

Cairns and Hinterland
Hospital and Health Service

Cases from Oceania

Annual ASTMH Clinical Update Course
27-28th September 2024

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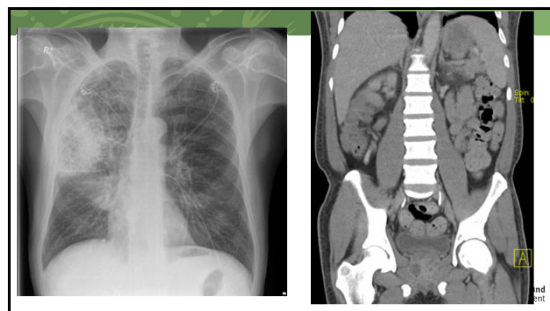
Oceania

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Case 1

- A 64-year-old man presents with 4 days of fever and breathlessness
- History of type II diabetes mellitus with suboptimal control
- Smokes 20/day and consumes 4 beers/night
- Returned from a 1-month trip to visit family in northern Australia 9 days ago

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Case 1

- Blood cultures isolate Gram-negative bacilli at 24 hours
- The organism is identified as *Burkholderia pseudomallei*

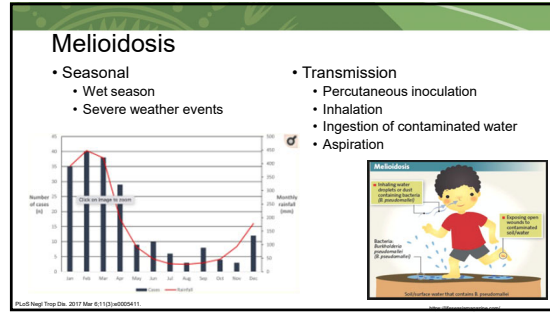
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Burkholderia pseudomallei – melioidosis

- Saprophytic Gram-negative bacterium
 - Present in soil and surface water
- Endemic to tropical regions
 - Northern Australia, South & Southeast Asia
 - Increasingly recognized outside these areas

Murray EM, Linnemann A, D. Daniels SJ, Whittam TS, Currie BJ. *Burkholderia pseudomallei*. *Microbiol Spectr*. 2018;6(2):00000-00000. doi:10.1128/spectr.00000-00000

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Melioidosis – opportunistic

- Related to issues with innate immunity
- Impaired neutrophil function

| Clinical risk factors | Patients, n (%) | Died from melioidosis, n (%) | RR (95% CI) | p value** |
|--|-----------------|------------------------------|------------------|-----------|
| Diabetes | 532 (45%) | 62 (22%) | 3.1 (0.78-1.5) | 0.72 |
| Hazardous alcohol use | 455 (40%) | 56 (22%) | 3.1 (0.80-1.5) | 0.72 |
| Chronic lung disease | 332 (27%) | 45 (14%) | 1.4 (0.98-1.9) | 0.13 |
| Chronic renal disease | 340 (27%) | 24 (7%) | 1.6 (1.06-2.4) | 0.10 |
| Malnutrition | 313 (26%) | 30 (10%) | 1.7 (1.07-2.6) | 0.10 |
| Immunosuppressive therapy and other immunosuppression† | 106 (9%) | 18 (27%) | 3.5 (0.98-2.4) | 0.13 |
| Rheumatic heart disease or congenital cardiac defect | 102 (9%) | 19 (29%) | 3.7 (1.10-2.7) | 0.10 |
| Kava use | 39 (3%) | 5 (13%) | 3.1 (0.48-2.6) | 0.80 |
| Other | 39 (3%) | 7 (18%) | 3.6 (0.79-3.2) | 0.29 |
| No clinical risk factors | 186 (16%) | 3 (2%) | 0.12 (0.04-0.37) | <0.0001 |

*p values were adjusted for multiple testing using the method of false discovery rate. †Clinical risk-factor parameters as defined in the appendix (p 5) and in previous publications.***Includes the only four patients with HIV infection (<1%), a prevalence similar to that seen at Royal Darwin Hospital for sepsis in general.

