Tropical ID Clinical Cases

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Outline

- Overview imported infectious causes neurological disease
- Confused febrile Nigerian traveler
- Honduran man with a generalized seizure
- One in a million trip to Thailand
- Somnolent Zambian hunter

Potential Etiological Categories

- Bacterial and TB (meningitis, brain abscess)
- Parasites
- Viruses
- Spirochetes (neurosyphilis, leptospirosis, tick-borne relapsing fever)
- Rickettsiae (scrub typhus, louse-borne typhus, RMSF)
- Endemic mycoses

Parasitic Brain Diseases (a partial list)

- Cerebral malaria
- African trypanosomiasis
- Toxoplasmosis
- Paragonimiasis
- Schistosomiasis
- Neurocysticercosis
- Hydatidosis
- Angiostrongylus cantonensis

Viral Encephalitis (a partial list)

- Flaviviridae
  - West Nile virus
  - Tick-borne encephalitis virus
  - Japanese encephalitis
  - Zika
- Bunyaviridae
  - Eastern and Western equine encephalitis
  - Venezuela equine encephalitis
  - Lacrosse encephalitis

Febrile Nigerian Man

- 42 year old Nigerian man who traveled to Nigeria to visit friends and relatives for 3 weeks in 9/02
- No pre-travel immunizations, education, or prescriptions
- Recalled having numerous mosquito bites
- 9/25/02: Drank some water provided to him by his mother that tasted foul

History (cont.)

- 9/26: Developed malaise, chills, and fatigue
  - Visited a local hospital where he was diagnosed with malaria and treated with chloroquine
- 9/28: Returned to the US
- 10/13: Presented to the ED with fever, chills, frontal headache, and fatigue

Past Medical and Social History

- Malaria
- Typhoid fever (?)
- Hepatitis-type unclear
- Negative HIV test 1999
- S/P appendectomy, hernia repair
- Medications: prn Tylenol, Advil
- No known drug allergies
- Has lived in the US for 8 years; works as a taxi driver. No h/o substance or alcohol abuse

Physical Examination: Notable Findings

- T - 39.3°C; pulse - 130; BP - 99/76 RR - 16
- Diaphoretic African man who appeared acutely ill and fatigued
- No focal findings but slightly confused
- Icteric sclerae; pale conjunctivae
- Liver span 10 cm mid-clavicular line with smooth, non-tender edge palpable
- No splenomegaly

Initial Laboratory Results

- WBC - 5900 with differential of 51% PMN, 14% bands, 27% lymph, 2% monocytes
- Hematocrit - 26.2%; hemoglobin 9.1
- Platelet count - 50,000
- Serum creatinine - 1.8
- AST - 158; ALT 69
- Total bilirubin - 6.8
- Urinanalysis - 3+ bilirubin, 1+ protein

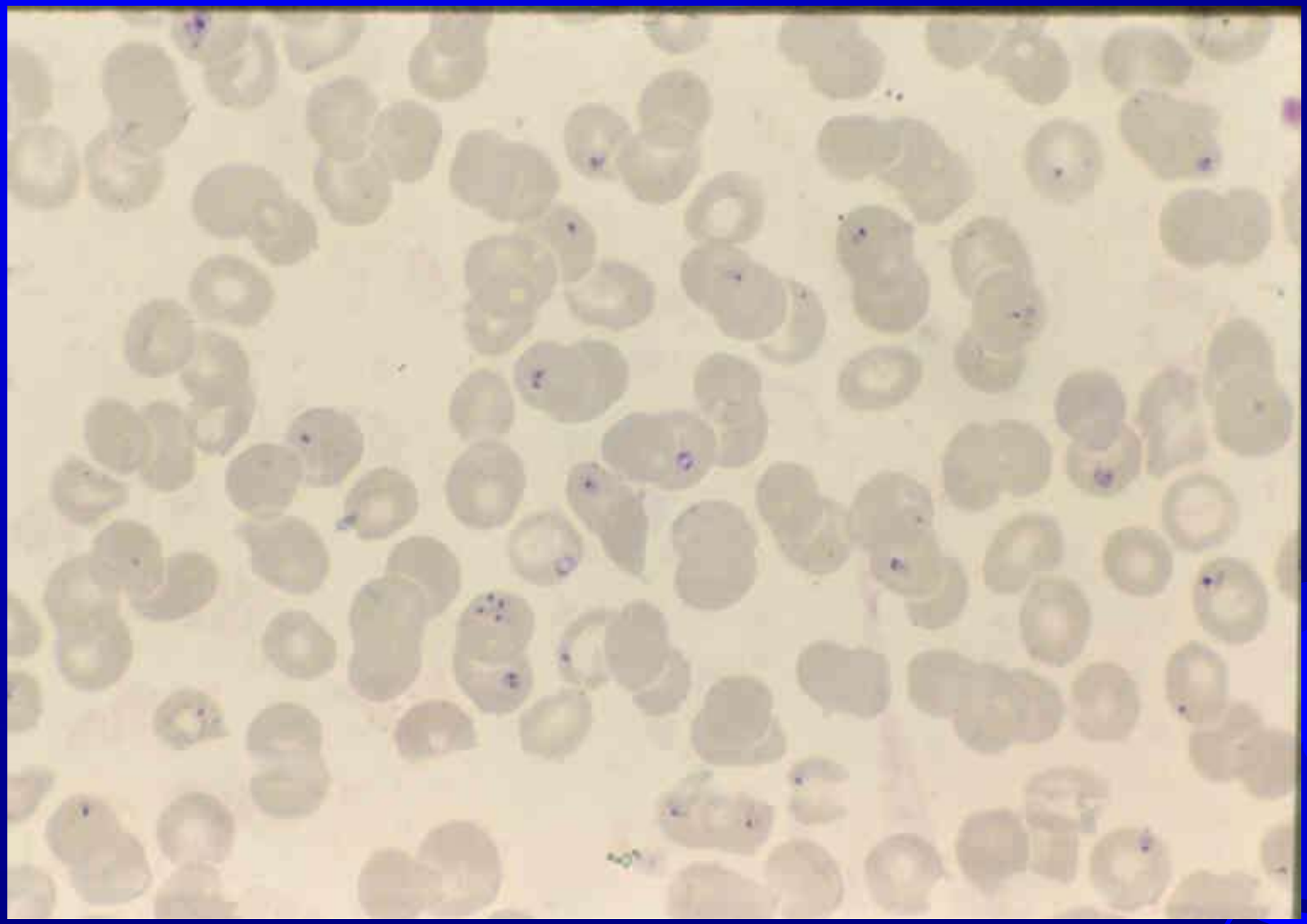
Diagnosis?

