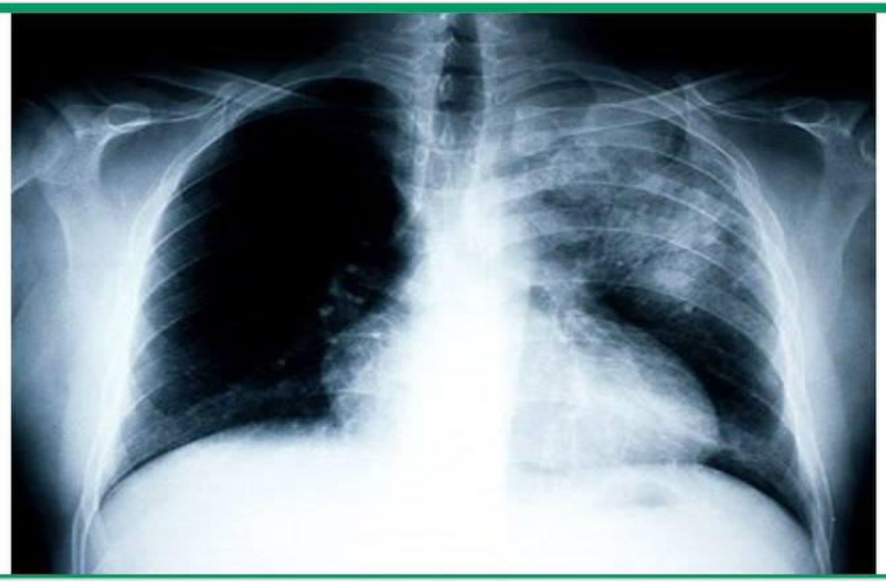
- 48.4% for sensitivity,
- 99.8% for specificity

FIGURE 1. Fluorescent microscopy of *Burkholderia pseudomallei* stained with Mab-IFA reagent. The bacteria shown were from laboratory cultures on Columbia agar (**A**) or LB broth (**B**), or from clinical samples (urine [**C**], pus [**D**], or sputum [**E**]) from patients with melioidosis. The atypical appearance of the bacterial morphology including bacterial elongation (**D** and **E**) and swollen cells (**C**) was not uncommon.

OTHER LABORATORY TESTS AND IMAGING

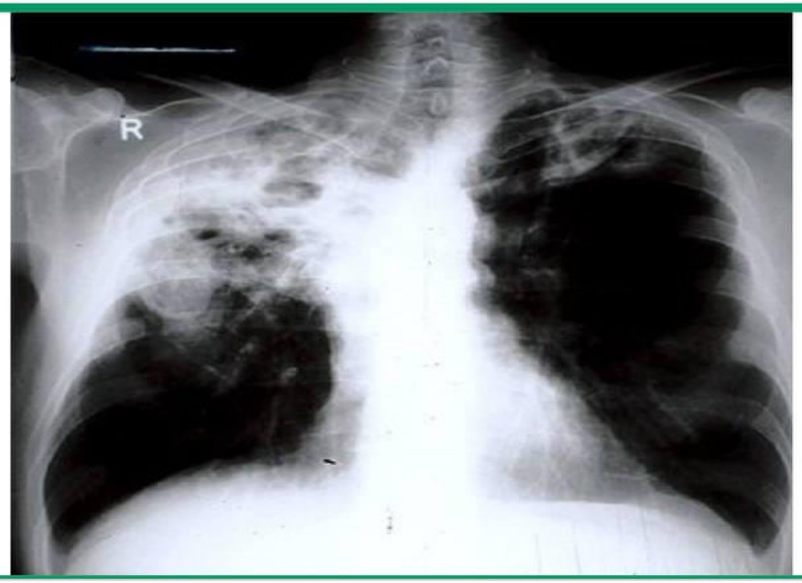
- CBP
- RFT
- LFT
- ABG
- CRP
- CHEST X RAY
- CT CHEST
- CT ABDOMEN , BRAIN

Chest radiograph of acute pulmonary melioidosis



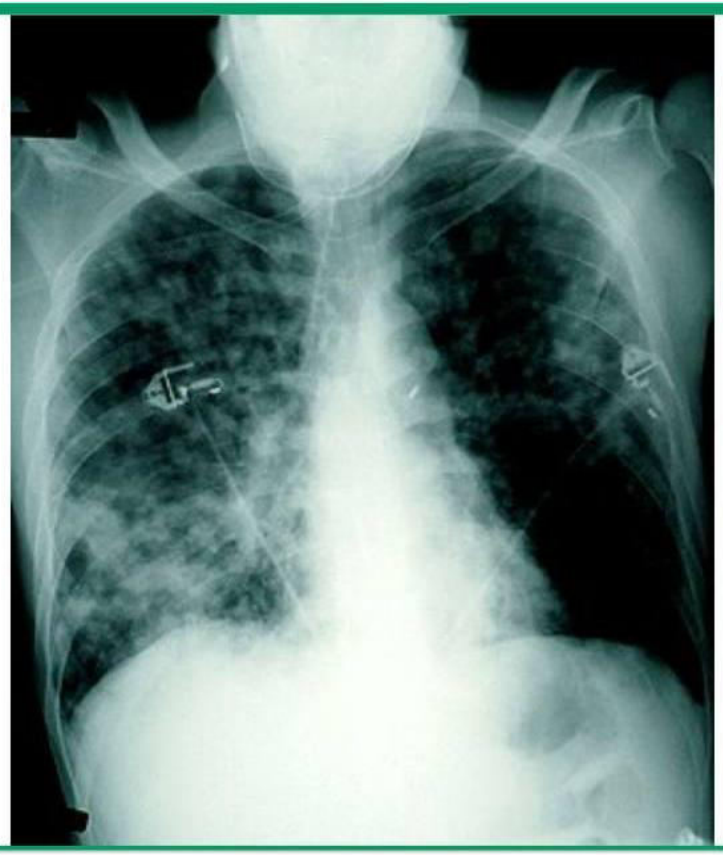
Acute melioidosis presenting as a left upper lobe infiltrate.

