Melioidosis in Arizona

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Case report

- A 76 year-old man from Prescott, AZ was admitted to the hospital with sore throat and fever 3 days after a bronchoscopy for a persistent RLL infiltrate
    - Polycystic renal disease requiring renal transplantation x 2, the last in 2022
    - Traveled to Goa, India from April to October, 2024
    - Persistent cough with a pulmonary infiltrate in February 2025
    - Prescribed amoxicillin/clavulanate without improvement
- On May 8, 2025, a PET/CT revealed a metabolically active mass in the RLL
- On May 28, he underwent bronchoscopy with robotic biopsy of the RLL mass and EBUS-guided lymph node biopsies
    - Caseating granuloma with negative Gram, AFB, and GMS stains

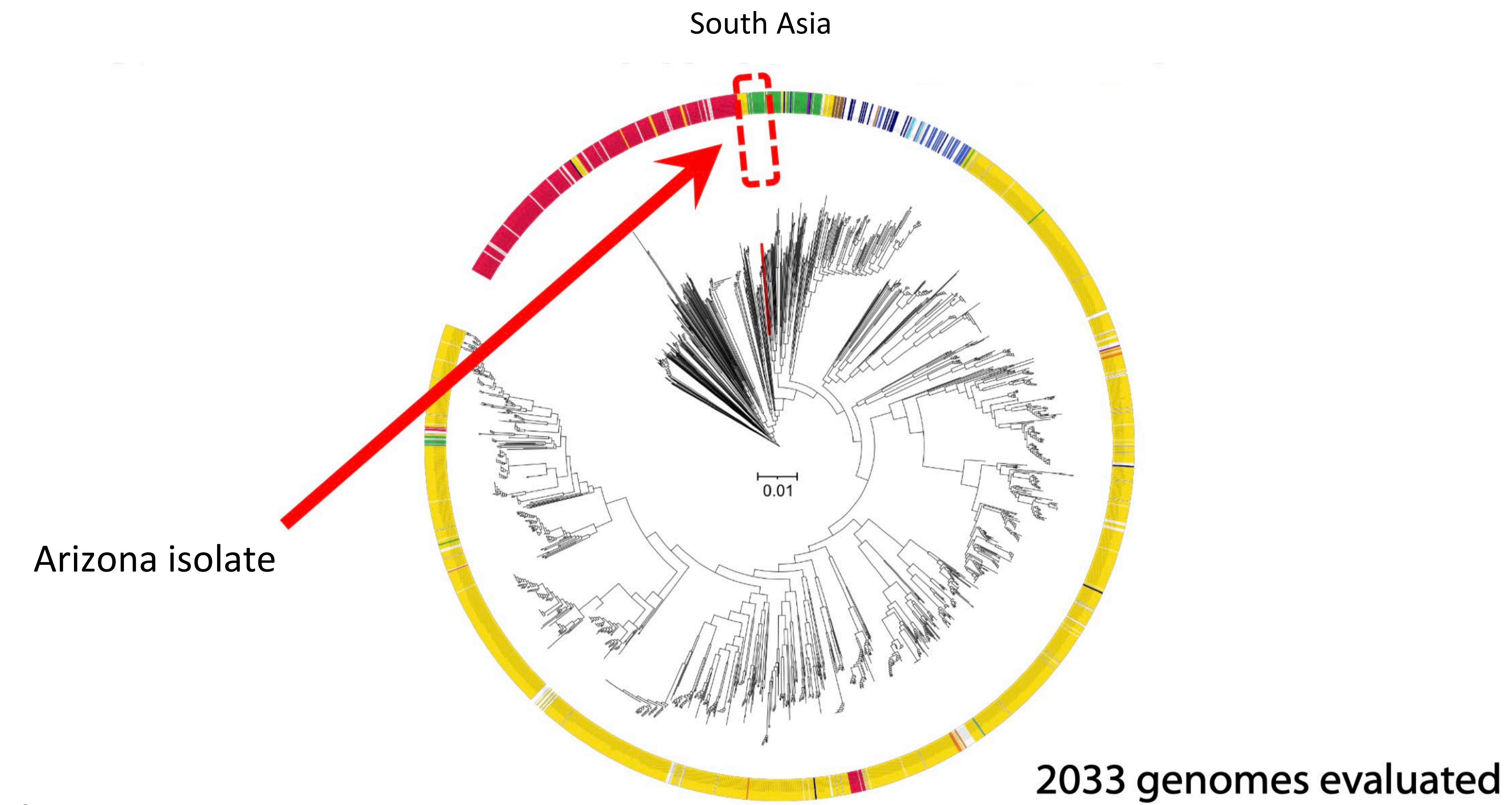
Case report

- Admitted to the hospital on June 1 because of fever and sore throat
  - Linezolid, piperacillin-tazobactam and doxycycline were initiated and the patient improved
  - A blood culture grew a Gram-negative rod identified as *Burkholderia* species
  - TB QuantiFERON, *Histoplasma* urinary antigen, coccidioidal serology negative
- Discharged on June 6 on doxycycline
- The *Burkholderia* species identified as *B. pseudomallei* by the Arizona State Public Health Laboratory (ASPHL)
- Received a course of IV meropenem 1 gm q8 hr for 2 weeks followed by oral doxycycline