1. Typhoid fever
2. Malaria
3. Ebola fever
4. Lassa fever
5. Leptospirosis
6. Rickettsial infection
7. Yellow fever

What Would You Do Next?

1. Isolate the patient
2. Thick and thin blood smears
3. Blood cultures
4. Call Dr. Hochberg
5. Empiric treatment with broad spectrum antibiotics
6. All of the above

Blood Smear Results



Initial Treatment

- IV quinidine (with cardiac monitoring) plus doxycyline
- IV fluids

- But after 48 hours, fever persisted

Thoughts on what to do next?

1. Call ID
2. Repeat blood smear
3. Contact CDC to obtain IV artesunate
4. Blood cultures
5. Initiate broad spectrum antibiotics

Lab Report

Positive blood culture:
Salmonella enterica serovar Typhimurium

Findings Suggestive of Severe (Complicated) Malaria

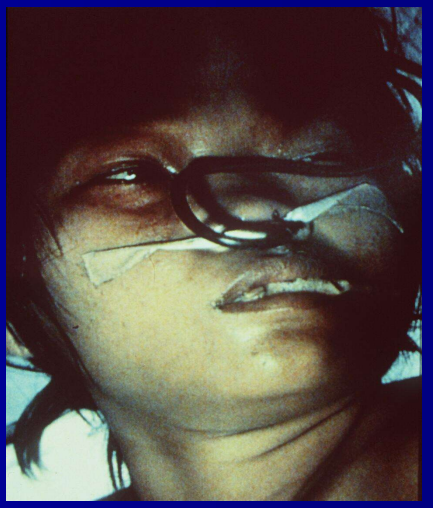
Clinical features

- Poor cognition--coma
- Retinal hemorrhages
- Repeated seizures
- Respiratory distress
- Shock
- Jaundice
- Inability to take oral meds

Lab features

- High parasite load (10% or greater)
- Severe anemia (Hb < 7 g/dL)
- Acute renal failure
- Acidosis
- Hypoglycemia
- Elevated bilirubin
- DIC

Clinical Manifestations Cerebral Malaria



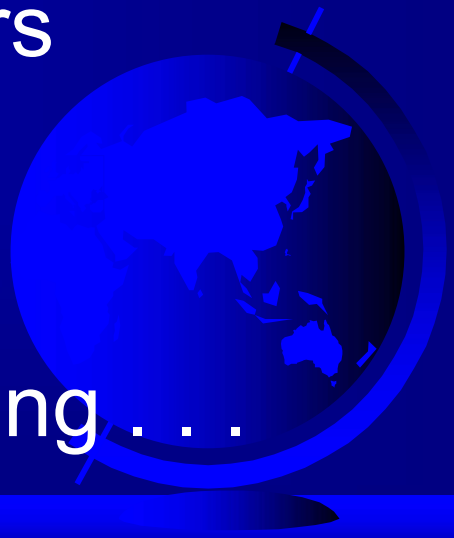
- Impaired consciousness including unrousable coma
- Prostration (generalized weakness such that patient cannot sit, stand or walk unassisted
- Deep breathing and respiratory distress
- May also have confusion, delirium, and focal neurologic deficits
  - WHO. Management of severe malaria 2013.

Discussion

- Quinidine treatment of choice in the US but requires ICU monitoring (QT interval)
- Ideally use IV artesunate, if available
- Intensive care supportive Rx
- Need to always consider current bacteremia
  - AQUAMAT trial found about 10% children were bacteremic (Lancet 2010)