Chest radiograph of chronic pulmonary melioidosis



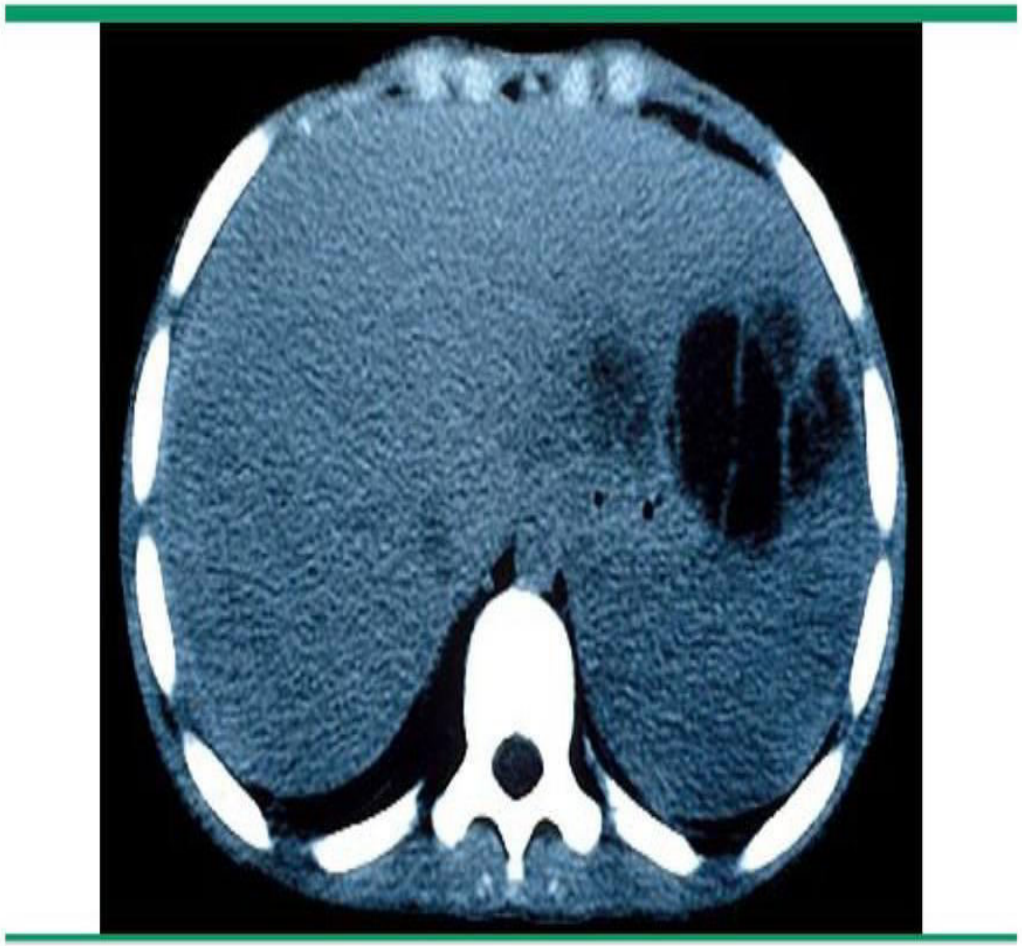
Chronic melioidosis in the lung mimicking tuberculosis.

Chest radiograph of melioidosis with fulminant septicemia



Chest radiograph in a patient with a fulminant presentation of melioidosis with septicemia.

Computed tomography of melioidosis liver abscess



Lobulated liver abscess by CT scan in a patient with melioidosis.