Genomic analysis

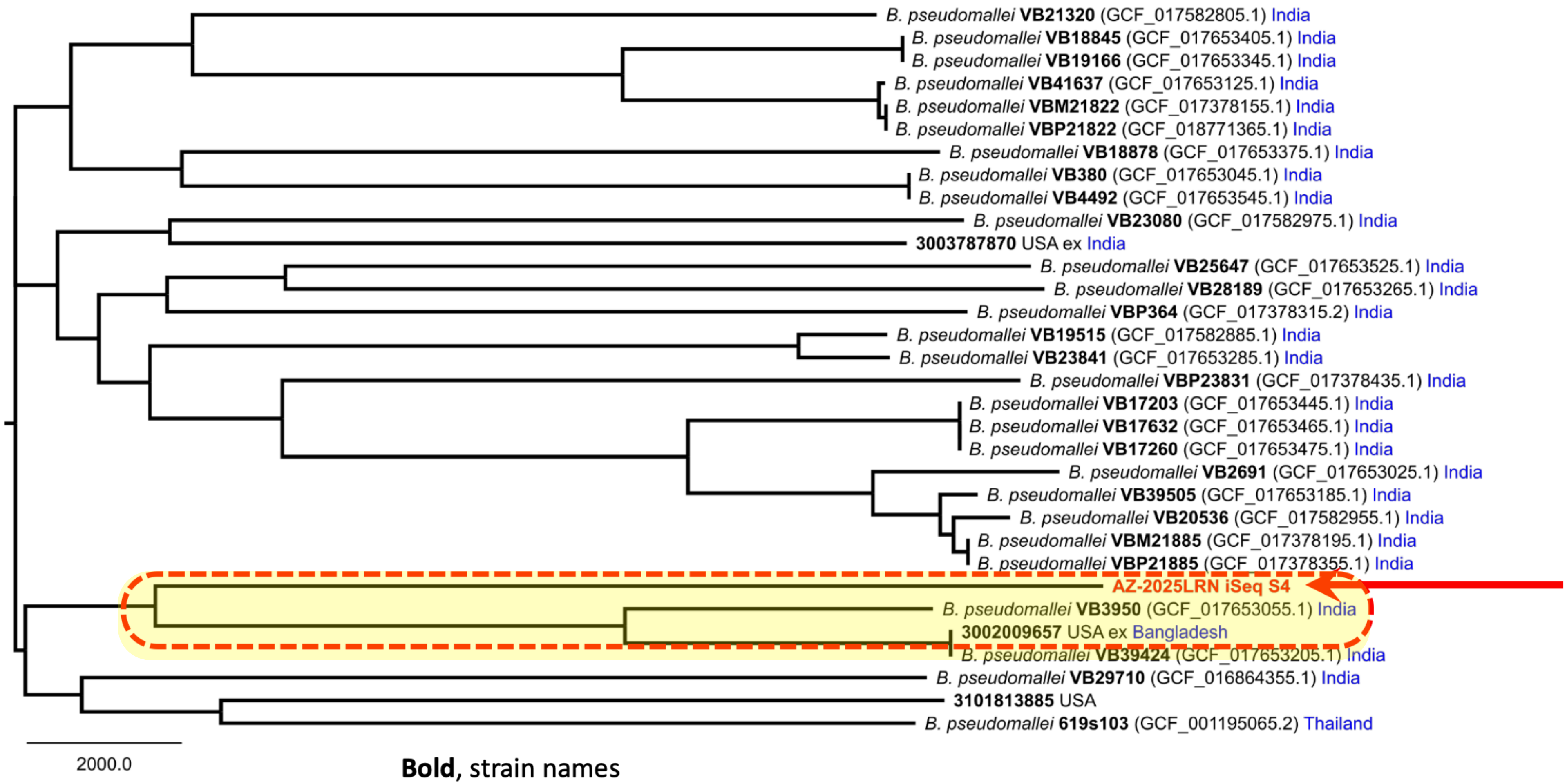
- ***Burkholderia* blood isolate at ASPHL**
  - real-time PCR positive for *B. pseudomallei* but unable to culture
  - Classified as AZ-2025LRN-001-iSeq-S4
  - Isolate sent to CDC - culture positive for *B. pseudomallei*
  - Later, a sample from the bronchoscopy was PCR-positive for *B. pseudomallei*
- **Whole genome sequencing (WGS)** noted a single 16S rRNA gene complex consistent with *B. pseudomallei*
- **Multilocus sequence typing (MLST)** identified a novel *ace* allele, representing a novel sequence type (ST)
- A **subpanel SNP** (single nucleotide polymorphism) **phylogenetic tree** related the isolate to organisms from India and Bangladesh

SNP phylogeography panel



from ASPHL

Subpanel SNP phylogenetic tree



Bold, strain names
(Parentheses), public genome accession
Blue, country origin

from ASPHL

Key issues of this case

- Patient with underlying immunosuppression
- Travel history to an area endemic for melioidosis
- Chronic signs and symptoms of pneumonia
- Granulomatous tissue response
- Similarity of presentation to more common diseases
  - tuberculosis
  - endemic mycosis
    - coccidioidomycosis
    - histoplasmosis
- Delay in diagnosis
  - melioidosis not considered
- Importance of molecular typing
  - established the diagnosis
  - confirmed acquisition of infection was travel-related and not local

History of melioidosis

- First described by Whitmore and Krishnaswami in 1912
  - post-mortem examination of a patient in Rangoon, Burma (Yangon, Myanmar) with a consolidated pneumonia resembling equine **glanders**
  - identified a fastidious Gram-negative bacillus similar to *Bacillus mallei*
  - Subsequently reported 38 cases with an association to opiate injection use
    - “morphia injectors’ septicaemia”
      - associated with contaminated water used for injection?
    - used the term “*pseudomallei*” to refer to the organism
  - Stanton and Fletcher in 1921 coined the term **melioidosis** - “r*esembling the distemper of asses”*

- No further mention until 1940’s
  - a disease of “friendless wastrels” of Rangoon
  - no reports of disease in Europeans
  - a neglected disease

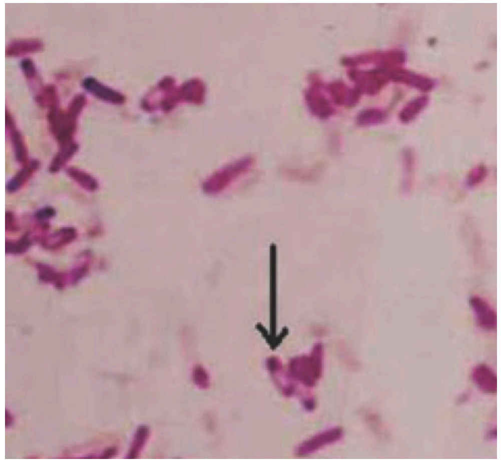
- Clinical diversity of presentation
  - localized skin ulcers or abscesses
  - bacteremia with septic shock
  - chronic pneumonia resembling tuberculosis

Alfred Whitmore

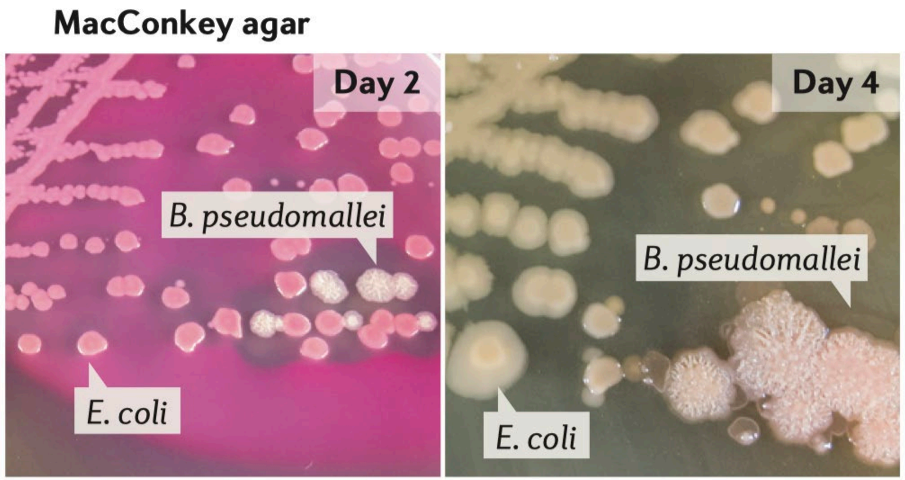
Savelkoel J and Dance DAB. Emerg Infect Dis 2024; 30:752

Bacteriology of *B. pseudomallei*

- An aerobic Gram-negative bacillus
  - possible bipolar staining (“safety pin”)
  - motile due to flagella
- Grows readily on blood and McConkey media
  - smooth, creamy-white colonies at 24 hr
  - may become dry or mucoid after 48 hours
- Biochemical reactions
  - oxidase and catalase positive
  - reduces nitrate
  - non-fermenter of sugars
  - indole, hydrogen sulfide, and urease negative
- Facultative intracellular pathogen
- It is a Tier 1 select agent of bioterrorism
- *B. mallei* (the cause of glanders) underwent genomic reduction from *B. pseudomallei*
  - lost the ability for environmental growth and is now an equine obligate pathogen