Table 1: Epidemiology, clinical risk factors, and outcomes for 1148 patients with melioidosis

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- ### Melioidosis – clinical presentation
- Incubation period 1-21 days
 - Most infections are asymptomatic
 - Acute
 - Symptoms <2 months
 - ~85-90% of cases
 - Chronic
 - Symptoms >2 months
 - ~10% of cases
 - Latent with reactivation
 - Long after exposure
 - Rare; <5% of cases

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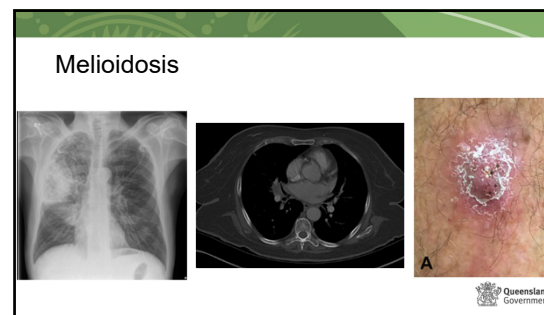
Melioidosis – clinical presentation

| | Total | Bacteraemia | Septic shock | Died from melioidosis |
|-----------------------------------|-----------|-------------|--------------|-----------------------|
| Pneumonia | 595 (52%) | 365 (62%) | 179 (30%) | 93 (16%) |
| Skin infection | 149 (13%) | 5 (3%) | 2 (1%) | 0 |
| Gastrointestinal infection | 140 (12%) | 79 (56%) | 16 (11%) | 9 (6%) |
| Bacteraemia with no evident focus | 130 (11%) | 129 (99%) | 26 (20%) | 20 (15%) |
| Soft tissue abscess | 46 (4%) | 9 (20%) | 3 (6%) | 1 (2%) |
| Septic arthritis | 29 (3%) | 21 (72%) | 7 (24%) | 4 (14%) |
| Neurological disease† | 19 (2%) | 4 (21%) | 0 | 4 (21%) |
| Osteomyelitis | 15 (1%) | 9 (60%) | 2 (13%) | 1 (7%) |
| Other | 25 (2%) | 12 (48%) | 5 (20%) | 3 (14%) |
| Total | 1148 | 633 (55%) | 240 (21%) | 133 (12%) |

Data are n (%). †33 blood cultures were not done, eight in patients presenting with pneumonia, four in those presenting with gastrointestinal infections, and one presenting with skin infection; eight of these patients were dead before arrival at hospital, six with pneumonia and two with gastrointestinal melioidosis. 106 patients assigned to this group did not have confirmed bacteraemia. 112 patients presented with meningitis/encephalitis, often with cranial nerve palsies, four with cerebral abscesses, two with myelitis, one with meningitis, and one with an epidural abscess.

Table 2: Clinical presentations and outcomes for 1148 patients with melioidosis

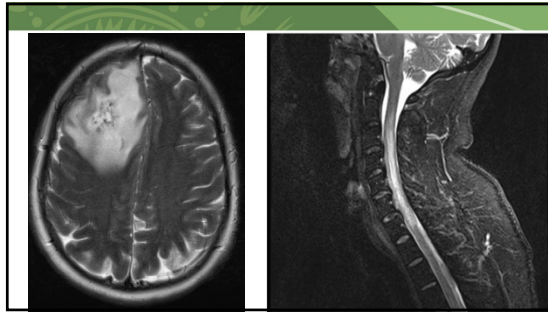
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Melioidosis – diagnosis


- Culture is mainstay of diagnosis
- Appropriate samples
 - Blood, sputum, urine, swab of skin lesion, abscess fluid
- Selective media: Ashdown's agar
- Serology
 - Not sensitive or specific enough for diagnosis
 - Background rates of seropositivity in people living in endemic areas
- PCR/Antigen detection not yet readily available

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Melioidosis – treatment

- Intensive phase – IV component
 - Meropenem or ceftazidime
 - Meropenem used in ICU and in CNS disease
- Intensive phase – oral component
 - Adjunctive TMP/SMX added to those with any abscess/collection
 - Unclear benefit; used for tissue penetration and intracellular activity
- Eradication phase
 - Oral TMP/SMX (preferred agent)
 - Doxycycline
 - Amoxicillin/clavulanate (pregnancy)
 - Folic acid with TMP/SMX




