



GRAVE EXPECTORATIONS

Daniel Stefanski
Monash Medical Centre
MIDG May 2011

Mr X

11 March 2011, GP referred:

- 50 yo man
- 3 weeks fever of unknown origin
- Vietnam (Ho Chi Minh City) – 19 Feb 2011 for 2 weeks
- FBE, U&E, LFT normal
- CXR – nodule RLL
- CT chest: “Multiple solid lesions containing air in Right lung, lower and middle lobes. Large necrotic nodule in left thyroid lobe.”
 - DDx: Metastatic malignancy – thyroid could be primary.
 - Multi foci of chest infection

ED assessment

HPC:

Fever commenced 3 days into trip to Ho Chi Minh City.

Drenching sweats, rigors. Constant fevers since then.

Anorexia and severe lethargy

Intermittent cough - non-productive

Reports weight loss of 15kg in 4 weeks

No arthralgia

No malaria prophylaxis or pre-travel vaccines

Clinical Examination

Unwell looking, sweating +++

T- 39.5, BP 130/70, HR 104, O2Sat 94% RA

CVS - dual HS, no murmur, no stigmata of endocarditis

No palpable lymph nodes

Thyroid: palpable L thyroid mass - non tender

Chest clear

Abdo - NAD

Past Hx

○ Smoker 40 pack years

○ Hypertension

○ Type II Diabetes Mellitus

poorly controlled - HbA1c

11.4 Jan 2011

11.1 Sept 2009

• Vitiligo 5 years

DHx

- Telmisartan 80mg/day
- Metformin 1g bd
- Gliclazide MR 120mg daily
- Paracetamol and ibuprofen prn

Social Hx

Born in Turkey

Works as cabinet maker

Minimal ETOH

No ill contacts, no TB contacts,

denies IVDU

Adult children by previous marriage + 10 month old grandchild

Remarried to Vietnamese lady - 2 year old child

Visits Vietnam 1-2 times per year

Pathology

Malaria negative - ICT and thick and thin films

FBE - Hb 145/9.6/314

Film: mild reactive lymphocytes

U&E - Na 127/3.8 / 96/22/2.1/74 eGFR >90

LFT - NAD

Alb - 31

CRP - 61.4

CXR



Differential Diagnoses

Open for suggestions

Neoplastic with metastases

TB

Abscess forming organisms - Strep milleri?

Infective Endocarditis with emboli?

Tie-in lungs and thyroid?

Basically, we wanted tissue diagnosis

Work-up

Blood Cultures x 5 - all negative

Sputum x 3 - AFB negative. M/C/S - no significant growth

- cytology: no malignancy. Macrophages, inflamm cells

T T Echo - Normal function. No valvular abnormalities.

QF Gold - negative

Thyroid USS - multinodular goitre with large L lobe mass/cyst

- **biopsy**: blood. no growth, no abnormal cytology

HBsAg Detected. HBV VL 81, log 1.91

HIV negative, Syphilis negative, HCV negative

Arboviral serology negative

Clinical Progress

11 - 21 March:

Daily fevers to 40 deg. Sweats ++

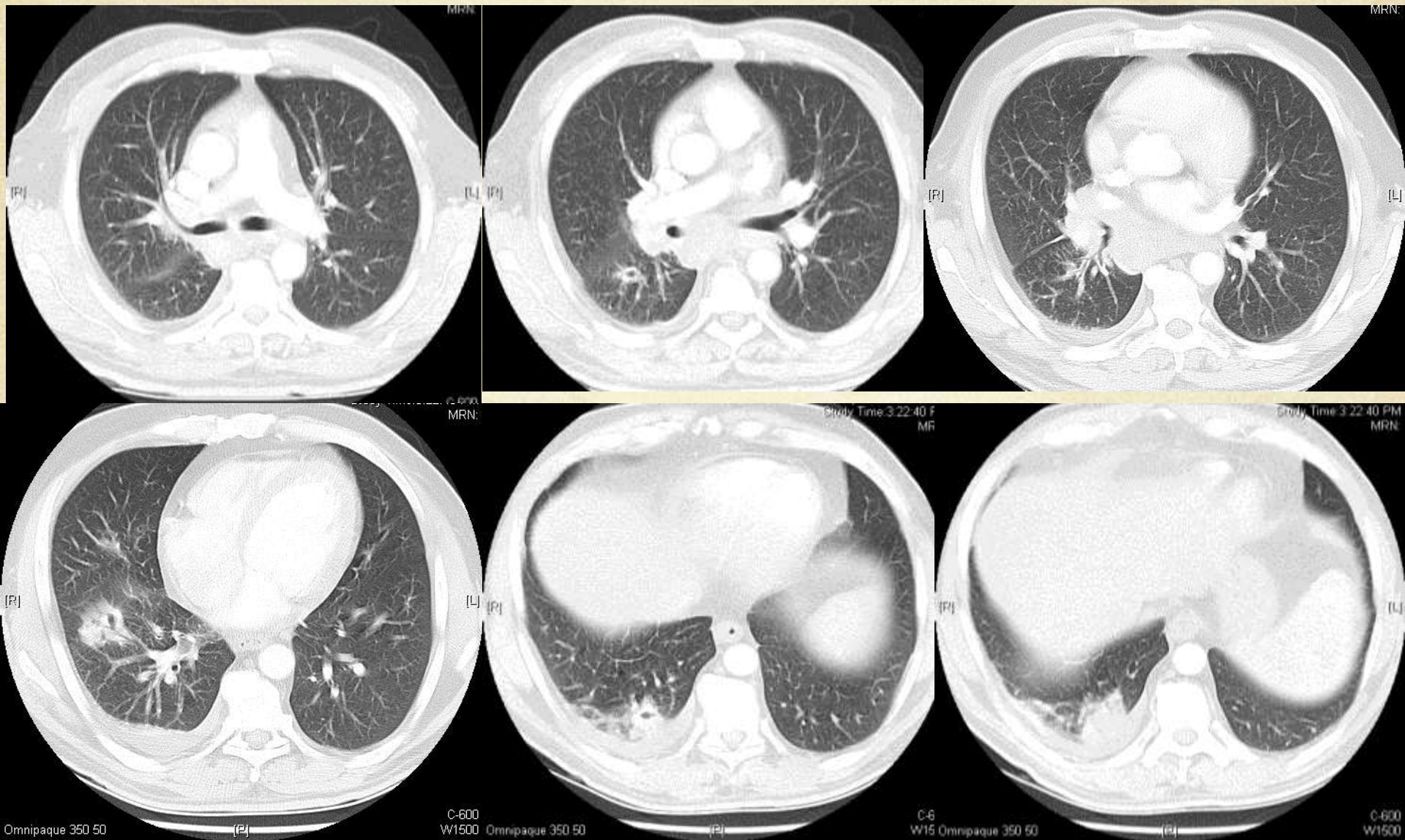
Mild Neutrophilia between 7.4 and 9.6

CRP increased to 140

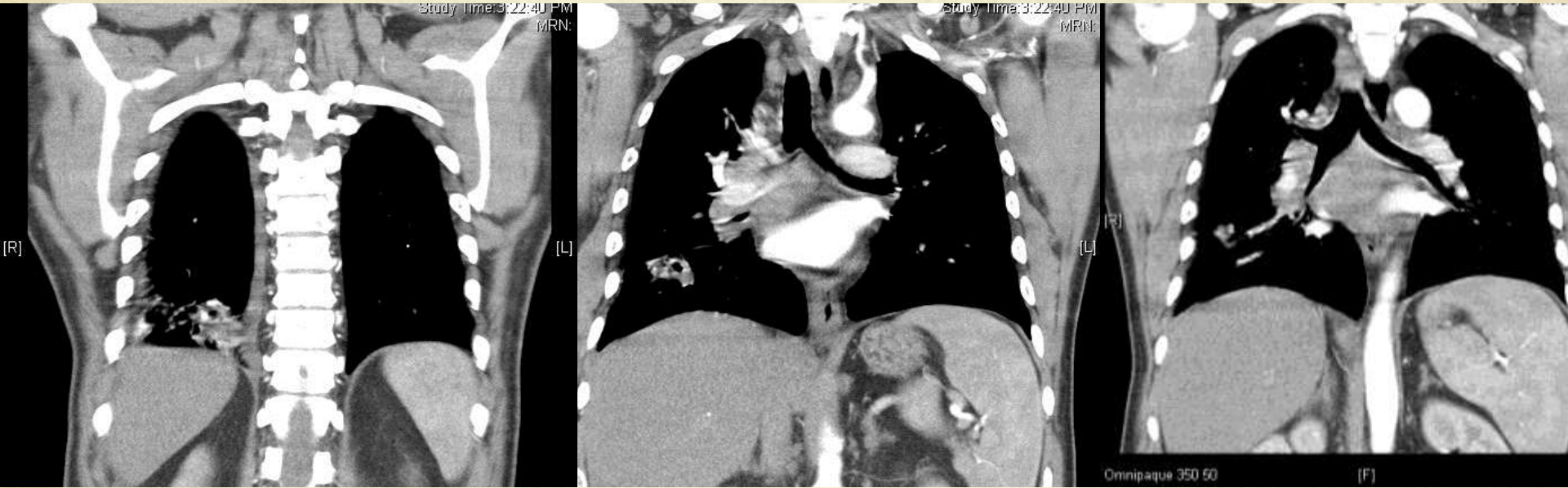
Developed 2 small sub-cutaneous nodules - flank and thigh

CT-guided biopsy of pulmonary lesion abandoned on Fri
18 March

CT chest 18/3



CT Chest 18/3



Repeat CT Report

Rapid evolution of the mediastinal and hilar lymphadenopathy

right-

sided pleural effusion together with **increased** size of the cavitating right lower lobe are all suggestive of an **infective aetiology** rather than neoplastic causes.

The 'CT halo' sign is characteristic but not specific for angioinvasive aspergillosis. Correlate clinically with ?immunosuppression

Tazocin

21 March - Tazocin commenced
Trial of anti-infective therapy...

Defervescence in 24 hours

Resolution of sweats

WCC and CRP normalised over 2 days

EBUS

Endoscopic Ultrasound Biopsy of Mediastinal Lymph Nodes

- Bronch washings - no growth
- Mediastinal biopsy
 - 1 Colony on Chocolate Blood Agar
 - 1 Colony on HBA



HBA/Maconkey

Metallic sheen of
colonies

Motile

Oxidase positive

Lactose Fermenter



"Safety pin"

"Safety pin"

Vitek 2

Burkholderia pseudomallei

99% probability

“Excellent identification”

MDU - confirmation

Direct Fluorescent Antibody POSITIVE
(compared to a control)

Biochemical tests – phenotypically consistent

Sensitivities

- Meropenem
- Ceftazidime
- Trimethoprim/Sulfamethoxazole
- (Piperacillin/Tazobactam - MIC 1.0)

Discussion:

Confirmatory Diagnostic Tests

Culture of organism is “gold standard”

- Ashdown's (selective) media for non-sterile specimens
- Gentamicin or colistin impregnated

API test panel

- conflicting study results. May be misidentified as *Chromobacterium violaceum*

Vitek 1 – reliable

Vitek 2 – not so reliable

Colony Morphology, Immunofluorescence, Latex Agglutination

Rapid Diagnostics?