Pandey et al. Ind J Orthop 2010; 2:216



Wiersinga et al. Nat Med 2018; doi: 10.1038/nrdp.2017.107

Coulon et al. J Bact 2025; doi: 10.1128/jb.00521-24;

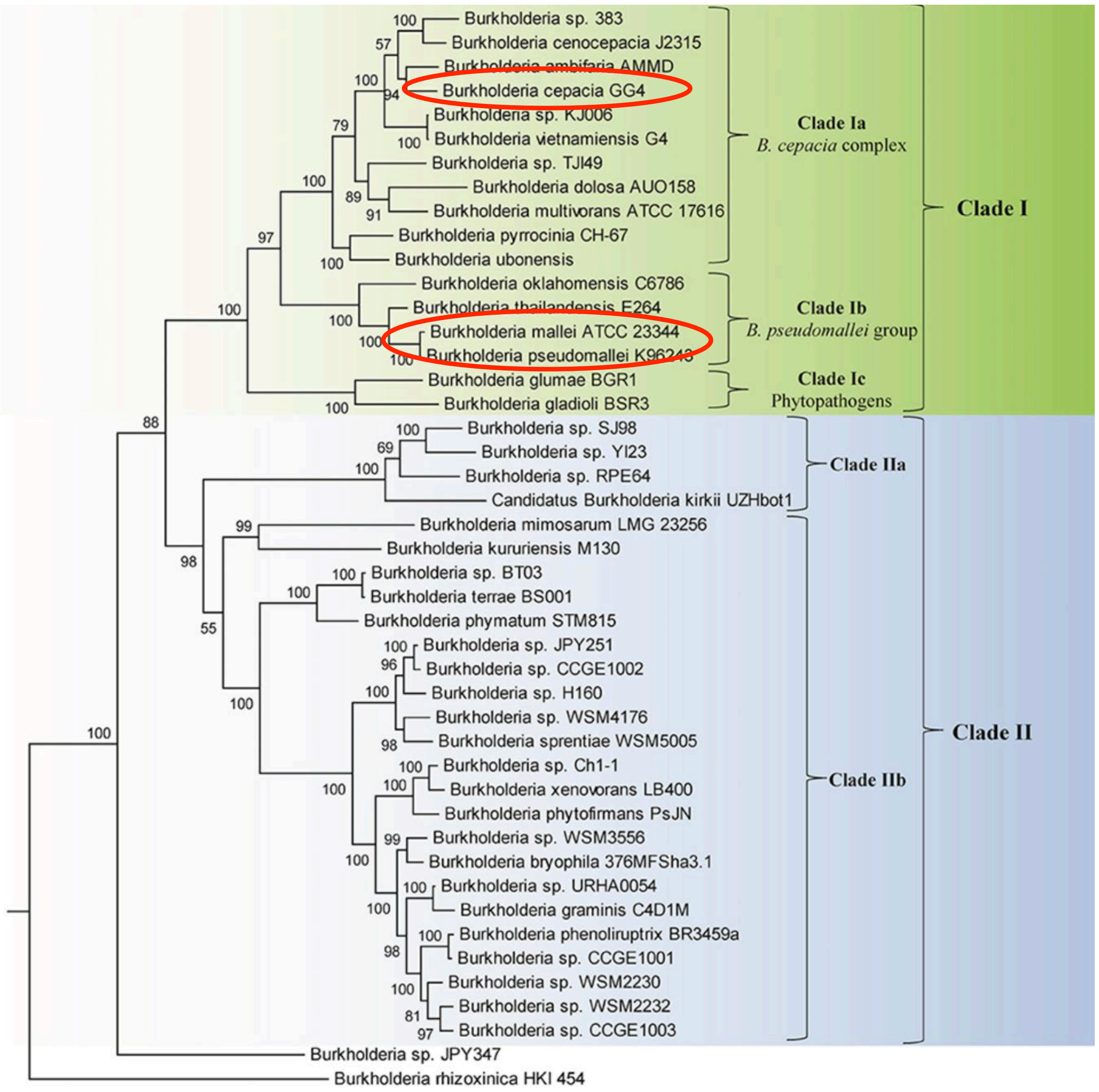
Classification

- *Burkholderia* species were originally classified with environmental *Pseudomonas* species
  - rRNA group II pseudomonads

- Yabuuchi et al named the genus *Burkholderia* in 1992 based on 16S rRNA sequencing
  - in honor of Walter H. Burkhold
    - in 1949, isolated the organism associated with onion sour rot (*Burkholderia cepacia*)

- Two major genomic clades
  - Clade I: pathogenic
  - Clade II: environmental

- There are at least 70 species of *Burkholderia*
  - *B. cepacia*, *B. cenocepacia, B. pseudomallei*, and *B. mallei* are the most common pathogenic isolates



Front Microbiol 2017; doi: 10.3389/fmicb.2017.01679

Genomics of *Burkholderia pseudomallei*

- The genome is composed of two circular chromosomes of 4.07 and 3.17 megabase pairs (7.24 Mbp)

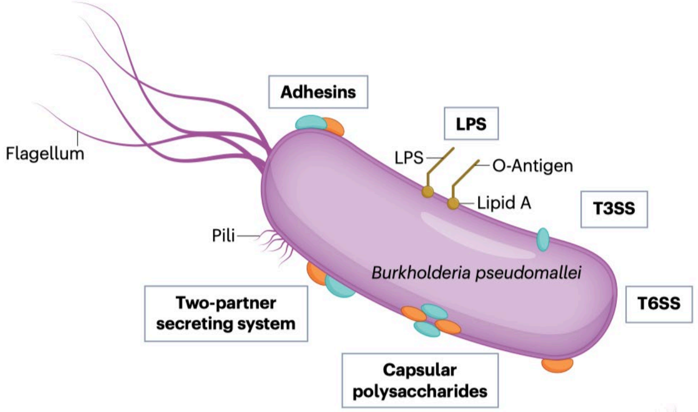
- *B. pseudomallei* shares a core set of 2590 genes with other members of the *Burkholderia* genus

- 86% of the *B. pseudomallei* genome is common among all strains
- 14% is variably present
  - this variable region includes multiple genomic islands acquired from other bacteria
    - inserted into transfer RNA genes
    - possibly contribute to virulence

- There is substantial genetic diversity within single patients, indicating the capacity of the organism to evolve within the host.