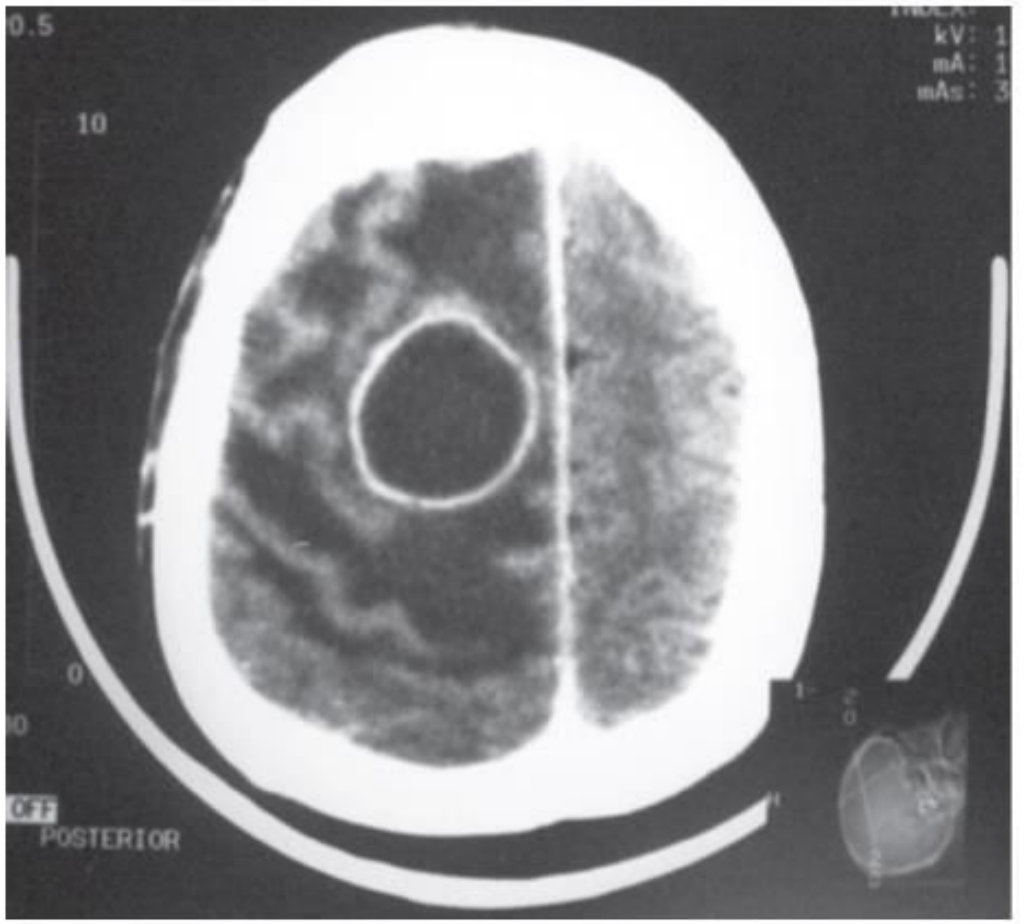
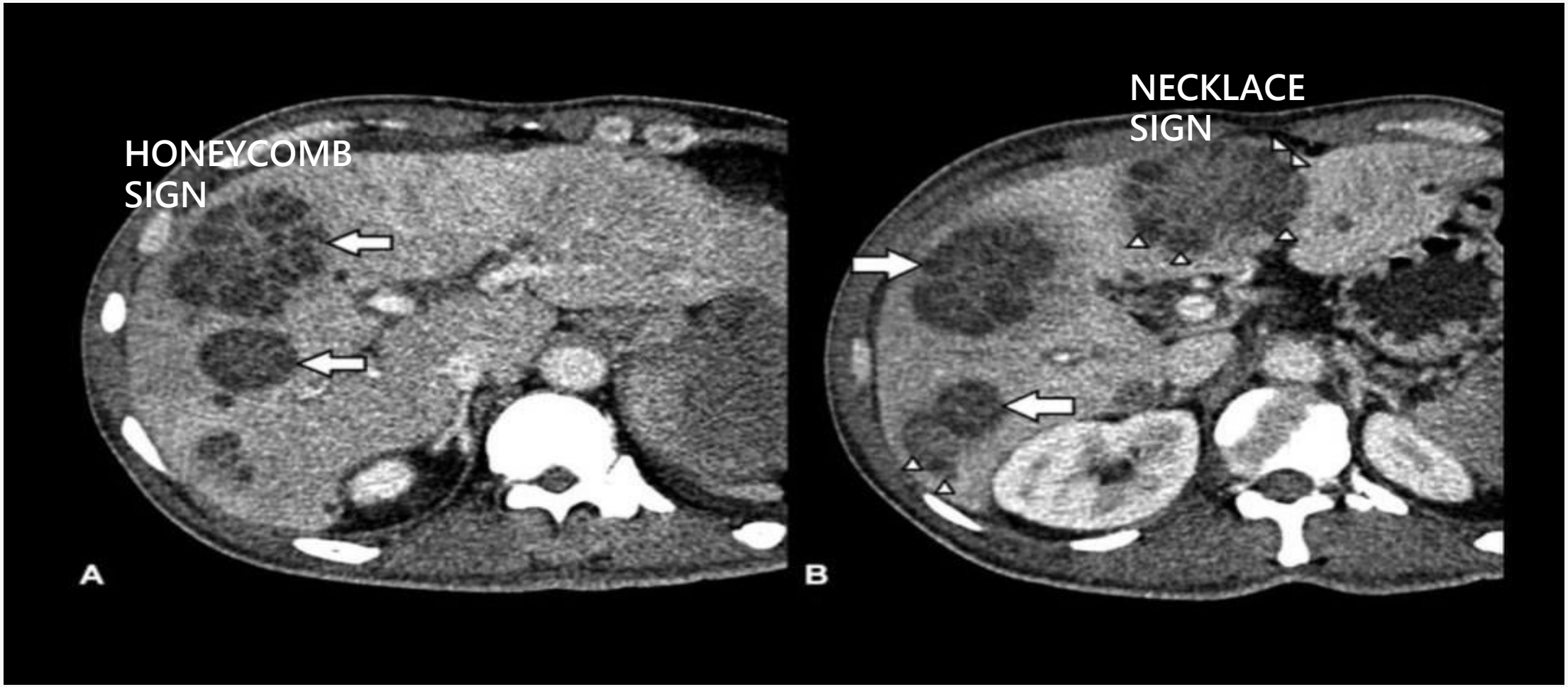


Fig. 8.6.16.3 CT brain scan of a patient presenting with fever, headache, confusion, and hemiparesis. The image shows a ring-enhancing lesion with surrounding oedema in the right frontoparietal lobe, pus from which grew *B. pseudomallei*.



Contrast-enhanced CT scan of the liver above (A) and at the level of (B) the main portal vein showed that some lesions were made up of asymmetric locules of varying sizes (arrows), while others had hypodense centre with small symmetric peripheral locules in radial fashion (arrowheads).

Management

- **Prolonged course of appropriate antibiotics is essential to achieve cure.**
- **Early diagnosis and initiation of therapy can greatly reduce mortality in melioidosis.**
- **The treatment includes**
  - ***an initial intensive phase of intravenous therapy followed by***
  - ***an eradicative phase of oral antimicrobial therapy.***

INITIAL INTENSIVE THERAPY

- Initial intensive therapy should last ***a minimum of 10–14 days***
- Longer intensive therapy for critically ill patients, including those with
  - extensive pulmonary disease,
  - deep-seated collections or organ abscesses,
  - osteomyelitis,
  - septic arthritis,
  - neurological melioidosis.

Initial parenteral therapy

- Ceftazidime 50 mg/kg per dose (up to 2 g) every 6 h, or meropenem 25 mg/kg per dose (up to 1 g) every 8 h.
- Intravenous amoxicillin/clavulanate can be used as a second-line agent and is associated with equivalent mortality but a higher rate of treatment failure compared with ceftazidime. Dosage 20/5 mg/kg every 4 h.

ERADICATIVE THERAPY

- Oral treatment is given for ***12 to 20 weeks or longer*** if clinically indicated

Oral eradication therapy

Adults

- Trimethoprim/sulfamethoxazole using a weight-based dosing schedule: 2 × 160/800 mg (960 mg) tablets every 12 h if more than 60 kg, 3 × 80/400 (480 mg) tablets every 12 h if 40–60 kg, and 1 × 160/800 mg (960 mg) OR 2 × 80/400 (480 mg) tablets every 12 h if less than 40 kg.

Children ≤8 years and pregnant women

- Amoxicillin/clavulanate 20/5 mg/kg orally every 8 h.
- For adult patients less than 60 kg, a dose of 1000/250 mg three times daily is suggested. In regions where amoxicillin/clavulanate is only available in fixed 2:1 combinations, use 500/250 mg three times daily with additional amoxicillin (500 mg three times daily). For patients more than 60 kg, use a maximum dose of 1500/375 mg three times daily.
- Duration of oral therapy: 12–20 weeks.