Antigen detection

- on direct specimens or blood culture supernatant
- Latex or direct ImmunoFluorescence

Promising, but not commercially available

Antibody detection

- IHA – low sens and spec.
 - 30 - 47% background seropositivity in endemic areas
- ELISA – not superior to IHA
- Immunochromogenic test – promising for non-endemic areas

PCR

- Not used clinically

Mr J - Treatment

Intensive Phase

- **Meropenem** 1g 8-hourly IV - 2 weeks
- Changed to **Ceftazidime** 6g/24hrs via HITH

Total of 6 weeks as per Antibiotic guidelines for deep-seated infection

Eradication Phase

- **Co-Trimoxazole** for 6 months

Guidelines

Intensive Phase at least 14 days

Ceftazidime (50 mg/kg, up to 2 g) q 6 hr

or

Meropenem (25 mg/kg, up to 1 g) q 8 hr

or

Imipenem (25 mg/kg, up to 1 g) q 6 hr

Sulfamethoxazole-
Trimethoprim

(40/8 mg/kg up to 1600/320 mg) bd

+/-

for
Neurologic,
cutaneous,
bone and
prostatic melioidosis

Increase duration to 4 - 8 weeks for deep seated, bone, septic arthritis
or prostate

Guidelines

Eradication Phase - at least 3 months

Sulfamethoxazole-trimethoprim

(40/8 mg/kg up to 1600/320 mg) every 12 hr

With or without

Doxycycline

(2.5 mg/kg up to 100 mg) every 12 hr

Intrinsic Resistance

3rd gen Cephalosporins

Penicillins

Rifamycins

Aminoglycosides

Relative resistance to Quinolones and Macrolides

Adjuvant Therapies

For Severe Sepsis:

G-CSF

- Theoretical reversal of neutrophil dysfunction
- Mortality benefit in Darwin vs. historical control
- Not replicated in Thailand

Activated Protein C?

Steroids?

Discussion

Pathogenesis

Worldwide distribution

Imported Melioidosis

Clinical Manifestations

Overview

Environmental saprophyte

Tropical mud and swamps

A “hardy organism”

Significant morbidity and severe sepsis

Wide variety of clinical presentations

Mode of Acquisition



Inhalation

Inoculation

Ingestion?

Incubation

Inhalation (esp with heavy rain and wind) associated with shorter incubation and more severe disease

Inoculation - ? Longer incubation

1 - 21 days

13% of patients report more than 2 months

“Vietnamese time bomb”

Decades - up to 30 years

Melioidosis and Aboriginal seasons in northern Australia

Allen C. Cheng^{a,b,*}, Susan P. Jacups^b, Linda Ward^{b,c}, Bart J. Currie^{b,c}

Hypothesis:

A shift from percutaneous inoculation to aerosol inhalation depending on the wet season

Transactions of the Royal Society of Tropical
Medicine and Hygiene (2008)