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Melioidosis – treatment

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



Bullman RP et al. Review and revision of the 2015 Darwin melioidosis treatment guideline: paradigm shift not shift. *PLoS Negl Trop Dis*. 2020



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Melioidosis – prevention


- Gloves and enclosed shoes when coming in contact with soil
- Remain indoors during wet and windy weather
- Wear mask when using pressure hose outside
- Limit alcohol consumption
- Serology prior to starting immunosuppressive treatment
- TMP-SMX prophylaxis
 - In high-risk patients

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Case 2


- A 72-year-old lady presents with breathlessness, weight loss and night sweats for 8 weeks
- Recalls good health
- Hospitalised for 10 days ~2 years ago with unexplained fevers after returning from a wildlife photography trip to northern Australia
- Examination – dual heart sounds and an ejection systolic murmur. Crackles at both lung bases.
- Blood cultures x3 are negative
- Echocardiogram – mixed aortic valve disease with both severe stenosis and moderate regurgitation. Possible small vegetation.



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Case 2





- Undergoes an aortic valve replacement
- Histology of resected valve – significant fibrosis, calcifications, mild inflammation and vascularization, and small vegetations
- Coxiella burnetii* PCR on the valve tissue is positive



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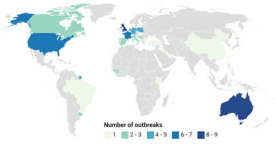
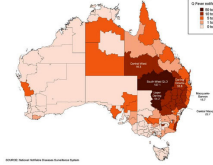
Q fever

- Caused by *Coxiella burnetii*
 - Facultative intracellular bacterium (grows/replicates inside host cell)
- Zoonotic infection
 - Main reservoirs: cattle, sheep, goats
 - Kangaroos, bandicoots, domestic animals, ticks, reptiles
- Humans infected by contact with infected animals/animal products
 - Birth products (highest concentration of bacteria)
 - Urine
 - Faeces
 - Milk
- Hardy bacteria – persists in dust and soil
- Transmission via inhalation of aerosolized bacteria in environment
 - Farmers, abattoir workers, zoo/animal refuge, veterinarians, living near/visiting a farm

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Q fever

Number of outbreaks

| | | | | |
|---|-----|-----|-----|-----|
| 1 | 2-3 | 4-5 | 6-7 | 8-9 |
|---|-----|-----|-----|-----|

Choropleth map of Q fever outbreaks reported globally that were included in a systematic review of global Q fever outbreaks.





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Q fever – clinical presentation

Most infections are subclinical or self-limiting

Acute

- Incubation period of 15-25 days
- Abrupt onset "influenza-like illness"
 - Fever, severe headache, rigors, myalgias, fatigue, gastrointestinal disturbance
- Pneumonitis
 - Non-productive cough
 - Can be rapidly progressive
- Hepatitis
 - Jaundice, hepatosplenomegaly
- Cardiac manifestations
 - Acute endocarditis, pericarditis/myocarditis
- Autoimmune complications
 - Antiphospholipid antibodies
- Rash (maculopapular or purpuric)
- Aseptic meningitis/encephalitis
- Pregnancy complications
 - Abortion, premature delivery, low infant birth weight

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Q fever – clinical presentation

Acute

- Severe disease up to 10%
- Illness lasts 2-6 weeks
- Post infectious syndrome
 - Headache, myalgias, fatigue, night sweats, mood changes, loss of libido 6-12 months
- Most patients asymptomatic by 1 year

Q fever fatigue syndrome (QFS)

- Symptoms >1 year post acute infection
- Headache, myalgias, fatigue, night sweats, mood changes, alcohol intolerance
- No overt organ involvement; no viable organisms
- Medium levels of antibody usually present

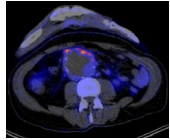



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Q fever – clinical presentation

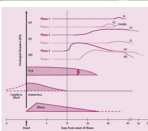
Persistent localised / chronic

- Occurs in ~5% of acute cases
- Infective endocarditis
 - Culture-negative
- Mycotic aneurysms
- Infection of vascular prosthesis
- Osteomyelitis
- Granulomatous hepatitis