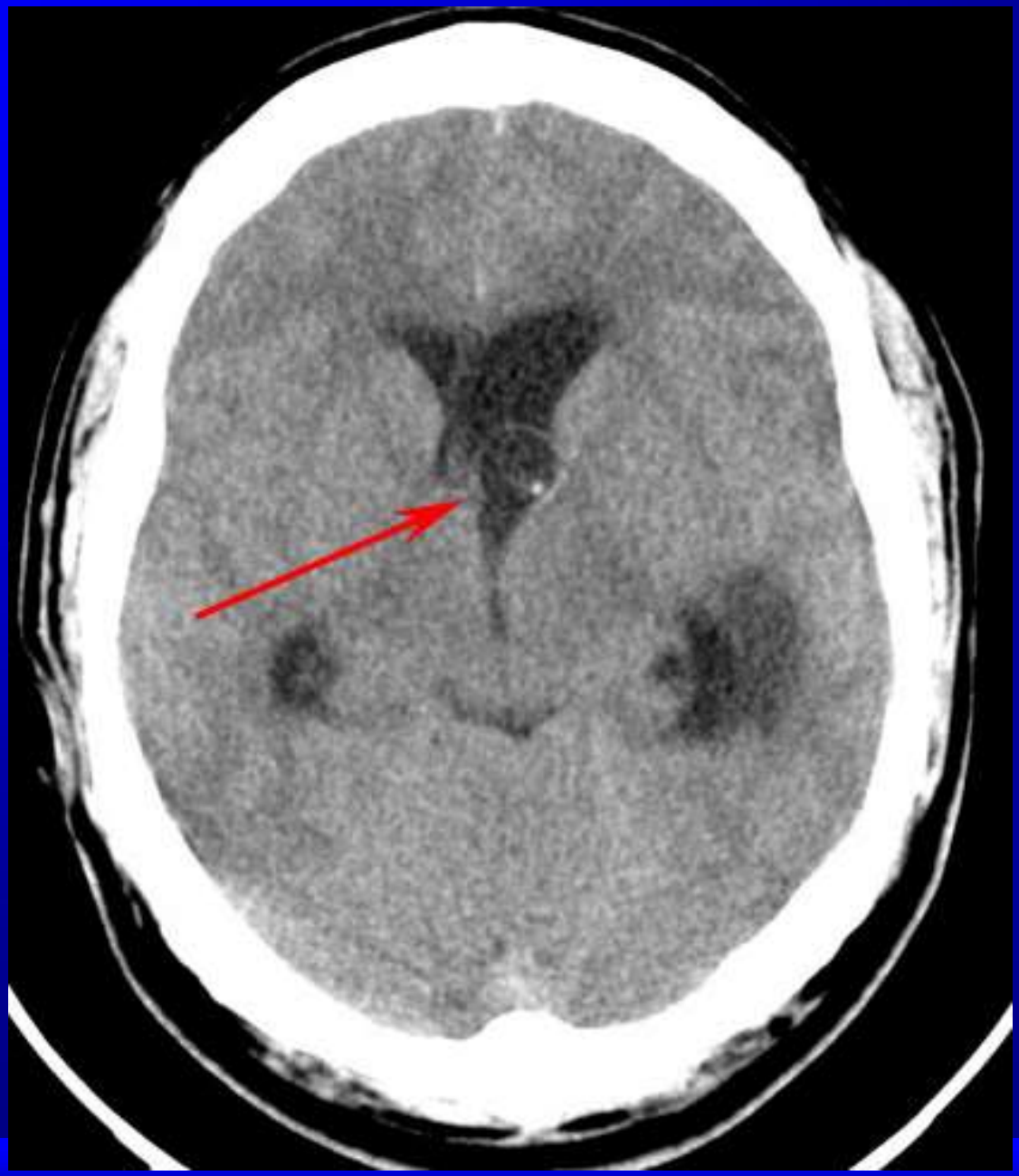
36 year old Honduran man with a grand-mal seizure

- Emigrated to US in 1986
- No prior neurological disease or head trauma
- No substance abuse history
- No prior history of headaches, fevers
- Strict vegetarian for past 30 years
- Lab work up essentially normal
- CT scan of brain showed the following . . .



What's the diagnosis?

That's not supposed to be there!