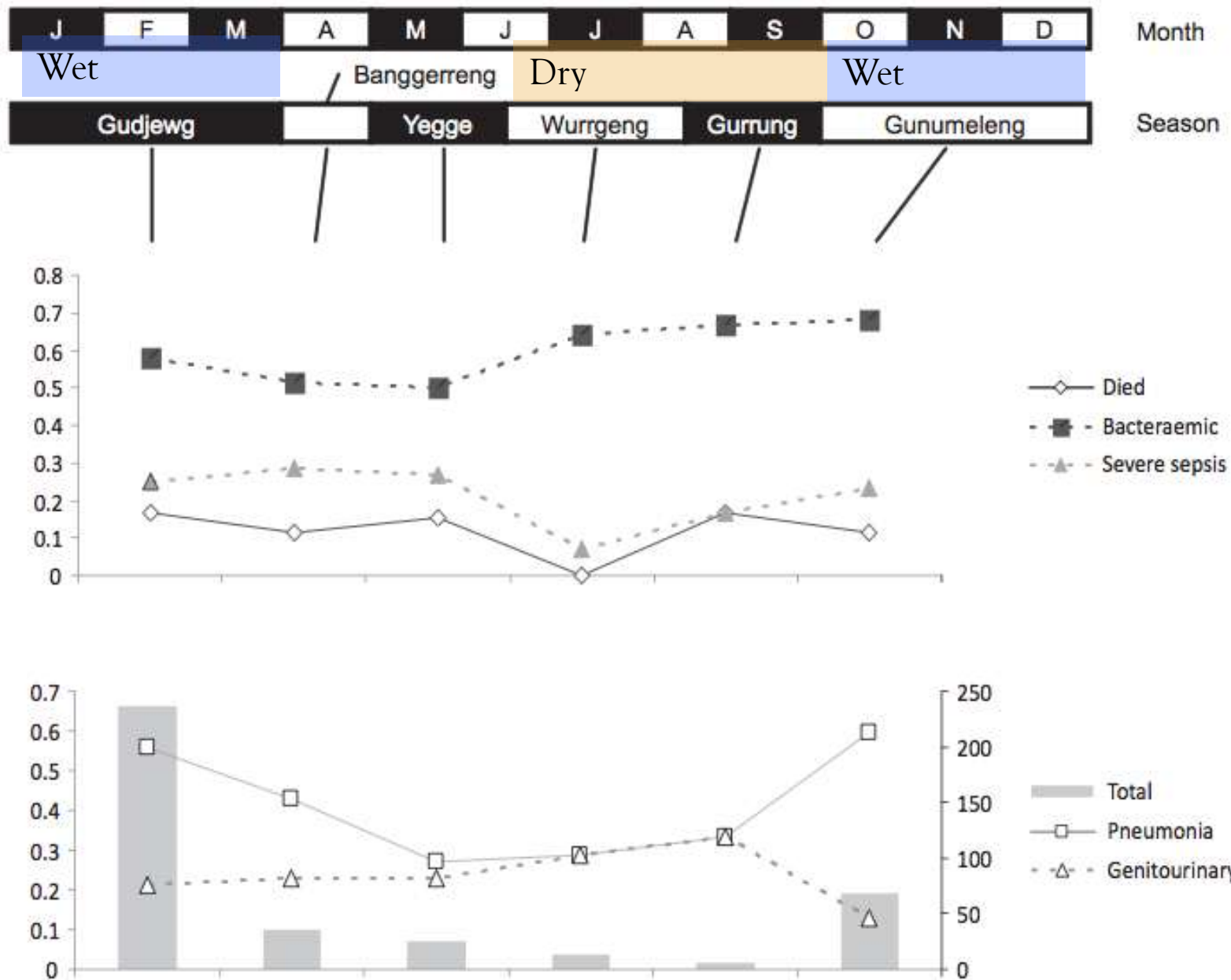


Fig. 2. Proportion (left axis) and number of presentations (right axis) with melioidosis in each Gundjeihmi Aboriginal season.

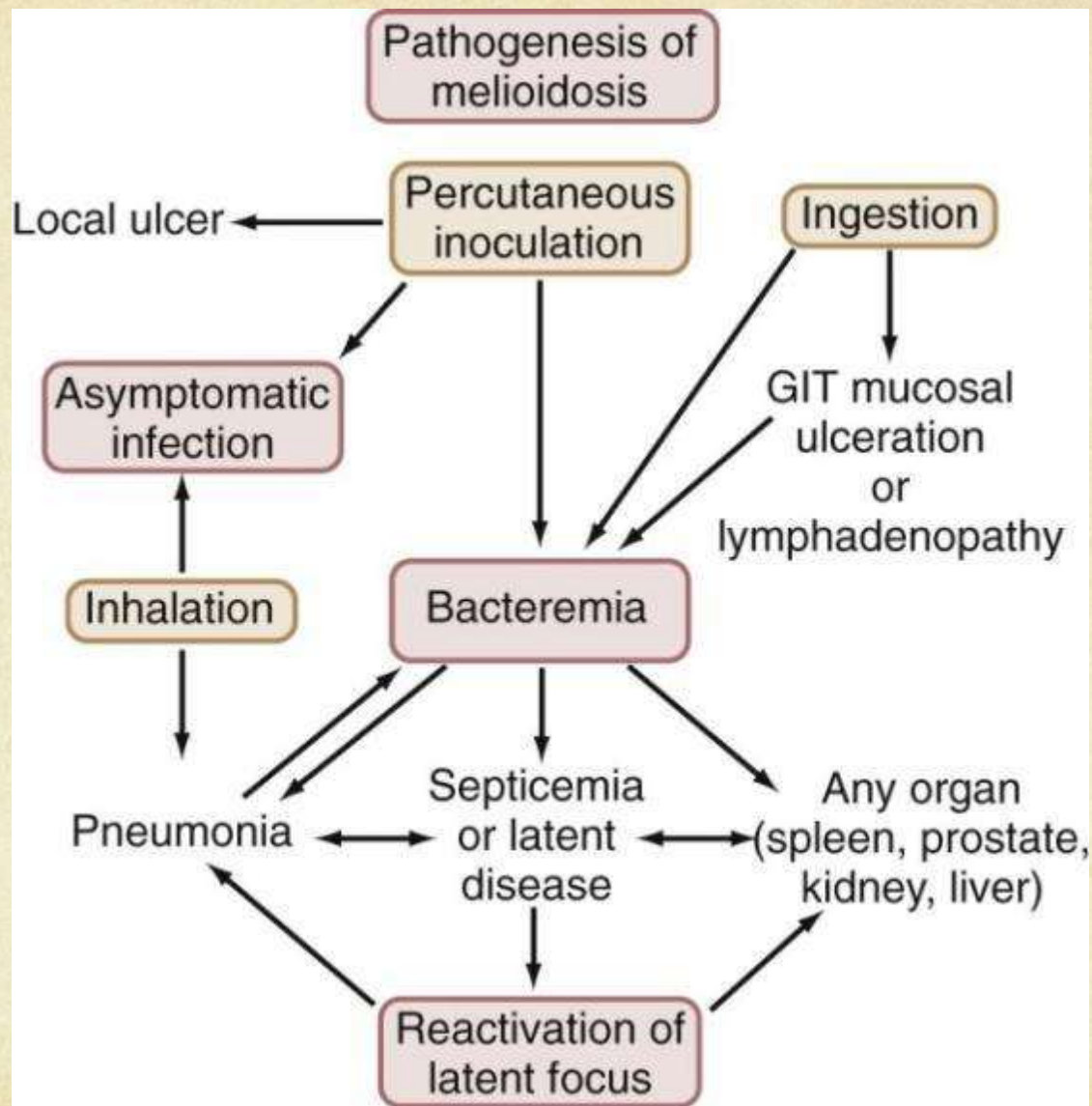
Laboratory infection

Two cases described:

- Sonication outside a safety hood
- Organisms were spilled during centrifugation