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Q fever – diagnosis



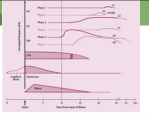
Acute

- Routine bloods
 - Leukocytosis
 - Thrombocytopenia
 - Elevated liver enzymes 2-3 x upper limit (most patients)
- Serology
 - Coxiella exhibits antigenic Phase variation in cell wall antigens (Phase I&II)
 - EIA, immunofluorescence (IF), complement fixation (CF)
 - IgM antibody to phase II antigen
 - IgG seroconversion or 24-fold increase in phase II antigen by CF or IFA (paired sera)
- PCR (blood)
 - Within first 10 days

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Q fever – diagnosis



Follow up

- Serology at 3, 6 and 12 months
- Baseline echocardiogram

Chronic

- Serology
 - Persistently high levels of phase I antibodies after treatment for acute Q fever
 - Anti-phase I IgG (e.g. >800 by IFA)
- PCR
 - Blood, tissue, fluid
- Look for end-organ disease
 - Echocardiogram, CT/PET scan

Table 17. Idealised serological patterns at various stages of Q fever infection*

| Group | Phase | Antibody titre | | | | |
|---------|-------|----------------|-----|-----------------|-----------------|-----------------|
| | | CF | IF | IF ₁ | IF ₂ | IF ₃ |
| Acute | 0-10 | 100 | 100 | 100 | 100 | 100 |
| | 10-20 | 100 | 100 | 100 | 100 | 100 |
| | 20-30 | 100 | 100 | 100 | 100 | 100 |
| Chronic | 0-10 | 100 | 100 | 100 | 100 | 100 |
| | 10-20 | 100 | 100 | 100 | 100 | 100 |
| | 20-30 | 100 | 100 | 100 | 100 | 100 |

*A guide to Q fever and Q fever vaccination. CDS, Brisbane

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Q fever – management and monitoring

- Acute Q fever
 - Doxycycline 2 weeks
 - Alternative macrolide or fluoroquinolone
 - Pregnancy – Trimethoprim-sulfamethoxazole
- Chronic Q fever
 - If organ involvement
 - Doxycycline plus hydroxychloroquine 18-24 months
 - Alternative doxycycline plus fluoroquinolone

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Q fever – prevention




- Vaccination
 - Purified killed suspension of *C. burnetii*
 - Used in abattoir workers since early 1990s
- Recommended age ≥15 years high risk
 - Abattoir workers, farmers, vets, wildlife workers, zoo keepers, laboratory staff
- Pre-vaccine testing
 - Serology and skin testing
 - Vaccine contraindicated if positive, previous Q fever infection or vaccine
- Vaccine efficacy 83-100%

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Case 3

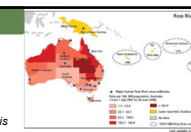
- A 24-year-old man presents with 4 days of fever, swollen and painful hands and feet and a rash
- Otherwise well, just returned from a 6-month backpacking trip throughout Australia
- He is pyrexial (39°C / 102.2°F), has a symmetrical arthritis affecting the fingers, wrists and toes and a widespread maculopapular rash
- Routine blood tests are normal
- Ross River Virus IgM is positive




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Department of Health

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Ross River Virus



- Arbovirus
 - Over 40 mosquito as possible vectors
 - Aedes vigilax*, *Aedes camptorhynchus*, *Culex annulirostris*
- Alphavirus
 - Chikungunya, Barmah Forest, Sindbis, O'nyong-nyong (Fever, arthralgia, rash)
 - Equine encephalitis viruses
- Reservoir hosts
 - Marsupials (kangaroos, wallabies)
 - Possums, horses, cows, pigs, dogs
 - Possibly birds and flying foxes
- "Epidemic polyarthritis"
 - Coastal areas with salt marshes
 - Seasonal
 - Outbreaks with higher rainfalls, high tides, flooding
 - Can persist in mosquito eggs in arid areas





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Ross River Virus


- Subclinical infection ~30%
- Usually younger adults
- Incubation period 7–9 days (range 3–21 days)
- Acute symptoms
 - Joint pain >95%; +/- joint swelling
 - Symmetrical, affecting fingers, wrists, elbows, toes, ankles and knees
 - Tiredness >90%
 - Fever, myalgias, headache
 - Rash ~50%
 - Before or after joint symptoms
 - Maculopapular on limbs and trunk, palms and soles
 - Rarely splenomegaly, haematuria, glomerulonephritis, meningitis and encephalitis