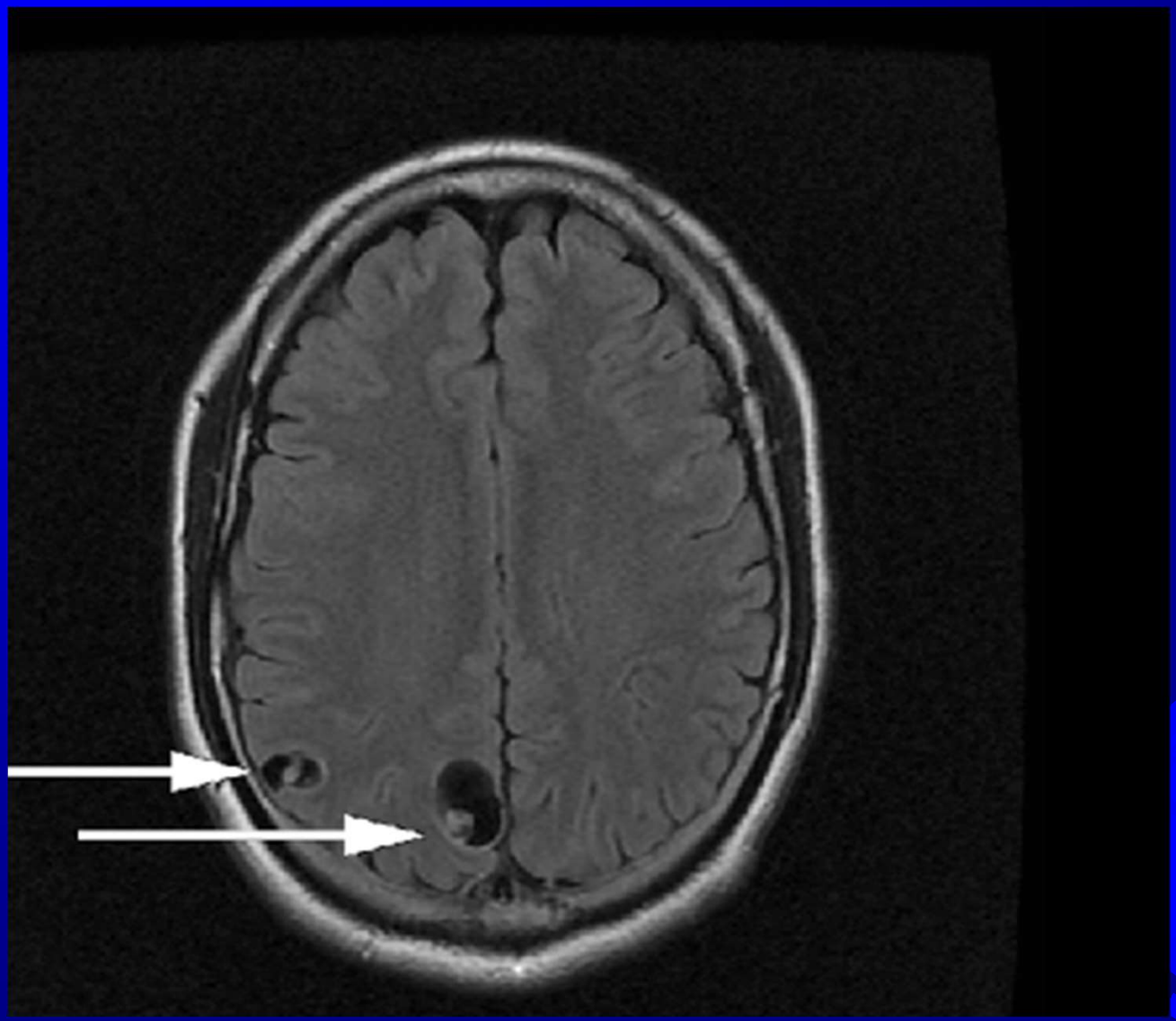
Epidemiology

- Larval stage of *Taenia solium* tapeworm
- Endemic to Central and South America, sub-Saharan Africa, Asia
- Transmitted by ingestion of eggs, which hatch in the small intestines and disseminate hematogenously
- Clusters in households

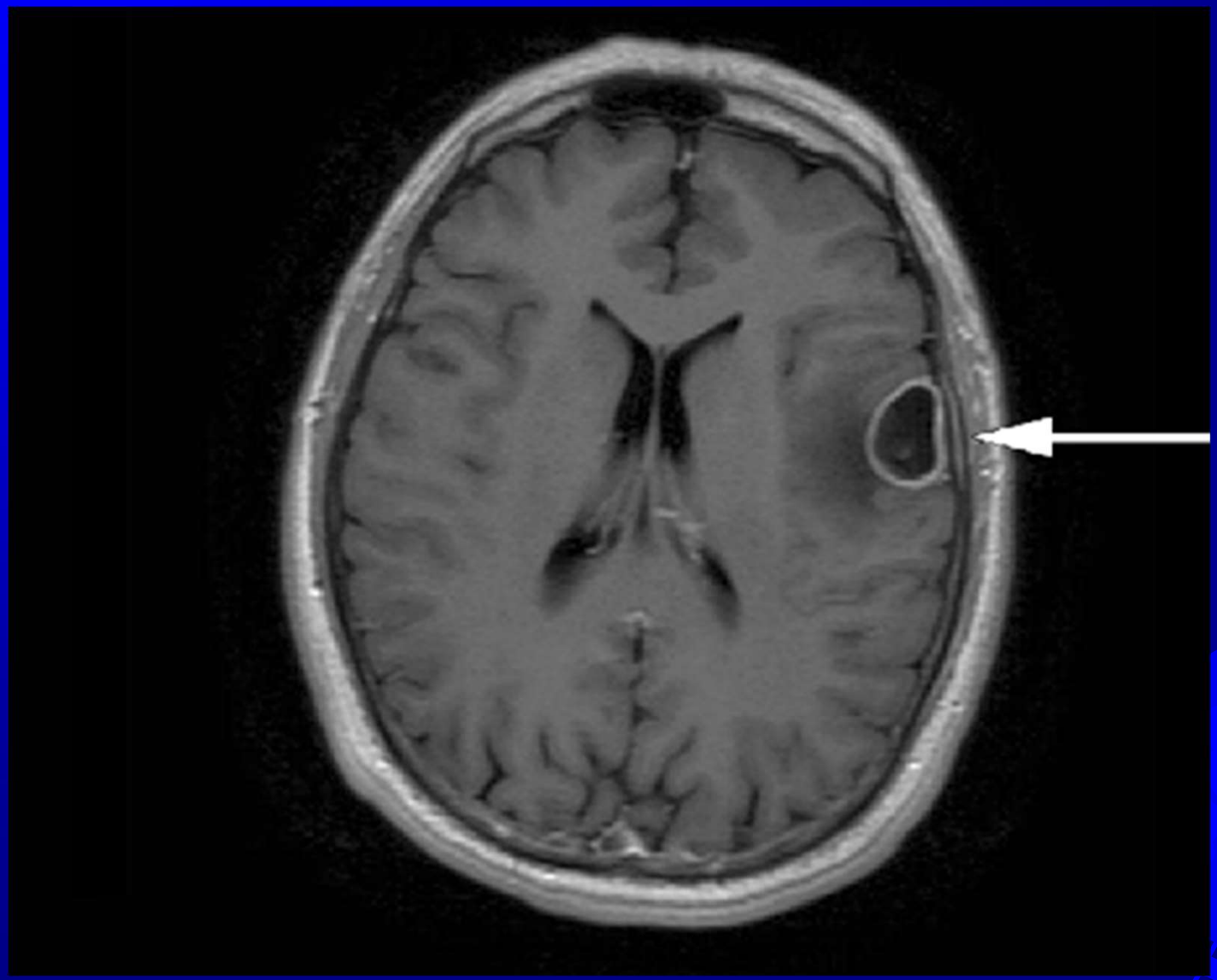
Stages

- Initial “viable” stage: do not cause inflammation; can persist for years
- Degenerating phase: lose the ability to evade host immune response
- Nonviable phase: calcified granulomas
- Can exist simultaneously at different sites