Need for biosafety

Risk during normal lab procedures is very low



Risk Factors

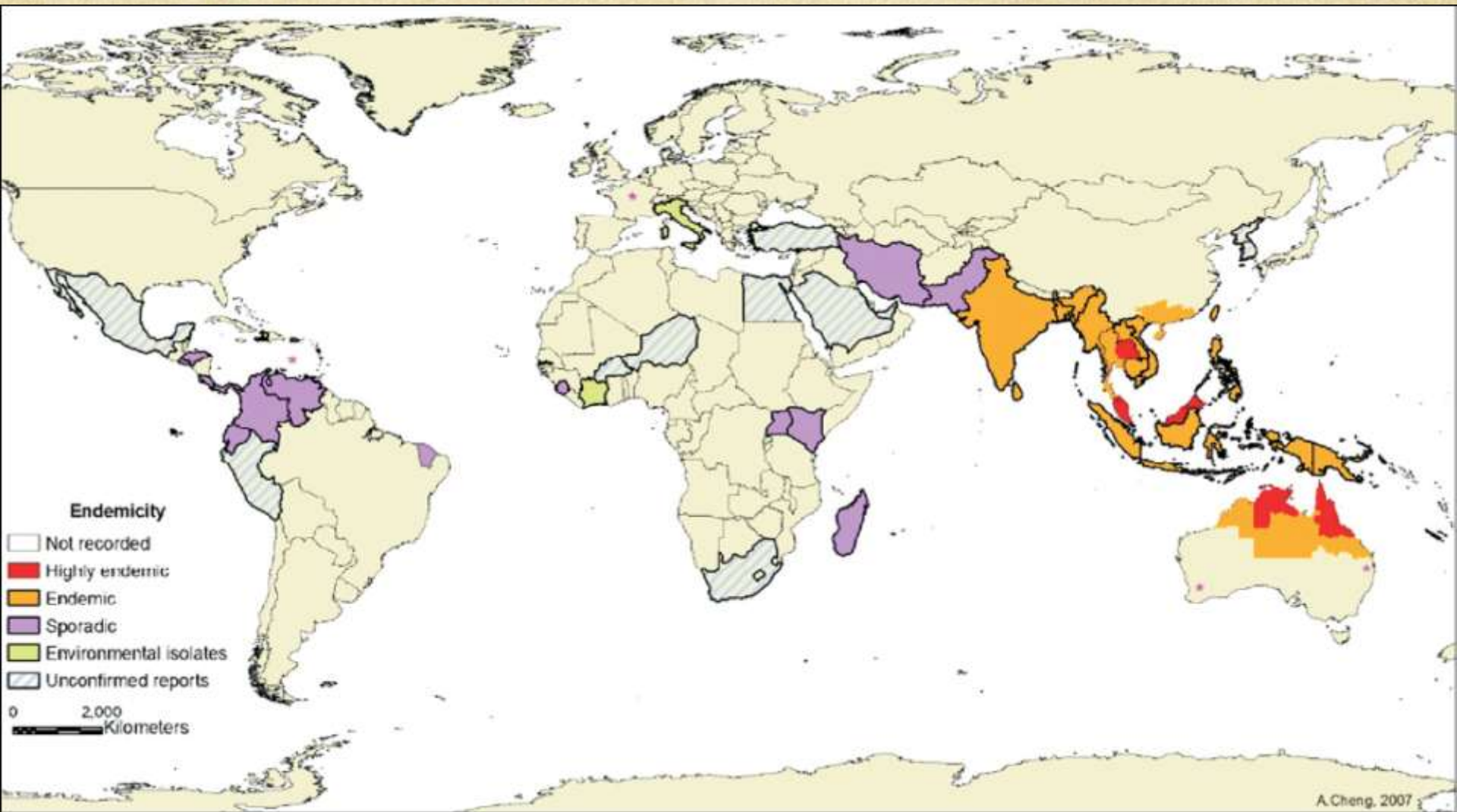
TABLE 221-1 -- Risk Factors for Melioidosis

Risk Factor*	Thailand (% of cases)	Australia (% of cases)
Diabetes	23-60	37
Alcohol excess	12	39
Renal disease	20-27	10
Chronic lung disease	NR	27
Thalassemia	7	Nil
No risk factors	24-36	20

Australia data from Currie BJ, Fisher DA, Howard DM, et al. Endemic melioidosis in tropical northern Australia: A 10-year prospective study and review of the literature. Clin Infect Dis. 2000;31:981-986.

NR, not reported.

Global Distribution



Global map showing the categories of distribution of melioidosis and *Burkholderia pseudomallei*. Pink asterisks indicate three documented temperate outbreaks of melioidosis: France, southeast Queensland and southwest Western Australia