Wiersinga et al. NEJM 2012; 367:1035; Meumann et al. Nat Rev 2024; 22:155

Pathophysiology

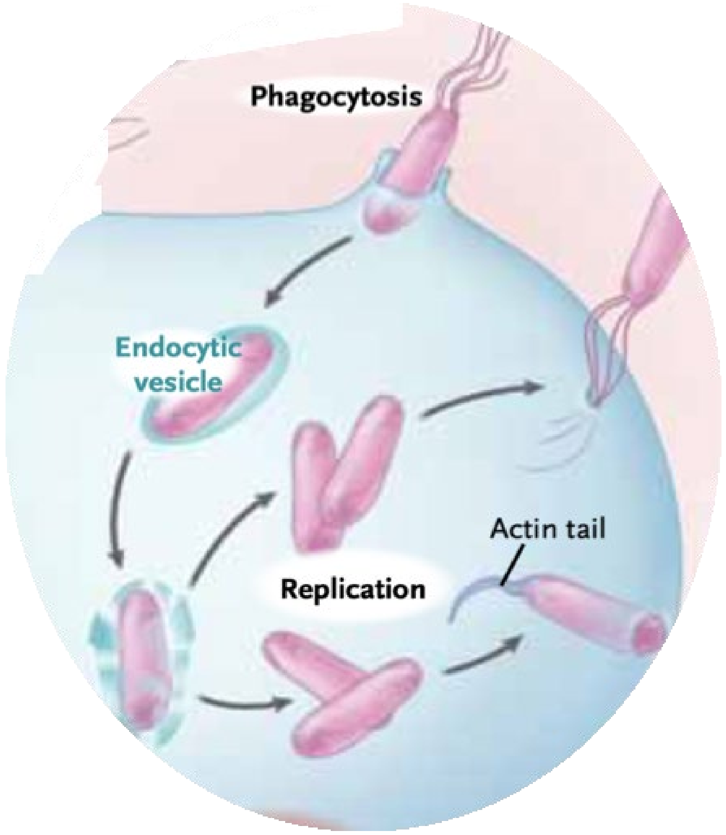


- *B. pseudomallei* is an opportunistic, facultative intracellular, motile saprophyte

- Cellular uptake → vacuole escape → cytosol replication → cell-to-cell spread

- Key virulence factors
  - type III secretion systems (T3SSs)
    - deliver bacterial effector molecules into the host cytoplasm
  - type VI secretion systems (T6SSs)
    - promotes intracellular survival using host glutothione
  - actin-based membrane protrusions
    - promotes movement inside cell and cell-to-cell spread

- Ability to survive intracellularly → latency



Wiersinga et al. NEJM 2012; 367:1035
Wiersinga et al. Nat Rev Dis Prim 2018; 4:17107
Meumann et al. Nat Rev Microbiol 2024; 22:156

Immune response

- Pathogen-recognition receptors (PRR) detect *B. pseudomallei* pathogen-associated molecular patterns (PAMPS) during cellular invasion
  - Toll-like receptors (TLRs), NOD-like receptors (NLRs)
  - LPS, peptidoglycan, flagella, DNA
- Recruitment of neutrophils, macrophages, and lymphocytes
  - CD4+ lymphocytes important in control
- TNF-α and IL-6 up-regulation → activates coagulation and complement
- Eventual increase in both humoral and cellular immunity

Wiersinga et al. NEJM 2012; 367:1035
Wiersinga et al. Nat Rev Dis Prim 2018; 4:17107
Meumann et al. Nat Rev Microbiol 2024; 22:156

Ecology

- *B. pseudomallei* is an environmental saprophyte
  - survives in soil at depths >1 foot
    - rising to the surface when
      - soil is wet (e.g. monsoon) or
      - disturbed (i.e. agriculture)
  - water
    - survives in biofilm and within amoebae
    - killed by chlorination and UV light
    - aerosolizes during severe weather events

low-land rice paddy in northern Laos

- *Burkholderia* species inhabit other environmental niches
  - in the rhizosphere among plant roots to help to fix nitrogen
  - as a plant endophyte
  - in wild and domestic animals
    - found in fecal material
      - contributes to dispersal

Pongmala et al. 2022, Sci Rep; doi: 10.1038/s41598-022-12795-0
Meumann et al. Nat Rev 2024; 22:155

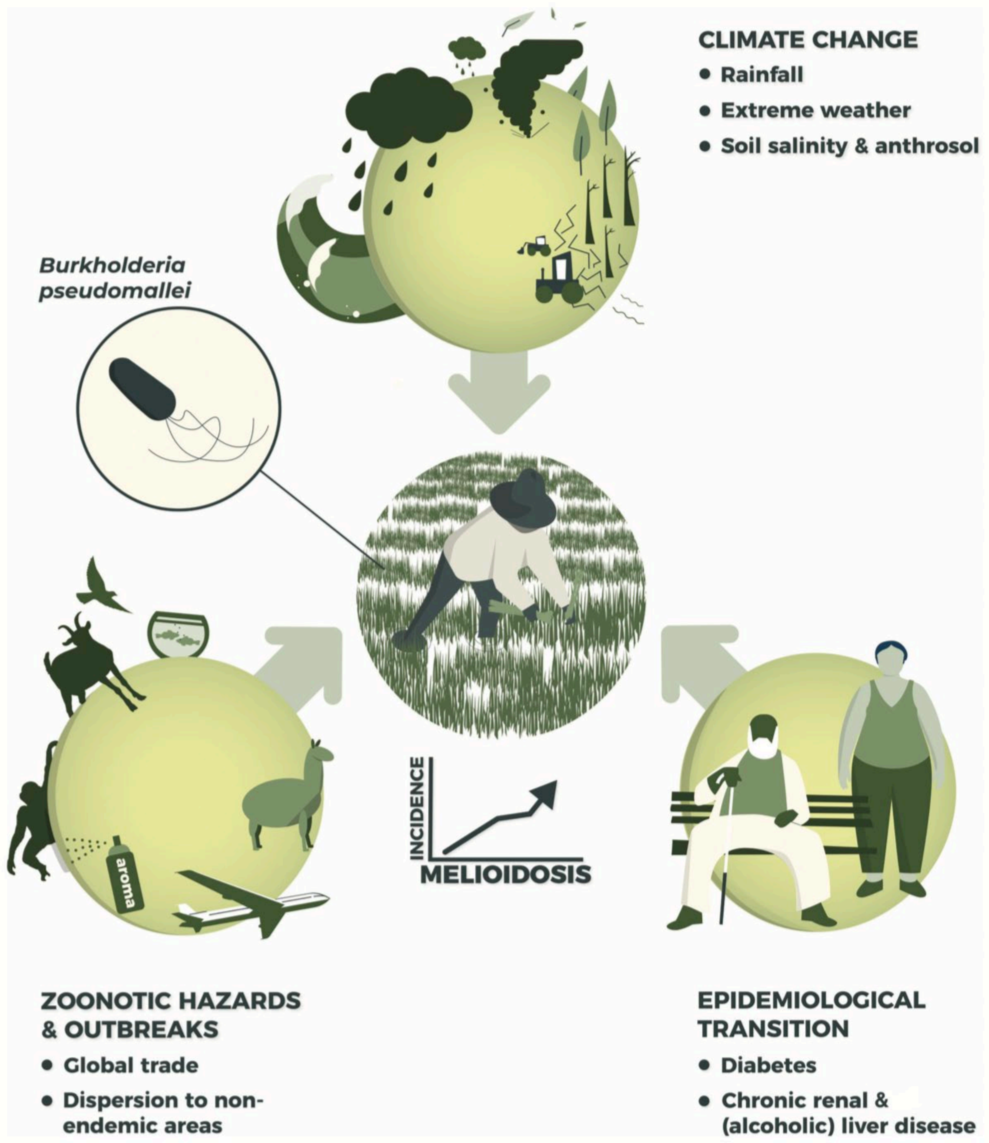
Epidemiology

- Originally thought to be confined to northern Australia and southeast Asia
  - Northern Territory in Australia and northeast Thailand most endemic
    - 3rd most common cause of mortality in Thailand
  - followed by Malaysia, Singapore, Vietnam, Cambodia, and Laos
- Melioidosis is currently recognized as endemic in 48 countries
  - in an additional 34 countries, it is likely endemic
  - Indian subcontinent, southern China, Hong Kong, Taiwan, various Pacific and Indian Ocean islands, and parts of the Americas as well as Africa increasingly recognized
- Annual case numbers in 2015 were estimated to be 165,000
  - 89,000 annual deaths
- Cases associated with land disturbance and water exposure
  - monsoons, inhalation of aerosolized bacteria, skin abrasions and injuries, ingestion of contaminated water
  - occupational risks
    - agriculture particularly rice farming
    - construction