- The routine addition of doxycycline to oral regimens has ceased following the outcome of a randomized controlled trial conducted in Thailand, which found equivalence between TMP- SMX alone and TMP-SMX plus doxycycline

2020 Revised melioidosis guideline.

Antibiotic Duration Determining Focus	Minimum intensive phase duration (weeks)[a]	Eradication phase duration (months)[f]
Skin abscess	2	3
Bacteraemia with no focus	2	3
Unilateral unilobar pneumonia without lymphadenopathy[b], ICU admission, and with negative blood cultures	2	3
Multilobar unilateral or bilateral pneumonia without lymphadenopathy[b], ICU admission and with negative blood cultures OR Unilateral unilobar pneumonia without lymphadenopathy[b], ICU admission, but with positive blood cultures	3	3
Pneumonia with either lymphadenopathy[b] or ICU admission OR Multilobar unilateral or bilateral pneumonia with positive blood cultures	4	3
Deep-seated collection[c]	4[d]	3
Osteomyelitis	6	6
Central nervous system infection	8	6
Arterial infection[e]	8[d]	6[g]

[a] Clinical judgement to guide prolongation of intensive phase if improvement is slow or if blood cultures remain positive at 7 days

[b] Defined as enlargement of any hilar or mediastinal lymph node to greater than 10 mm diameter

[c] Defined as abscess anywhere other than skin, lungs, bone, CNS or vasculature. Septic arthritis is considered a deep-seated collection

[d] Intensive phase duration is timed from the date of the most recent drainage or resection where culture of the drainage specimen or resected material grew *B. pseudomallei* or where no specimen was sent for culture; clock is not reset if specimen is culture-negative

[e] Most commonly presenting as mycotic aneurysm

[f] If concurrent oral therapy is not indicated in the intensive phase, oral eradication therapy to commence at the start of the final week of planned intensive intravenous therapy, with the timing of eradication duration commencing from the day after last intravenous therapy.

[g] Life-long suppressive antibiotic therapy may be required following vascular prosthetic surgery.

https://doi.org/10.1371/journal.pntd.0008659.t005

ADJUVANT TREATMENT

- Early recognition of sepsis, adequate fluid resuscitation, and management of seriously ill patients in intensive care units reduces the mortality.
- Immunomodulating therapy such as granulocyte-macrophage colony-stimulating factor, Interleukin-7, and anti-programmed cell death protein 1 are under investigation.
- Parenteral treatment may consists of ceftazidime or meropenem plus granulocyte colony stimulating factor (G- CSF) if the patient has septic shock.

SURGICAL INTERVENTION

- surgical or guided drainage of single large abscesses of the liver, muscle, and prostatic abscesses, when feasible.

- Debridement and washout in osteomyelitis and septic arthritis are usually necessary.

- In the setting of multiple small abscesses, serial imaging can help assess response to therapy.

PROGNOSTIC FACTORS

- Several features can be used to predict risk of death.in a septicemic patient
  - **Time to blood culture positivity**
    - within 24 h - mortality rate of 74%
    - after 24 h - mortality rate of 41%
  - **Positive blood culture**
    - counts of more than 100 CFU/ ml - mortality rate of 96%
    - counts of less than 1 CFU/ ml - mortality rate of 42%
  - **B. pseudomallei count in urine**
    - urine culture was negative - mortality rate of 39%
    - urine culture was positive - mortality rate of 71%
  - **sputum culture**
    - Negative - 42%
    - Positive – 72%

Recurrence

- Melioidosis is notoriously difficult to eliminate. Recurrence is the second most dreaded complication, after death.
- Can be due to **relapse** (failure to eradicate infecting strain) or **re-infection** with a new bacterial strain.
- It can occur in **5%–25% of cases**, and risk factors include
  - choice and duration of antimicrobial therapy,
  - patient compliance,
  - bacteremia, and
  - multifocal disease.

PREVENTION

- **Avoiding exposure**
- **Post-exposure prophylaxis**
  - Trimethoprim-sulfamethoxazole
  - amoxicillin-clavulanate is the alternative
  - Each is given for 21 days and should be started as soon as possible following the exposure.

Studies and case reports

Indian Melioidosis Research Forum

Kasturba Medical College
Manipal University, Manipal, Karnataka

ABOUT IMRF | MELIOIDOSIS | PUBLICATIONS | PAST EVENTS | UPCOMING EVENTS | PHOTO GALLERY | RESOURCES | MEMBERSHIP | CONTACT US

WHO ARE WE AND WHAT IS IMRF

Indian Melioidosis Research Forum (IMRF) is an interactive web portal created and administered by a dedicated research team working in the field of melioidosis at the Department of Microbiology, Kasturba Medical College, Manipal University, Manipal, India. During the past few years, our research team under the leadership of Professor Dr. Chiranjay Mukhopadhyay was instrumental in standardizing the microbiological laboratory procedures using serological, culture and molecular techniques for the diagnosis of Melioidosis. With the able guidance of international experts in various aspects of melioidosis and the financial support from both national and international funding agencies, we are currently working in few research areas such as:

- Epidemiological data of melioidosis from India and other South Asian countries.
- Environmental sampling for the isolation of a *Burkholderia pseudomallei*.
- Genomic characterization of clinical and environmental isolates of *Burkholderia pseudomallei*.
- Evaluating the diagnostic utility of few commercial and in house developed assays for the diagnosis of melioidosis.
- Standardizing Loop Mediated Isothermal Amplification assay for Melioidosis.

National Centre for Disease Control,
Directorate General of Health Services. Government of India

April 2019

MELIOIDOSIS

INTRODUCTION

Melioidosis is an infectious disease caused by a Gram negative bacterium, *Burkholderia pseudomallei*. It is seasonal, with 75–85% of cases occurring during the rainy season. The clinical spectrum of illness is diverse and ranges from pulmonary consolidation and localized abscesses to rapidly fatal septicemia. Melioidosis has a high case fatality rate (CFR) ranging from 16% to 50% in known endemic regions. Several risk factors are associated with melioidosis including immunosuppressive conditions such as diabetes and other diseases like chronic kidney disease, and certain drug treatments. Diabetes mellitus is the most common risk factor and increases the relative risk of melioidosis. The disease is endemic in Southeast Asia and Northern Australia. It is classified as category B bioterrorism agent.