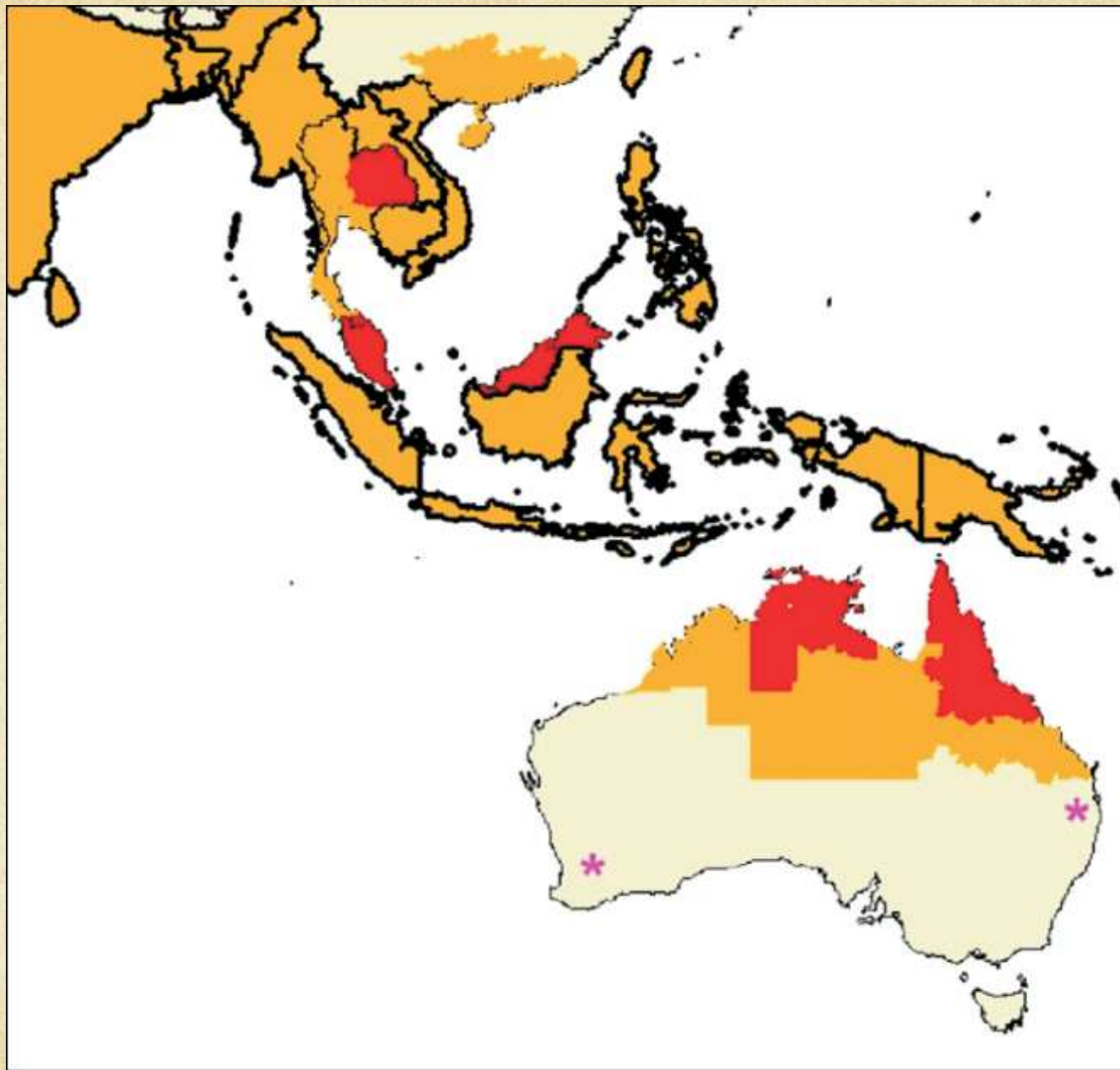
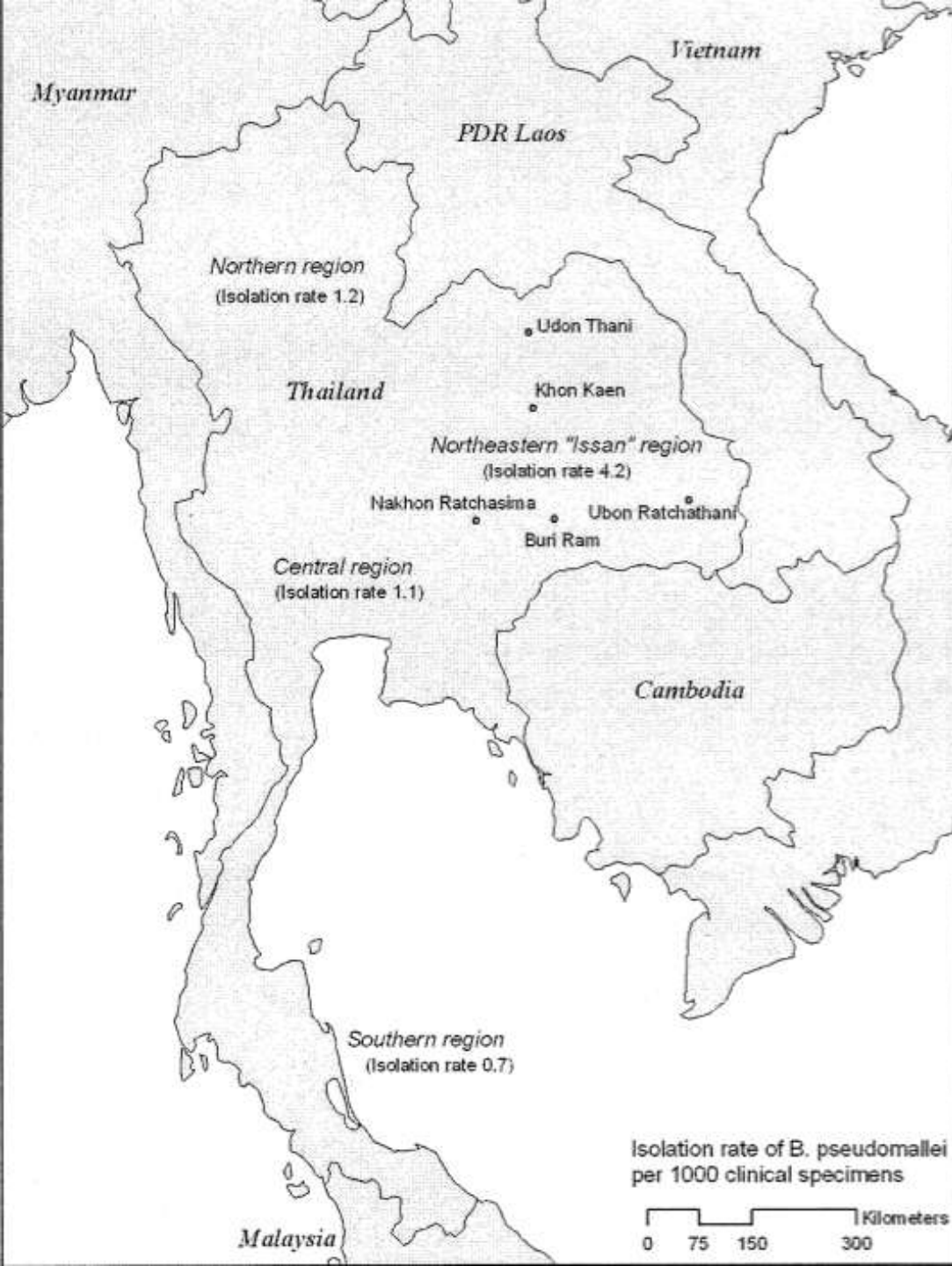