Currie BJ. Current Opinion Infect Dis 2022; doi: 10.1097/QCO.0000000000000869

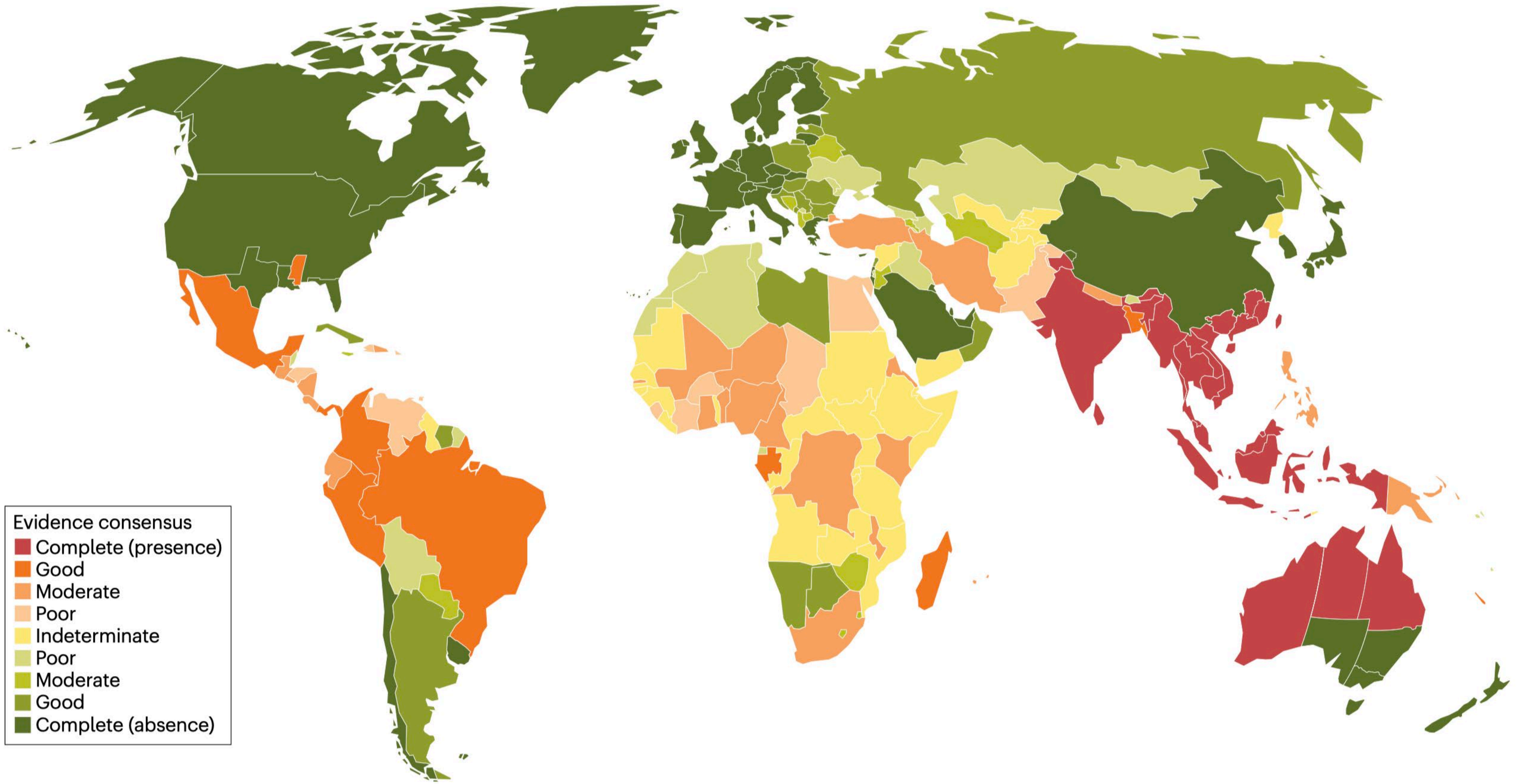
Drivers of the spread of melioidosis

- **Climate change**
  - ↑environmental spread of organism
    - ↑rainfall
    - ↑temperature
    - ↑extreme weather events
- **Zoonoses**
  - shedding into the environment by domestic and wild animals
  - geographically disperse the organism
- **Epidemiological transitions**
  - Changing population risks
    - ↑aging
    - ↑diabetes mellitus
    - ↑chronic renal disease
    - ↑chronic liver disease
      - excessive alcohol use



Bimie et al. Curr Opin Infect Dis 2022; doi: 10.1097/QCO.0000000000000827

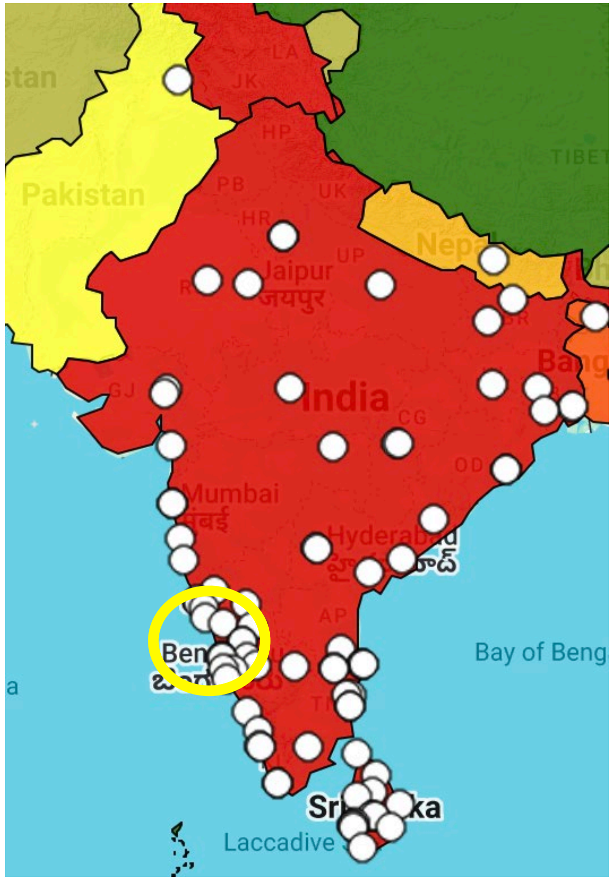
Global distribution of human, animal, and environmental *B. pseudomallei*