HISTORICAL BACKGROUND

Alfred Whitmore and CS Krishnaswami first described melioidosis as a "Glanders-like disease" among morphine addicts in Rangoon in 1911. Stanton and Fletcher in 1932 proposed the name "melioidosis", derived from the Greek melis meaning "a distemper of asses" and suffixes -oid (similar to) and

-osis (a condition).

EPIDEMIOLOGY

Burden Worldwide

Melioidosis is an infectious disease endemic in Southeast Asia, northern Australia, much of the Indian subcontinent, southern China, Hong Kong, and Taiwan (Figure 1). In northern Australia and northeast Thailand, it accounts for 20% of all community- acquired septicemias. It is the most common cause of severe community- acquired pneumonia in northern Australia.

Figure 1: Global distribution of *Burkholderia pseudomallei* and burden of melioidosis

Reproduced with permission (https://www.nature.com/articles/nmicrobiol20158/figures/1)

Indian literature - Pseudomallei

- 1991 first reported from Bombay
  - Raghavan KR, Shenoi RP, Zaer F, Aiyer R, Ramamoorthy P, Mehta MN. Melioidosis in India. Indian Pediatr 1991;28:184-8

- Later onwards several case reports/series from CMC/JIPMER/MANGLORE/St Johns

2003 - AIMS

Review Article

Melioidosis; the Remarkable Imitator : Recent Perspectives

Loveleena, Rama Chaudhry, Benu Dhawan

Abstract

Melioidosis is an important public health problem in some regions of the world. It is endemic in South East Asia. The clinical spectrum of melioidosis is extremely broad, and melioidosis requires awareness on the part of the clinician and the existence of a laboratory capable of isolating and identifying *Burkholderia pseudomallei*, the etiological agent of melioidosis. Beta-lactams such as ceftazidime is currently the treatment of choice. There is no vaccine licensed for human use. There is an urgent need for rapid diagnostic techniques and effective treatments that are affordable in countries where the disease is endemic. ©

INTRODUCTION

reported in the medical literature, indicating the presence of

Indian Journal of Medical Microbiology, (2007) 25 (3):245-8

Brief Communication

MELIOIDOSIS: AN UNDER-DIAGNOSED ENTITY IN WESTERN COASTAL INDIA: A CLINICO-MICROBIOLOGICAL ANALYSIS

***K Vidyalakshmi, B Shrikala, B Bharathi, U Suchitra**

Abstract

Clinico-microbiological analysis of a series of 25 patients with culture proven melioidosis was done. All patients came from the coastal regions of Kerala and Karnataka and presented between June 2005 to July 2006. They were analysed with respect to clinical presentation, occupation, epidemiology and microbiological features. No single presenting clinical feature was found to be typical of melioidosis. The disease was found to mimic a variety of conditions, including tuberculosis and malignancy. *Burkholderia pseudomallei* was isolated from blood, sputum, pus, urine, synovial, peritoneal and pericardial fluids. Diabetes mellitus was the most common predisposing factor and 80% of the cases presented during the Southwest monsoon (June to September). It is probable that melioidosis is highly prevalent in western coastal India and yet, greatly underestimated. Better awareness, both among clinicians and microbiologists, coupled with improved diagnostic methods to allow early diagnosis and hence early treatment, will significantly reduce the morbidity and mortality associated with this disease.

Key words: *Burkholderia pseudomallei, diabetes mellitus, melioidosis*

2008 - From SJMC

Case Report

Melioidosis

P Krishnan*, Sushmitha Fernandes*, Jayanthi Savio**, Cecil Reuben Ross*, Rekha Pradeep*, Ratnamala Choudhary*, AS Shet*, P Pais*

Abstract

Melioidosis is an emerging infectious disease in India acquired through percutaneous inoculation or contaminated water. Known risk factors include diabetes mellitus, renal failure, cirrhosis, and malignancy. Melioidosis presents with a febrile illness, with protean manifestations ranging from septicemia to localized abscess formation. We present the case of a 42 year old male from a non-endemic region who presented with fever of 2 months duration, sepsis, persistent pneumonia, right hip joint pain and hepatic and splenic abscesses. Aspiration of the joint and soft tissue fluid collection and subsequent culture yielded gram negative bacilli identified as Burkholderia pseudomallei. The epidemiology, clinical features, and laboratory diagnosis of this rare infection and its treatment is reviewed. ©

Introduction

Emergence of Burkholderia pseudomallei and pandrug-resistant non-fermenters from southern Karnataka, India

C. Mukhopadhyay et al *Trans R Soc Trop Med Hyg (2008)*

Summary points

- ……..**outcome of 25 patients with melioidosis and 46 patients with MDR non-fermenters** (*Pseudomonas aeruginosa* and *Acinetobacter* spp.) infection were documented during the period 2005- 2007.

- Skin and soft-tissue involvement (16%), liver abscess (16%) and bone and joint involvement (16%) were the most common presentations of melioidosis in diabetic patients. The presence of septicaemia (44%) and major organ failure (48%) resulted in death. Relapse was seen in patients with inappropriate treatment. …

- **More awareness among clinicians and laboratory staff, and environmental investigations of soil are required for accurate diagnosis and prompt treatment of melioidosis.**

Neonatal melioidosis: A case report from India..JIPMER

- *Indian Journal of Medical Microbiology, Vol. 27, No. 3, July-September, 2009, pp. 260-263*

- Melioidosis, caused by *Burkholderia pseudomallei* , is an infectious disease of major public health importance in Southeast Asia and Australia. ..

- A pre-term female baby developed respiratory distress soon after birth. The child was febrile, had tachypnea, grunting, normal heart rate with a low pulse volume and poor peripheral perfusion. Chest X-ray revealed right-sided bronchopneumonia. *B. pseudomallei* was isolated from the blood culture of the neonate collected aseptically. The neonate was successfully treated with meropenem.