Fig. 2 – Melioidosis in northern Australia, Southeast Asia and Asia, highlighting the highly endemic locations. Pink asterisks indicate two documented temperate outbreaks of melioidosis in Australia: southeast Queensland and southwest Western Australia.



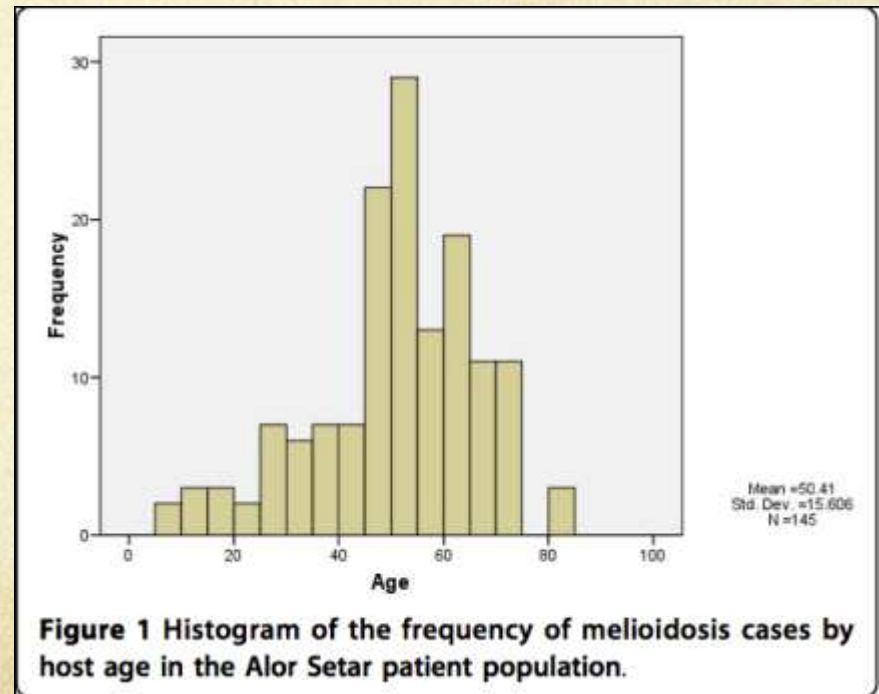
Predominant in Issan region of Thailand

Cheng and Currie, 2005

Incidence, risk factors and clinical epidemiology of melioidosis: a complex socio-ecological emerging infectious disease in the Alor Setar region of Kedah, Malaysia

Muhammad RA Hassan¹, Subhada P Pani², Ng P Peng¹, Kirtanaa Voralu³, Natesan Vijayalakshmi², Ranjith Mehanderkar², Norasmidar A Aziz¹, Edwin Michael^{4*}

- Incidence : 16.35/100,000 per year
- Crude mortality 33.8%
- Diabetes major risk factor



Imported melioid

<u>Year</u>	<u>Sex</u>	<u>Age</u>	<u>Origin</u>	<u>Latency</u>	<u>Underlying disease</u>
1988	M	60	Pakistan	>2y	DM
1989	M	40	Malaysia	-	NK
1990	M	54	Bangladesh	>6m	DM
1992	M	53	Thailand	1m	DM
1994	M	58	Bangladesh	-	TB
1995	M	55	India	1m	DM
1996	F	51	Thailand	-	Steroids
1997	M	61	Thailand	-	NK
1997	M	49	Indonesia	-	DM
1998	M	20	Malaysia	3y	CF
1998	M	47	Bangladesh	-	NK
1998	M	39	Thailand	2y	DM
1998	M	49	Bangladesh	1y	NK
1998	M	59	Bangladesh	-	DM
1998	M	19	Thailand	-	NK

m=months; y=years; CF=cystic fibrosis; DM=diabetes mellitus; NK=none known; TB=tuberculosis

Confirmed culture-positive melioidosis in England and Wales, 1988–September 1998

Fatal acute melioidosis in a tourist returning from Martinique Island, November 2010

1st report of Melioidosis from Martinique

Swiss man in 30's

Previously well. Walked through flooded mud forest 2 months after a hurricane and floods. Scratches and mosquito bites.