Meumann et al. Nature 2024; doi: 10.1038/s41579-023-00972-5

Melioidosis in India

- An extensive soil sampling study from southwest India showed the wide environmental distribution of *B. pseudomallei*
- Modeling studies estimate between 20,000–52,000 new cases annually
- The overall prevalence of melioidosis in many states across India remains under-explored
- Majority of cases are from southern India
- Northern and western India are emerging areas



reported cases of melioidosis from melioidosis.info

Kannan et al. Pathogens 2025; doi: 10.3390/pathogens14040379

Melioidosis in the United States

- Until recently, most cases of melioidosis in the U.S. were uncommon and associated with patient travel to known endemic regions (*Benoit et al. MMWR 2015; 64(5):1*)

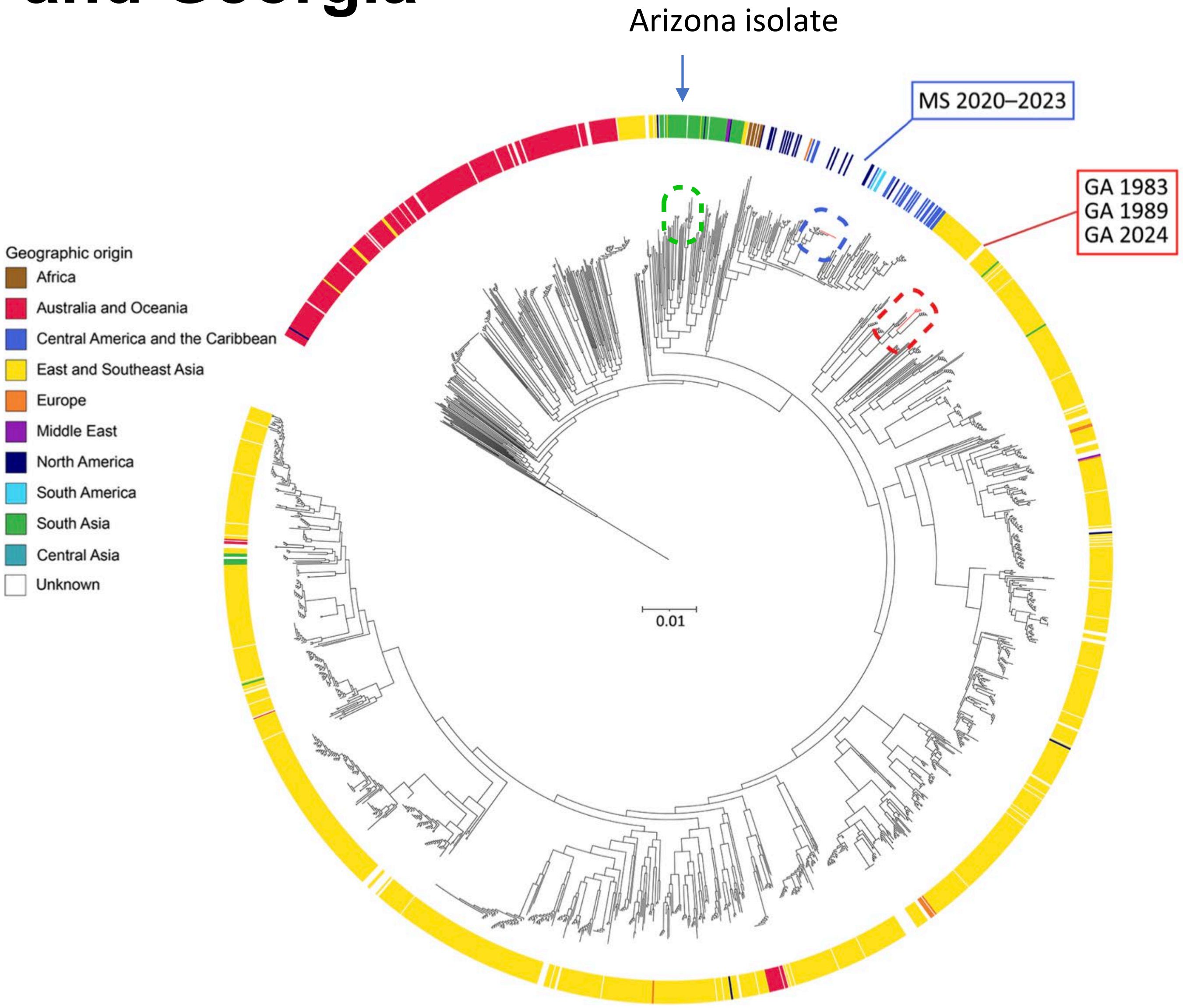
- Some cases have been acquired by exposure to household products imported from endemic areas
  - A case in Maryland associated with a home fresh-water aquarium (*Dawson et al, Emerg Infect Dis 2021; 27:3030*)
    - Unclear if source was fish, aquatic plants, gravel, or water
  - Four cases in multiple states associated with spray aromatherapy imported from India (*Gee et al. NEJM 2022; 386:862*)
    - a pet raccoon subsequently died of melioidosis when it stepped onto the contents of the aromatherapy liquid (*Petras et al, MMWR 2022; 71:1597*)

- There is evidence of endemicity in Puerto Rico based on serology and soil sampling (*Doker et al. Clin Infect Dis 2015; 60:243*)

- In 2022, three cases over a 3-year period were linked to environmental exposure on the Mississippi Gulf Coast (*Petras et al, NEJM 2023; 389:2355*)
  - *B. pseudomallei* was isolated from a puddle and soil near the home of one case
  - Patient and environmental samples were all ST92 and were clonally related

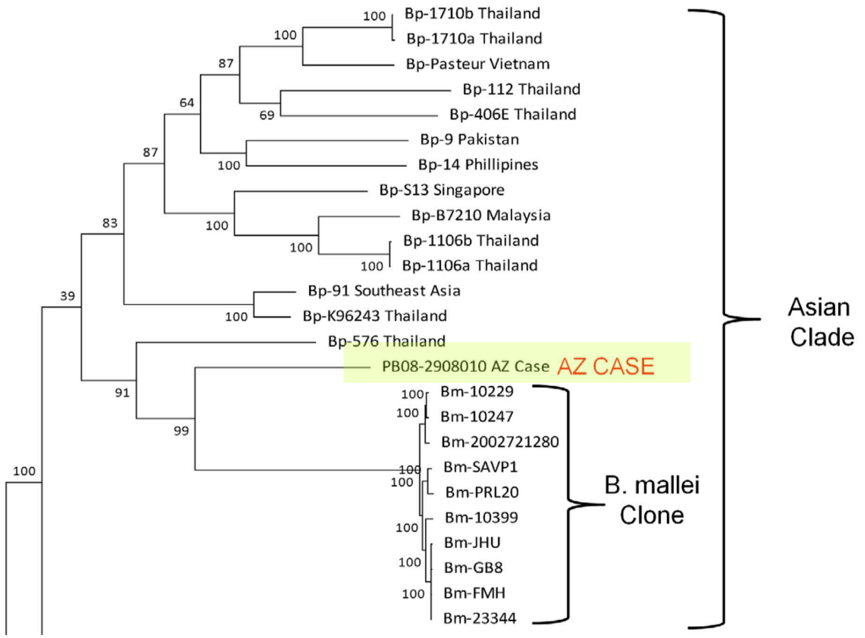
- In 2025, four cases of presumptive autochthonous melioidosis were described from Georgia occurring between 1983 and 2024 (*Brennan et al, Emerg Infect Dis 2025; 31:1802*)
  - 2 were associated with Hurricane Helene (26 Sep 2024)
    - shared a common worksite with exposure to mud, dust, wind, and 10” of rain
  - All patient isolates were ST41