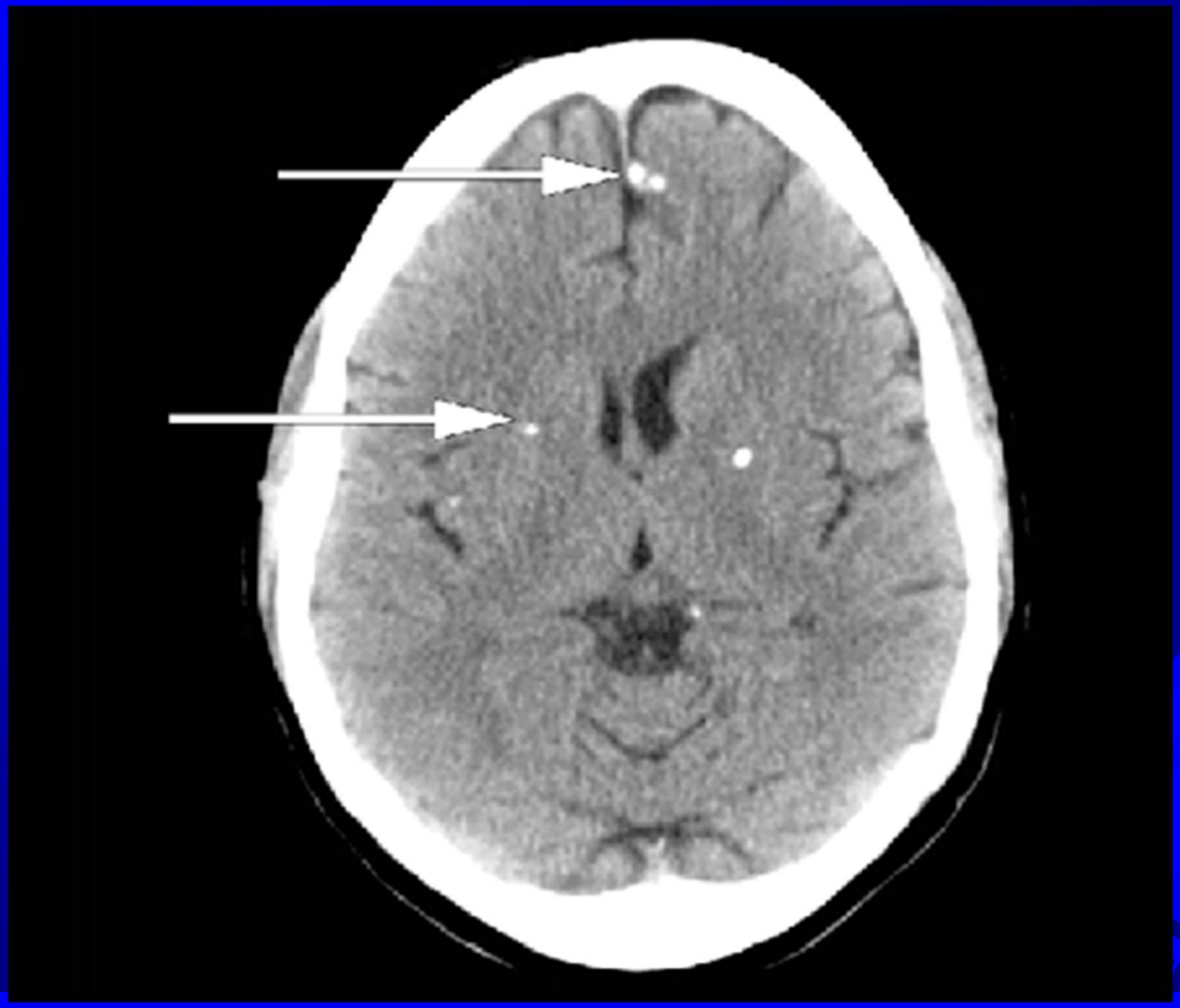
Viable Cysts



Degenerating Cyst



Nonviable Cysts



Localization

- Neurocysticercosis
  - Parenchymal
  - Extraparenchymal
    - Intraventricular, subarachnoid, spinal, ocular
- Extraneural cysticercosis
  - Muscle, subcutaneous
  - Cardiac cysticercosis

Management

- Prior to therapy
  - Eye exam
  - Screening for tuberculosis, strongyloidiasis
- ICP management
  - Edema: dexamethasone 0.2-0.4 mg/kg/day
  - Hydrocephalus: Surgical removal of obstructing cysts or placement of EVD or VP shunt
  - Antiparasitic therapy is CONTRAINDICATED

Antiparasitic Therapy

- Carries a risk of inflammation around degenerating cysts
- Do NOT treat if: elevated ICP/hydro, high cyst burden, only calcified lesions
- Burden of disease
  - 1-2 cysts: albendazole, 15 mg/kg in BID dosing up to 1200 mg/day
  - >2 cysts: albendazole + praziquantel 50 mg/kg in TID dosing