International Journal of Infectious Diseases 16 (2012) e491–e497

Contents lists available at SciVerse ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Emerging clinico-epidemiological trends in melioidosis: analysis of 95 cases from western coastal India

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ARTICLE INFO

Article history:
Received 25 October 2011
Accepted 14 February 2012

Corresponding Editor: William Cameron, Ottawa, Canada

Keywords:
Melioidosis
Burkholderia pseudomallei
Rainfall
Epidemiology
Musculoskeletal melioidosis
Dental abscess

SUMMARY

Objectives: To study the clinico-epidemiological trends in melioidosis, an emerging disease in the western coastal region of India.
Methods: Data of 95 patients with melioidosis in the western coastal region of India were retrospectively analyzed with respect to monthly rainfall, risk factors, clinical presentations, and outcome.
Results: A strong linear correlation was seen between average monthly rainfall and the occurrence of cases ($p = 0.002$). Mortality was seen only in patients with bacteremia ($p < 0.001$). Nine (40.9%) patients with septic shock died ($p < 0.001$). Age ≥40 years and diabetes mellitus were seen in 75.8% of cases, each. Pneumonia was the most common clinical presentation (32.6%), followed by musculoskeletal disease (20%), melioidotic lymphadenopathy (7.4%), and dental abscess (6.3%). Only 36.8% of patients had exposure to wet soil/surface water.
Conclusions: Melioidosis is quite prevalent in the western coastal region of India, and is strongly associated with rainfall, age, and diabetes mellitus. Higher proportions of musculoskeletal, dental, and lymph node melioidosis were seen in this region as compared to endemic areas. Bacteremic melioidosis has a poorer prognosis than non-bacteremic melioidosis. The presence of septic shock is a strong predictor of mortality. Percutaneous inoculation may not be the main portal of entry for *Burkholderia pseudomallei* in this region.

JUNE 2012 • VOL. 60

Case Report

Disseminated Melioidosis Presenting as Septic Arthritis

Anjali Rajadhyaksha*, Archana Sonawale**, Shruti Khare, Chetan Kalal****, Rahul Jankar*****

*Professor, **Associate Professor, ***Assistant Professor, ****Registrar, *****House Officer, Department of Medicine, Seth GS Medical College and KEM Hospital, Mumbai

Received: 07.02.2011; Revised: 21.04.2011; Accepted: 29.04.2011

Abstract

Melioidosis is an infection caused by Burkholderia pseudomallei. The disease is known as a remarkable imitator due to the wide and variable clinical spectrum of its manifestations. Septic arthritis is rare but well-recognized manifestation of this disease.

We report a case of melioidosis in a 52 year male with uncontrolled diabetes mellitus (DM) presenting with a rare combination of septic arthritis and abscesses in the chest wall, liver and subcutaneous tissue. The patient responded to prolonged treatment of intravenous ceftazidime followed by oral co-trimoxazole.

Introduction

Melioidosis is a disease of public health importance that is associated with high case-fatality rates in humans. It is endemic in tropical Australia and Southeast Asia with highest number of reported cases from Thailand. Melioidosis is increasingly being recognized as an important cause of life-threatening infections in India. It is underdiagnosed and underreported in India and there is increased need of creating awareness in clinicians, microbiologists and public health professionals in diagnosing melioidosis.1,2

Tropical Medicine and Infectious Disease

Review

Melioidosis in South Asia (India, Nepal, Pakistan, Bhutan and Afghanistan)

Chiranjay Mukhopadhyay [1,2,*], Tushar Shaw [1], George M. Varghese [3] and David A. B. Dance [4,5,6]

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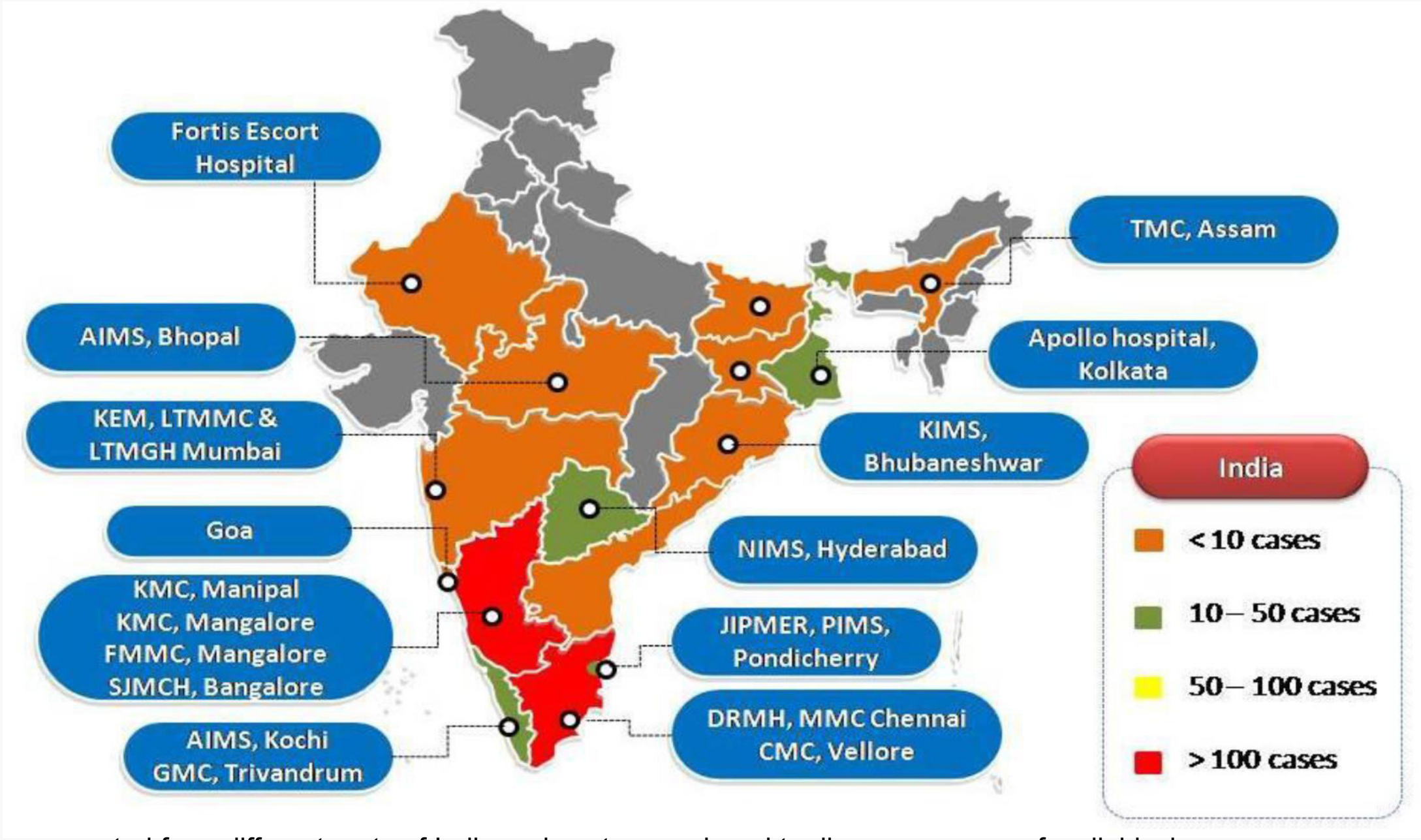
Received: 12 March 2018; Accepted: 18 May 2018; Published: 22 May 2018