Phylogenetic tree for *B. pseudomallei* isolates from Mississippi and Georgia



Melioidosis in Arizona

- One case of possible autochthonous melioidosis has been described from southern Arizona
- 32 year-old man with diabetes mellitus presented with knee pain
  - Blood, knee aspirate, and sputum grew *B. pseudomallei*
  - No travel or other exposure history to known endemic areas of melioidosis were elicited
- Genomic analysis
  - The isolate was confirmed as *B. pseudomallei* based on multiple PCR targets
  - Alleles by MLST were identical to a previous isolate from a patient with severe melioidosis in Australia (ST426)
  - WGS phylogenetic analysis grouped the case genome with southeast Asian strains, particularly from Thailand



Engelthaler et al. PLoS Negl Trop Dis 2011; doi:10.1371/journal.pntd.0001347

Clinical infection

- Infection is acquired by exposure to *B. pseudomallei* in the environment
  - non-intact skin
  - inhalation
  - ingestion

- Environmental conditions may increase the risk of exposure
  - tropical storms
  - certain occupations with outdoor exposures (e.g. rice farming)
  - most cases occur during the rainy season

- Most infections are clinically latent

- Active disease generally occurs in those with risk factors
  - diabetes mellitus
  - liver disease associated with heavy alcohol use
  - chronic lung disease
  - chronic renal disease
  - immunosuppression

- Active disease can be either
  - acute
  - chronic (symptoms >2 months)

Wiersinga et al. Nat Med 2018; doi: 10.1038/nrdp.2017.107

Clinical presentation

- Incubation period
  - 1-21 days
  - but prolonged onset after infection not uncommon
- Protean manifestations
  - pneumonia
  - bacteremia without focus
    - septic shock in 20%
    - internal organ and secondary abscesses
  - genitourinary tract infection
  - skin infection and abscesses
  - osteomyelitis

Wiersinga et al. NEJM 2012; 367:1035; Wiersinga et al. Nat Rev 2018; 4:1

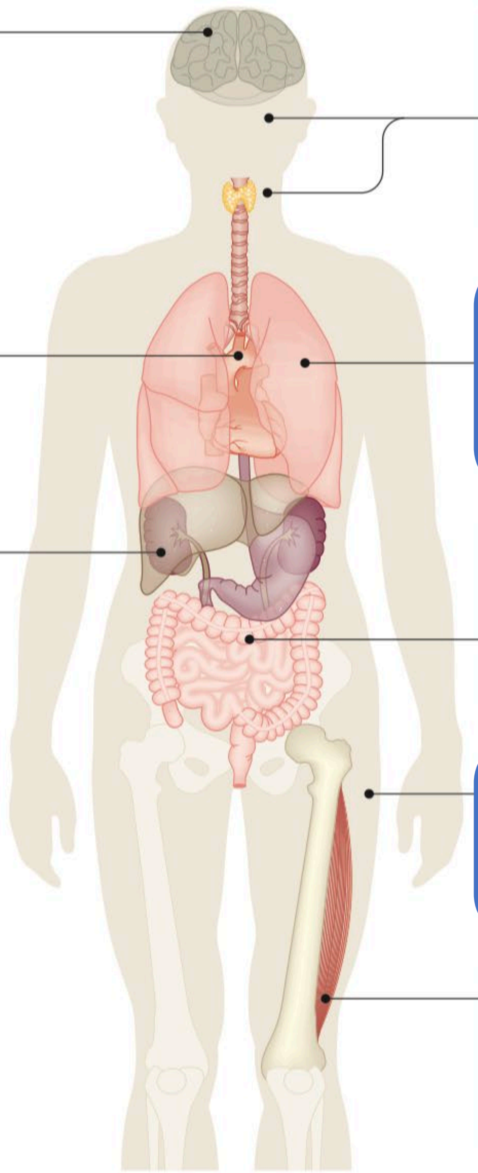
Clinical manifestations

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

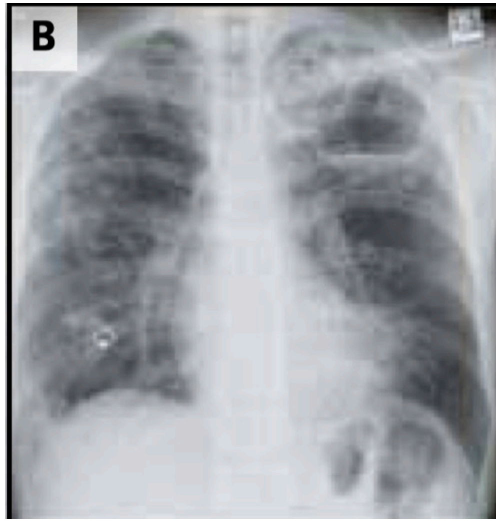
Musculoskeletal system (4–14%)
- Septic arthritis
- Myositis
- Osteomyelitis

Wiersinga et al. Nat Med 2018; doi: 10.1038/nrdp.2017.107

Clinical manifestations

Cutaneous abscess

Birnie et al Trav Med Inf Dis 2019; 32:101461



Pneumonia

Dissemination from bacteremia

Wiersinga et al. NEJM 2012; doi: 10.1056/NEJMra1204699

Diagnosis

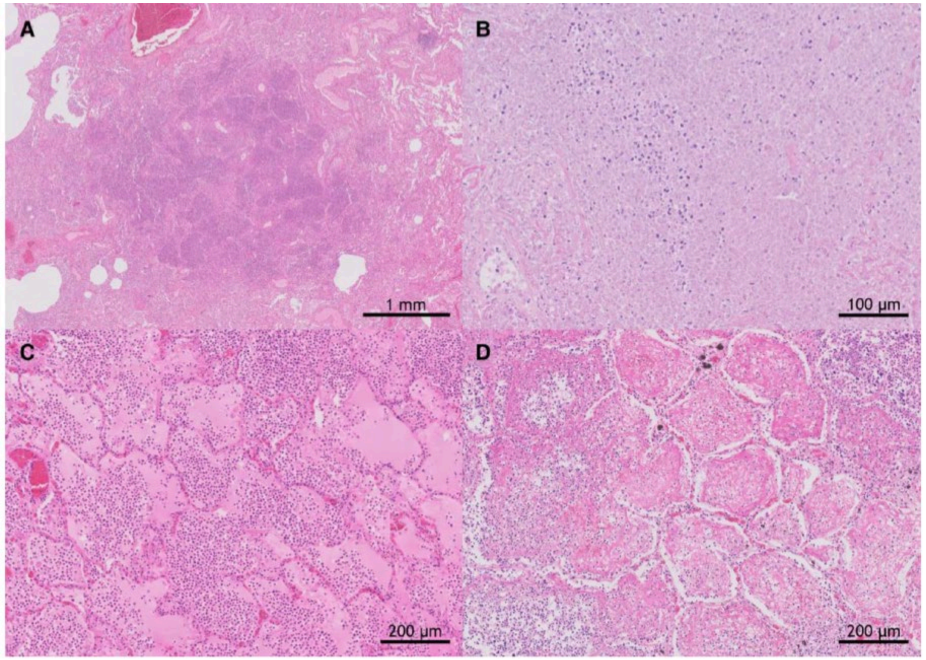
- **Culture from any site is definitive**
  - *B. pseudomallei* grows readily on routine media
  - problem is delay or mis-identification by the clinical laboratory