Duration of Therapy

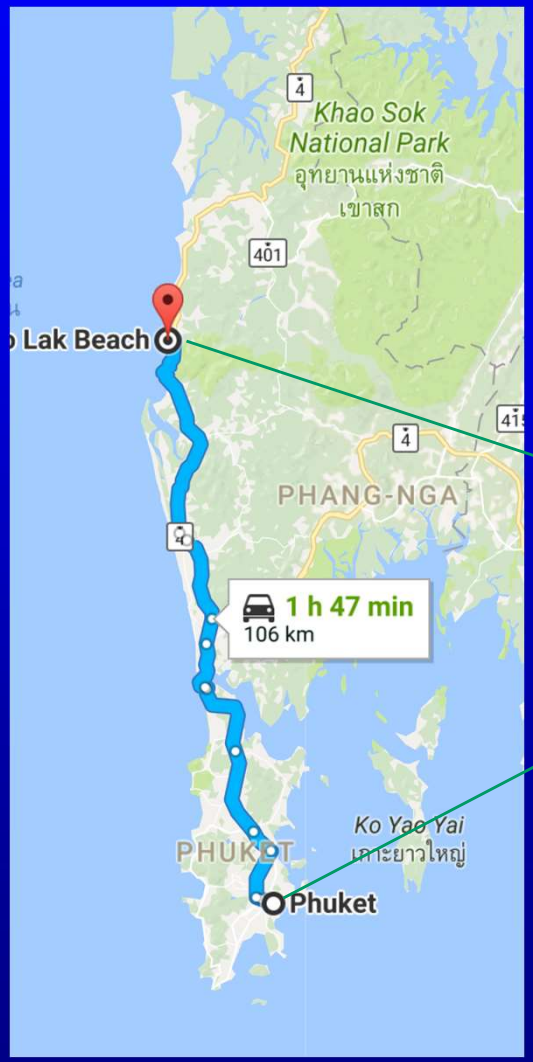
- 10-14 days in most cases
- Subarachnoid less responsive to therapy
  - Treat until radiographic resolution of cysticerci, may require >1 year of treatment
  - Imaging Q6 months
  - Monitor for hepatotoxicity and leukopenia on prolonged albendazole
  - Treat with prednisone 60 mg or dexamethasone 12-24 mg a few days before starting antiparasitics
  - Case reports using methotrexate, TNF-alpha inhibitors instead