Blood culture: GNB after 24 hours

MALDO-TOF : *B.pseudomallei*

Confirmed by 16S on all BC specimens

Imported Melioidosis, Israel, 2008

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 11, November 2009

Thai Migrant agricultural worker in Israel

Risk factor: newly diagnosed Diabetes Mellitus

Latency: at least 8 months

'Imported' melioidosis in Germany: relapse after 10 years

Transactions of the Royal Society of Tropical Medicine and Hygiene (2008) 102/S1, S40–S41

62yo German

Abdominal abscess

Risk factor: Type II Diabetes, Chronic renal impairment

Presumably acquired on holiday in Thailand in 1996

patient had been hospitalised for severe pneumonia and lung abscess

“several weeks” treatment in a local hospital

The surgeon who aspirated the abscess seroconverted

Post-Tsunami 2004

Reports of melioidosis in people returning to:

Finland

Sweden

Australia

Italy

Inhalation and inoculation

Pro-med and multiple references via PubMed



Imported Melioidosis --- South Florida, 2005

1. 48yo man – pneumonia, perirectal abscess → epidural abscess

Risk factors: Type II Diabetes

Presumed inoculation in Honduras 1 month before presentation

2. 80yo woman – pneumonia. Died of sepsis. Melioid isolated post-mortem from initial blood culture

Patient was a resident of Honduras, who arrived in USA to visit family 2 weeks prior.

USA: 5 cases reported annually. Not mandatory reporting.

Melioidosis: An Imported Case From Madagascar

First case reported from Madagascar - 2005

Changing epidemiology of melioidosis? A case of acute pulmonary melioidosis with fatal outcome imported from Brazil

Second case reported from Brazil - 2005

Clinical Spectrum

1. Multifocal infection with septicemia
(45% of cases, 87% mortality)
2. Localized infection with septicemia
(12% of cases, 17% mortality)
3. Localized infection
(42% of cases, 9% mortality)
4. Transient bacteremia (0.3%)

Clinical Spectrum

TABLE 221-2 -- Clinical Presentations and Outcomes of Melioidosis in Northern Australia

Parameter	Total No. Deaths (Mortality)	Bacteremic No. Deaths (Mortality)	Nonbacteremic No. Deaths (Mortality)
Septic Shock	111 59 (53%)	99 49 (49%)	12 13 (81%)
Pneumonia	85 44 (52%)	75 36 (48%)	10* 8 (80%)
Genitourinary	95 (56%)	84 (50%)	1[†] 1 (100%)
Osteomyelitis, septic arthritis	42 (50%)	42 (50%)	0 0 (0%)
No focus	138 (62%)	127 (58%)	1 1 (100%)
No Septic Shock	403 17 (4%)	181 13 (7%)	222 4 (2%)
Pneumonia	177 9 (5%)	78 8 (10%)	99 1 (1%)
Genitourinary	64 2 (3%)	39 2 (5%)	25 0 (0%)
Skin abscess(es)	64 0 (0%)	1 0 (0%)	63 0 (0%)
Soft tissue abscess(es)	14 0 (0%)	1 0 (0%)	13 0 (0%)
Neurologic	14 3 (21%)	3 0 (0%)	11 3 (47%)
Osteomyelitis, septic arthritis	12 0 (0%)	6 0 (0%)	6 0 (0%)
Other	58 3 (5%)	53 3 (6%)	5 0 (0%)
Total	514 76 (15%)	280 62 (22%)	234 14 (6%)

Adapted from Currie et al 2000. In Mandell PPID 7th edition

Clinical differences b/w Thailand and N. Australia

Suppurative parotitis

up to 40% of children with melioidosis in Thailand

Hepatic and Splenic abscesses

more in Thailand

Encephalomyelitis

approx 4% in N. Australia

Prostatic abscesses

18% in N. Australia. (sample bias?)

Other sites described

Mycotic aneurysms

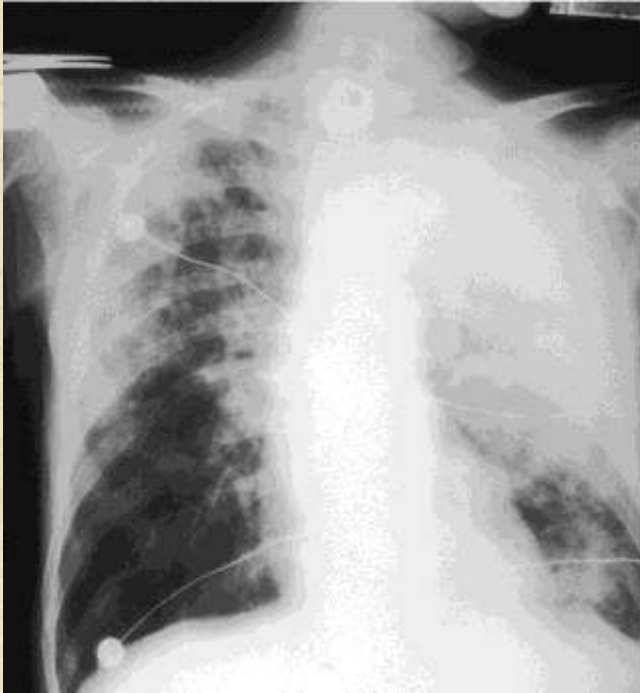
Mediastinal infection

Thyroid abscesses

Scrotal abscesses

Ocular infections

Examples



Upper lobe pneumonia or cavitation.

DDx: TB



BJ Currie in Mandell - PPID 7th edition



Cutaneous melioidosis



Conclusion

Variable presentation

Multiple abscesses and travel history may give clues

Possibly increasing imported cases to non-endemic areas