- PCR is definitive but less sensitive than culture

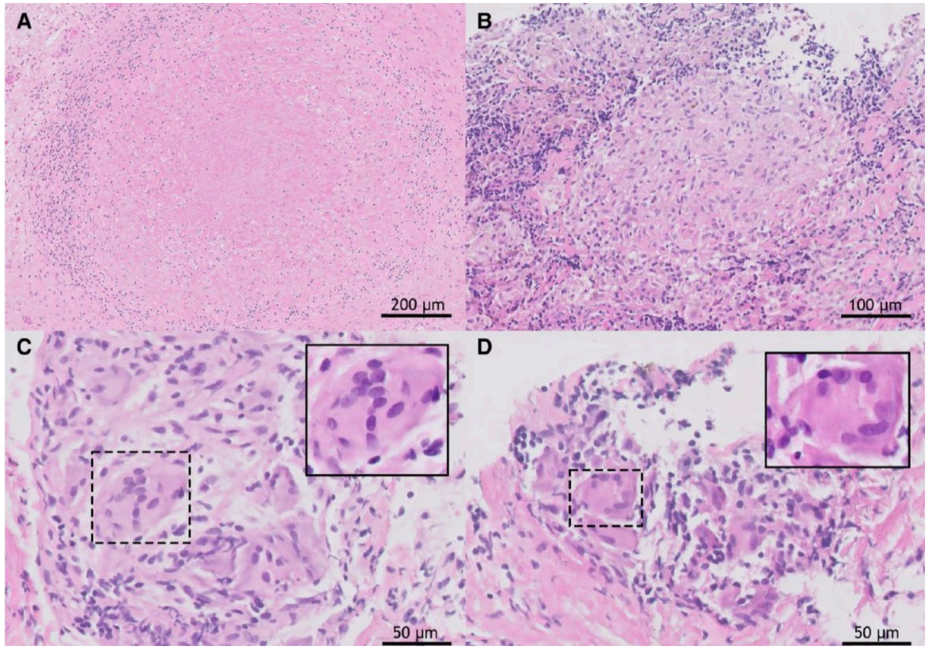
- Serologic testing is useful epidemiologically but not clinically
  - 50% positivity in endemic regions

Pathology

- Hallmark is necrotizing and suppurative inflammation
  - abscess formation
  - granulomatous inflammation
  - occasionally multinucleated giant cell formation
  - may resemble tuberculosis and other granulomatous infections



necrotizing and suppurative pneumonia



granulomatous inflammation

Savelkoel et al, Open Forum Infect Dis 2023; doi: 10.1093/ofid/ofad367

Antibiotic susceptibility

- *B. pseudomallei* is inherently resistant to
  - penicillin
  - ampicillin
  - 1st- and 2nd-generation cephalosporins
  - aminoglycosides (gentamicin, tobramycin, streptomycin)
  - polymyxin
  - fluoroquinolones
    - ciprofloxacin and moxafloxacin have weak activity

- Antibiotics with activity against *B. pseudomallei*
  - Extended-spectrum β-lactams
    - Amoxicillin-clavulanate
    - Antipseudomonal 3rd-generation cephalosporins (ceftazidime)
    - Carbapenems (but not ertapenem)
  - Trimethoprim-sulfamethoxazole (TMP-SMX)
    - resistance in up to 13% of strains, depending on geography
  - Doxycycline
    - not as effective for initial therapy as β-lactams
    - MIC 0.25-2 μg/mL
    - resistance noted in <1.0%

Wiersinga et al. NEJM 2012; 367:1035

Antibiotic susceptibility

Minimum inhibitory concentrations (MICs) and percent susceptibility (%S) of four antimicrobial agents against 234 *Burkholderia pseudomallei* isolates from the Northern Territory, Australia.

Antibiotic	% of isolates with a particular MIC (μg/mL)															MIC (μg/mL)		%S[a]
	0.064	0.125	0.19	0.25	0.38	0.5	0.75	1	1.5	2	3	4	6	8	>12	MIC_{50}	MIC_{90}	
Ceftazidime							2.1	19.7	60.7	13.7	3.8					1.5	2.0	100
Doxycycline						0.4	1.3	8.1	29.9	35.5	14.5	6.8	2.1	1.3		2.0	4.0	96.6
Meropenem						17.9	57.3	19.2	3.8	1.7						0.75	1.0	100
TMP/SMX	1.7	1.3	4.3	3.8	15.0	18.4	27.8	13.2	9.0	4.7	0.4	0.4				0.75	1.5	99.1

Crowe et al. Int J Antimicrob Agents 2014; 44:160

Treatment

- **Initial phase**

10-14 days

ceftazidime or a carbapenem

(meropenem or imipenem)

± TMP-SMX

- **Oral eradication phase**

3-6 months

TMP-SMX

Doxycycline

- **Drainage** of large abscesses

especially prostate

Meumann et al. Nat Rev 2024; 22:155

Antimicrobial Drug	Dose
Initial intensive therapy†	
Ceftazidime	50 mg/kg of body weight (up to 2 g), every 6–8 hr
Meropenem	25 mg/kg (up to 1 g), every 8 hr
Imipenem	25 mg/kg (up to 1 g), every 6 hr
Oral eradication therapy‡	
TMP-SMX	
Body weight	
>60 kg	2×160 mg of TMP–800 mg of SMX (960 mg), every 12 hr
40–60 kg	3×80 mg of TMP–400 mg of SMX (480 mg), every 12 hr
<40 kg, adult	1×160 mg of TMP–800 mg of SMX (960 mg) or 2×80 mg of TMP–400 mg of SMX (480 mg), every 12 hr
<40 kg, child	8 mg of TMP/kg–40 mg of SMX/kg, every 12 hr

Wiersinga et al. NEJM 2012; 367:1035

Conclusion

- *Burkholderia pseudomallei* is an environmental bacterium that can cause a variety of clinical infections, particularly in compromised hosts

- Solid organ transplants are at risk

- A travel history is critical to determining the risk for melioidosis

- *B. pseudomallei* grows on routine media and a positive culture is conclusive to establish a diagnosis

- Molecular analysis is useful for
  - confirming the diagnosis
  - establishing where the infection was acquired