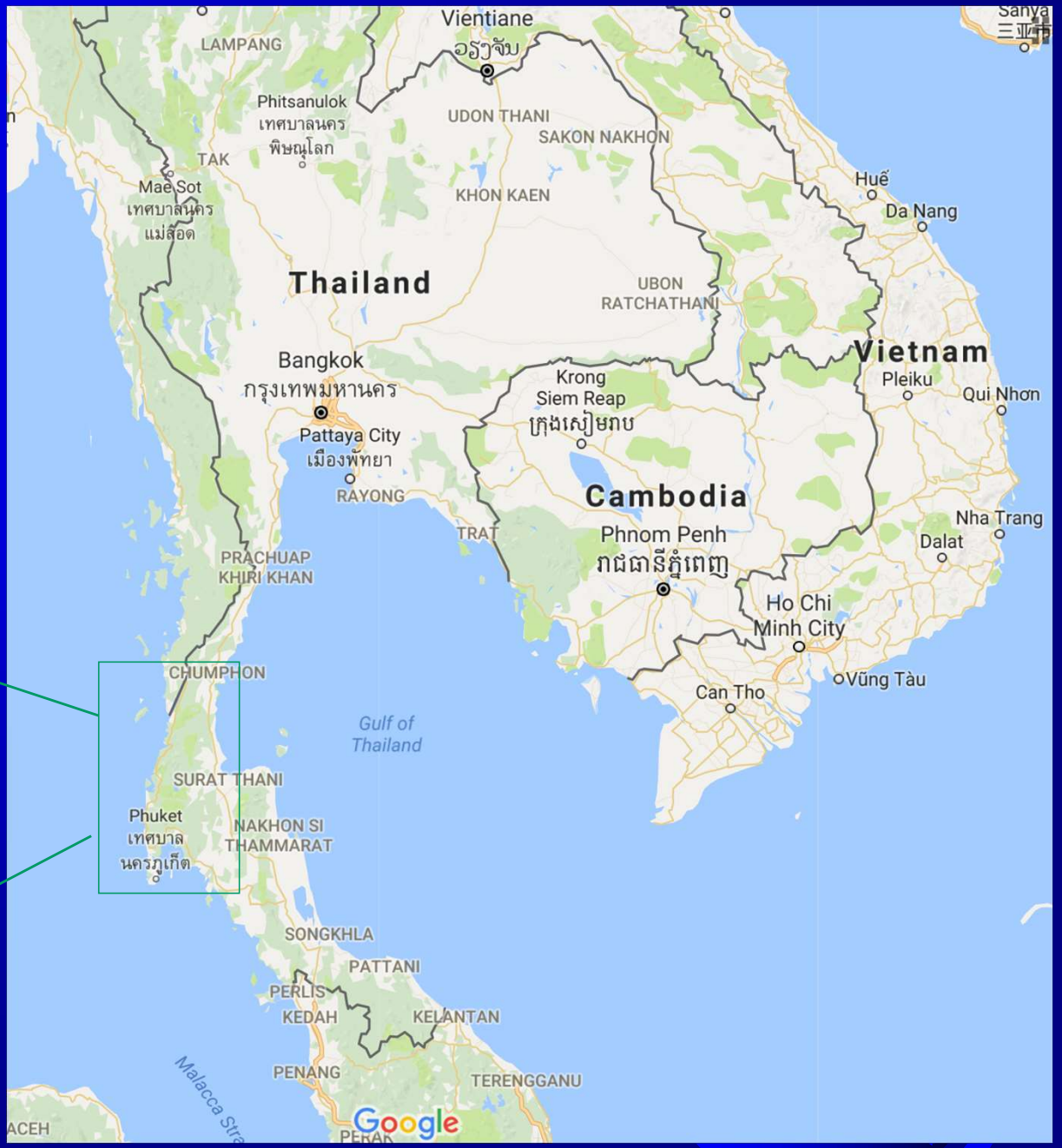

One in a Million

Travel and Past Medical History

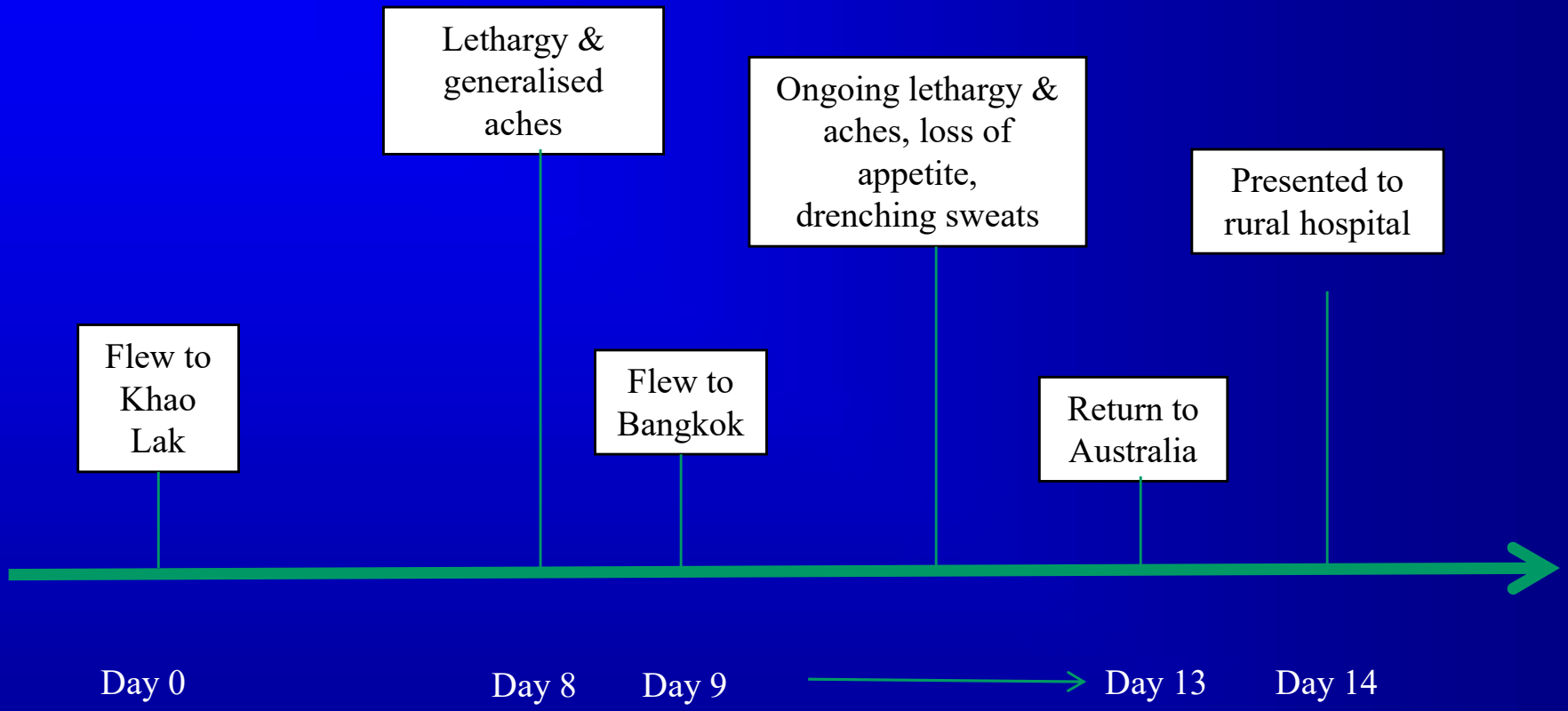
- 69 M, retired farmer from rural Victoria, Australia
- Previously well
  - Hypertension and prostatectomy
- No pre-travel vaccines
- 12 day trip to Thailand with wife and 4 friends early May 2017
  - Phuket then Khao Lak
  - No rural areas
  - Heavy rain, numerous mosquito bites