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Ross River Virus



- Rash usually resolves within 1 week
- Chronic symptoms
 - Arthralgias
 - Usually resolve within 1-3 months
 - Fatigue
- Chronic symptoms may be underlying rheumatological condition or mood disorder



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Ross River Virus – diagnosis


- Routine blood tests
 - Atypical lymphocytes
 - Often normal
- Serology
 - IgM (ELISA, HI)
 - Present ~day 7
 - May persist for months/years
 - IgG seroconversion or increase in IgG antibody level (fourfold rise in titre)
 - IgM and IgG in same specimen (unless known IgG positive previously)
 - IgM prone to false positives
- PCR (blood)
 - Limited by short duration of viraemia
- Viral culture (uncommon)

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Ross River Virus – treatment



- Supportive care
 - Acetaminophen (paracetamol)
 - NSAIDs
- Physiotherapy, exercise for chronic symptoms



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Ross River Virus – prevention

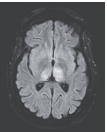

- Avoidance of mosquito bites
 - Repellants
 - Window screens
 - Drainage of mosquito breeding areas
- No vaccine available (experimental only)

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Case 4

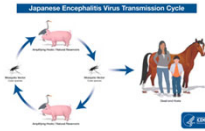
- A 42-year-old man just arrived from a fishing trip to Australia presents with a 3-day history of acute confusion and fever
- He becomes increasingly drowsy and requires intubation
- CSF – 250 WBC/mm³ (lymphocyte predominance)
- Mildly elevated protein; normal glucose
- An MRI scan shows T2 hyperintensity in both thalami
- Japanese encephalitis virus (JEV) IgM and PCR is negative on CSF
- Repeat CSF 12 days later – JEV IgM is positive

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Japanese encephalitis virus

- Mosquito-borne
 - Isolated >30 species; *Culex* sp.
- Flavivirus
 - West Nile, St. Louis encephalitis, Murray Valley encephalitis
- Enzootic cycle
 - Pigs (high viraemia), wading birds
- Transmission
 - Seasonal (temperate regions)
 - Year-round (tropical regions)
 - Outbreaks



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JEV – Australia



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Japanese encephalitis virus – clinical presentation

- Incubation period 5-15 days
- Most cases are asymptomatic
- Non-specific illness
 - Fever, headache, abdominal pain, gastrointestinal disturbance
- Neurological disease (1% cases)
 - Confusion
 - Cranial nerve palsies, hemiplegia
 - Abnormal movements
 - Seizures
 - Extrapyrmidal symptoms
 - Coma

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Japanese encephalitis virus – diagnosis

Routine bloods

- Leukocytosis; thrombocytopenia
- Hyponatraemia
- Elevated liver enzymes

CSF

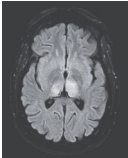
- Pleocytosis (usually 10-500 WBC/mm³)
- Lymphocyte predominance
- Mildly elevated protein; normal glucose

EEG

- Diffuse slow waves
- Epileptiform discharges (seizure activity)

MRI brain

- Abnormal signal intensity in thalamus, basal ganglia midbrain, pons, cerebellum



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Japanese encephalitis virus – diagnosis

- Serology
 - IgM, IgG
 - Serum (can take up to 10 days to be positive)
 - CSF (can be earlier than serum)
- PCR
 - Blood/CSF
 - Can be insensitive

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Japanese encephalitis virus – treatment

- Supportive care
 - Intracranial pressure
 - Seizure control
- Outcome
 - Mortality ~25%
 - Persisting neurological deficits in 50%



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Japanese encephalitis virus – prevention

- Avoidance of mosquito bites
 - Repellants, window screens, permethrin in clothing
- Serosurveillance (piggeries, chickens, mosquito trapping)
- Several human vaccines available
 - Inactivated Vero cell-derived vaccine
 - Live-attenuated chimeric vaccine
- Vaccination
 - Moving to a JE-endemic country
 - Travel > 1 month to JE-endemic areas
 - Regular travel to JE-endemic area
 - Laboratory workers
 - Increased risk of JE



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