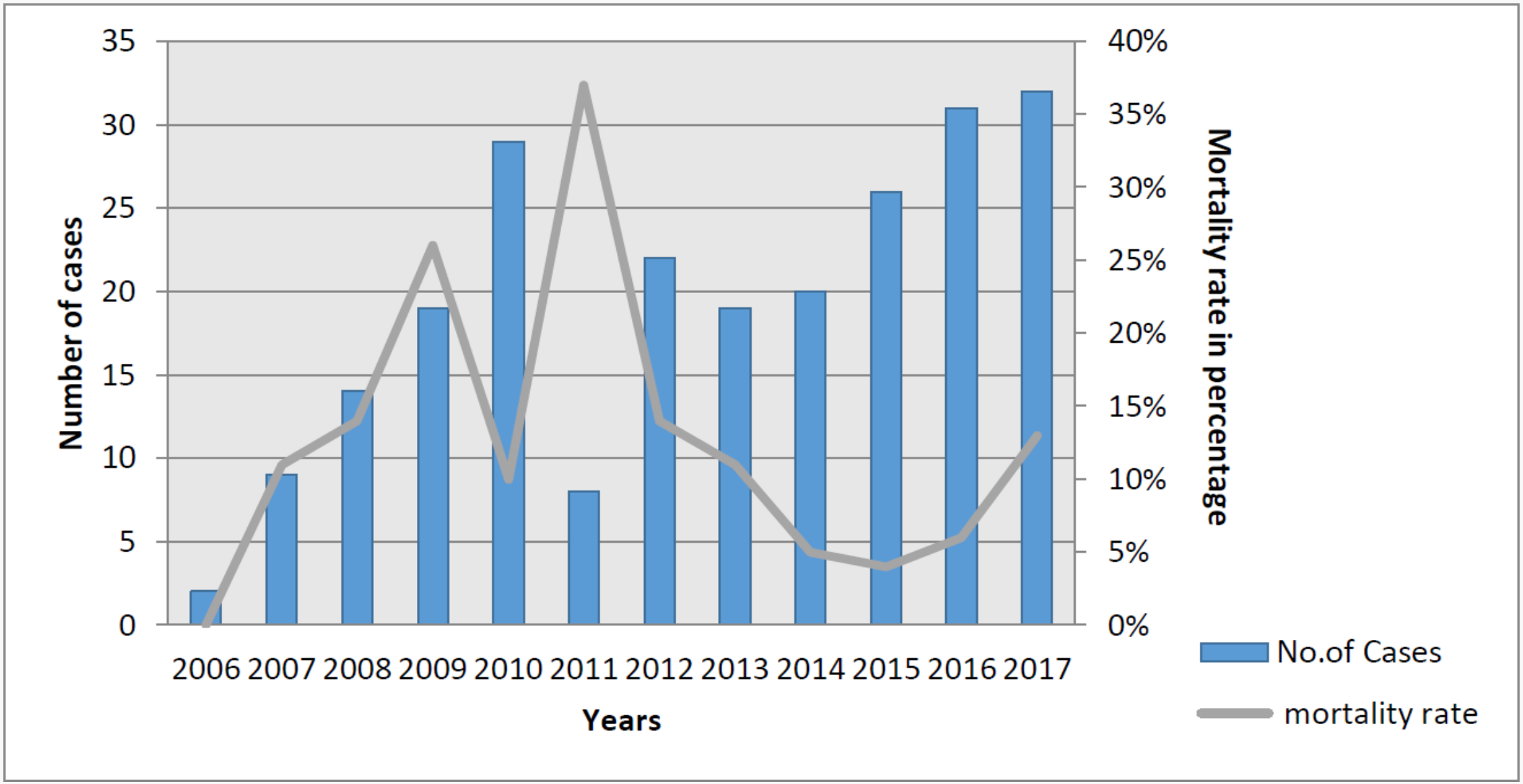
Abstract: Despite the fact that South Asia is predicted to have the highest number of cases worldwide, melioidosis is a little-known entity in South Asian countries. It has never been heard of by the majority of doctors and has as yet failed to gain the attention of national Ministries of Health and country offices of the World Health Organization (WHO). Although a few centers are diagnosing increasing numbers of cases, and the mortality documented from these institutions is relatively high (nearly 20%), the true burden of the disease remains unknown. In India, most cases have been reported from southwestern coastal Karnataka and northeastern Tamil Nadu, although this probably simply reflects the presence of centers of excellence and researchers with an interest in the disease. As elsewhere, the majority of cases have type 2 diabetes mellitus and occupational exposure to the environment. Most present with community-acquired pneumonia and/or bacteremia, especially during heavy rainfall. The high seropositivity rate (29%) in Karnataka and isolation of *B. pseudomallei* from the environment in Tamil Nadu and Kerala confirm India as melioidosis-endemic, although the full extent of the distribution of the organism across the country is unknown. There are limited molecular epidemiological data, but, thus far, the majority of Indian isolates have appeared distinct from those from South East Asia and Australia. Among other South Asian countries, Sri Lanka and Bangladesh are known to be melioidosis-endemic, but there are no cases that have conclusively proved to have been acquired in Nepal, Bhutan, Afghanistan or Pakistan. There are no surveillance systems in place for melioidosis in South Asian countries. However, over the past two years, researchers at the Center for Emerging and Tropical Diseases of Kasturba Medical College, University of Manipal, have established the Indian Melioidosis Research Forum (IMRF), held the first South Asian Melioidosis Congress, and have been working to connect researchers, microbiologists and physicians in India and elsewhere in South Asia to raise awareness through training initiatives, the media, workshops, and conferences, with the hope that more patients with melioidosis will be diagnosed and treated appropriately. However, much more work needs to be done before we will know the true burden and distribution of melioidosis across South Asia.

Keywords: *Burkholderia pseudomallei*; India; melioidosis; South Asia



Cases reported from different parts of India and centers equipped to diagnose cases of melioidosis.

State	Number of Cases	Age Range	Gender (Male: Female)	Diabetes n (%)	MER	CAZ	SXT	Others	Mortality n (%)
Karnataka	306	0–84	3:1	241 (79)	24	294	235	50	39 (13)
Tamil Nadu	146	4–65	3:1	75 (50)	3	82	80	2	37 (28)
Telangana	35	30–66	2:1	27 (77)	8	7	11	3	4 (11)
Kerala	34	9–66	5:1	24 (77)	3	15	14	2	5 (13)
Pondicherry	14	0–58	3:1	3 (21)	2	2	-	4	2 (14)
West Bengal	11	29–71	11:0	9 (82)	6	4	9	1	2 (18)
Maharashtra	9	10–72	7:1	5 (50)	0	4	4	0	4 (50)
Orissa	8	47–51	7:0	5 (63)	0	6	5	0	1 (12.5)
Assam	6	0–57	2:1	3 (50)	3	0	1	1	2 (33)
Goa	5	34–53	5:0	5 (100)	2	2	1	1	0
Bihar	4	50–65	4:0	4 (100)	2	1	2	1	0
Jharkhand	2	32–33	2:0	1 (50)	1	1	1	0	1 (50)
Rajasthan	1	49	1:0	0	1	0	1	0	0
Madhya Pradesh	1	56	1:0	1 (100)	0	1	0	0	0
Andhra Pradesh	1	23	1:0	1 (100)	0	0	0	0	1 (100)



.Annual numbers of melioidosis cases and mortality from Manipal

Melioidosis in a Tertiary Care Center from South India—A 5-year Experience

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How to cite this article: Ganesan V, Murugan M, Sundaramurthy R, Soundaram GVG. Melioidosis in a Tertiary Care Center from South India—A 5-year Experience. Indian J Crit Care Med 2021;25(3):327–330.

Source of support: Nil
Conflict of interest: None

Abstract

The present study was done with the objective to know the clinical presentation, microbiological features, and treatment outcome of melioidosis patients in our hospital, which is an emerging infection in India, and to know the differences in clinical course and outcome between bacteremic and nonbacteremic patients. This retrospective observational study was carried out over a period of ***5 years from January 2015 to December 2019***. Thirty-five cases of culture-confirmed melioidosis were identified with age range between 5 and 74 years. A large number of patients (*n* = 31) presented with uncontrolled diabetes mellitus. Six patients died of septic shock, and the outcome of eight patients was unknown as they were discharged against medical advice. There were no relapses observed. Melioidosis growing as a neglected tropical disease in India warrants awareness among all clinician s across the country

Indian Journal of Critical Care Medicine (2021): 10.5005/jp-journals-10071-23766

Melioidosis mimicking tuberculous vertebral osteitis: Case report and review of literature

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Abstract:

Whitmore's disease or melioidosis is an infectious disease caused by *Burkholderia pseudomallei*. The reported cases are but the tip of the iceberg. This pathogenic saprophyte is commonly found in wet soil and water. An accidental or occupational exposure (in field workers, farmers, gardeners or villagers) to *B. pseudomallei* contaminated soil or pooled water is the primary source of infection. Neurosurgeons need to consider this as a possible rare cause of back pain and possible neurological deterioration. A diabetic type 2 rice farmer with severe lumbago and fever, misdiagnosed as vertebral tuberculous osteitis based on his radiological findings, was confirmed to harbour *Burkholderia Pseudomallei*, which was diagnosed using laboratory cultures. He made a remarkable recovery with antibiotic therapy. The empiric anti-tuberculous (ATT) drugs were stopped. The rare differential diagnosis of melioidosis should be thought of in diabetic patients with a psoas abscess and vertebral osteitis, especially in rice farmers from endemic regions that includes India.

Key Words:

Burkholderia Pseudomallei, low back pain, melioidosis, psoas abscess, spinal infection, vertebral osteitis, Whitmore's disease

Whitmore's disease or melioidosis is an infectious disease caused by *Burkholderia pseudomallei*, a pathogenic saprophyte commonly found in wet soil and water. An accidental or occupational exposure to *B. pseudomallei* present in the contaminated soil or pooled water is the primary source of infection. The manifestations of vertebral osteitis with paraspinal and psoas abscess, caused by *Burkholderia Pseudomallei,* in a diabetic rice farmer, who was misdiagnosed as having tuberculous affliction of the spine, is being reported. The patient was erroneously being administered empiric anti-tuberculous (ATT) medication

Case Report

A 40-year old, type 2 diabetic farmer from a village near Tirupati, Andhra Pradesh, India, presented with excruciating low back pain and intermittent high-grade fever of 45-days duration. The patient reported pain involving both the lower extremities with a high intensity specifically on the right side. However, no typical history of radiculopathy or myelopathy was found. There were no neurological deficits. His single leg raising test was positive bilaterally, but was nonconclusive due to the presence of severe pain. His past medical history revealed the presence of pulmonary tuberculosis infection 5 years ago for which he had been administered a 9-month course of essential anti-tuberculous (ATT) medications. His coronal magnetic resonance imaging (MRI) scan of the lumbar spine with contrast (done in another medical facility) revealed enhancing lytic areas in the L4 vertebral body and the right iliac bone, associated with peripherally enhancing, centrally necrotic, multi-loculated,

Key Message:

Vertebral osteitis with paraspinal and psoas abscess can be caused by *Burkholderia Pseudomallei*. Reported cases of melioidosis or Whitmore's disease are just the tip of the iceberg. Neurosurgeons need to consider this as a possible rare cause of lumbago often associated with neurological deterioration. Empiric anti-tuberculous (ATT) drugs should be used cautiously, especially in diabetic rice farmers. Reporting these rare cases is essential to assess the true burden of this serious, and occasionally, lethal illness.

THANK YOU