Travel Route in Thailand





Symptom Progression and Travel Itinerary



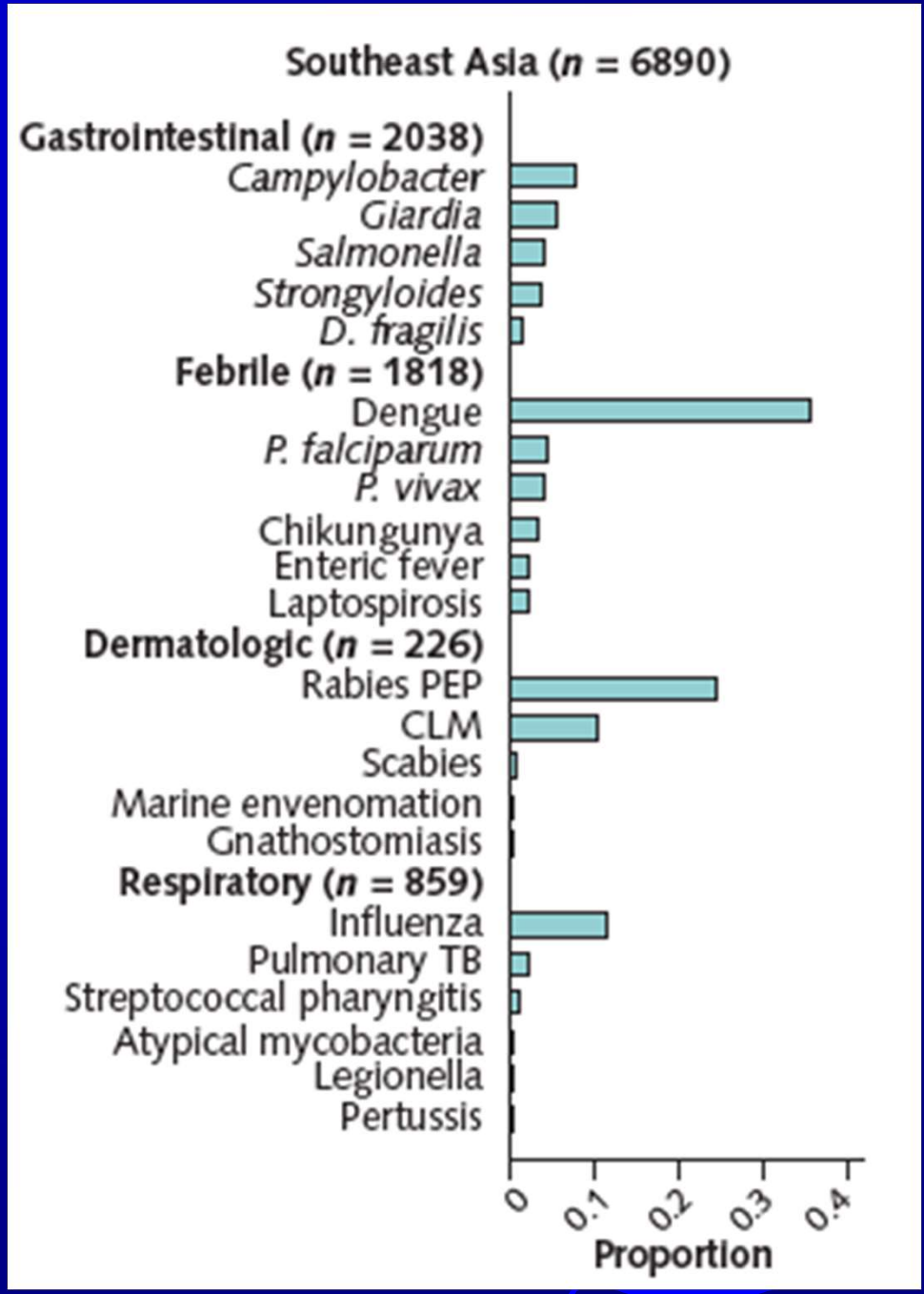
Differential Diagnosis?

- Main symptoms:
  - Lethargy
  - Sleepiness
  - Poor appetite
  - Drenching sweats

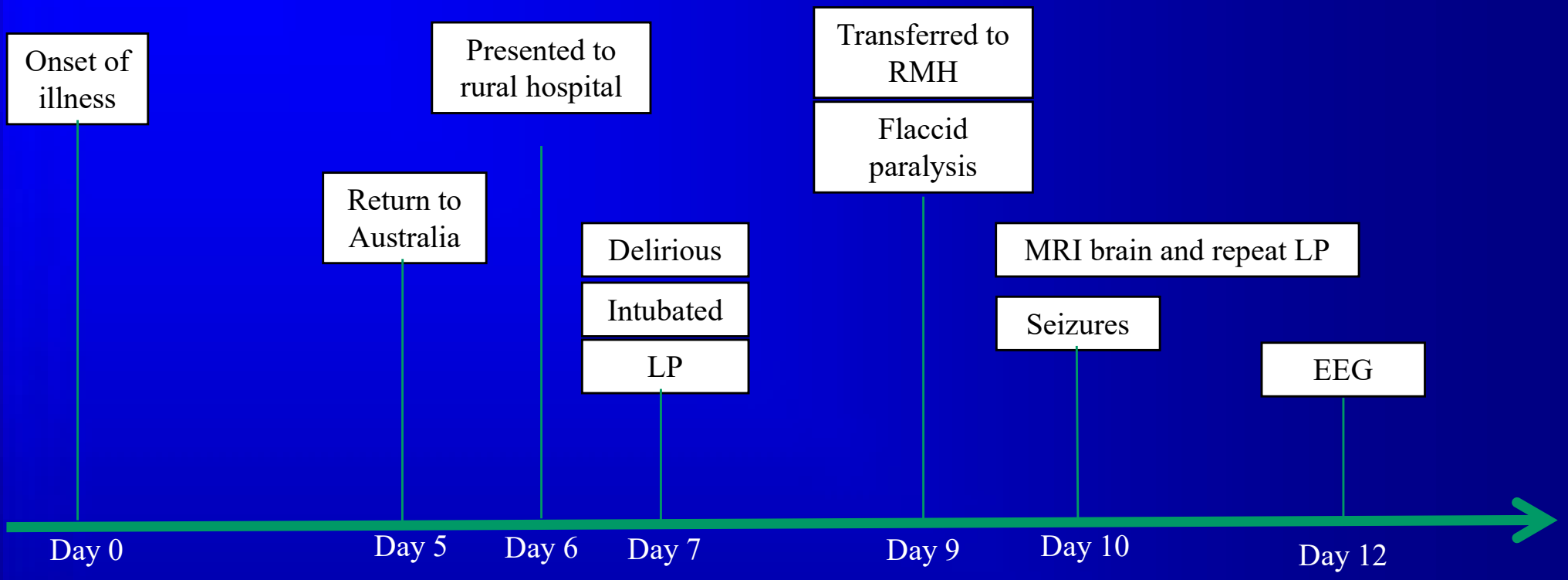
Dengue fever
Malaria
Typhoid fever
Scrub typhus
Influenza
Meningitis
Encephalitis

Proportion of major syndromic groupings for GI, fever, dermatologic, and respiratory: SE Asia

Leder K et al. GeoSentinel Surveillance of Illness in Returned Travelers 2007-2011 Ann Int Med 2013



Course of Illness



(Day 8 – 12 of the trip)

Laboratory and Radiological Investigations

What tests would you order?

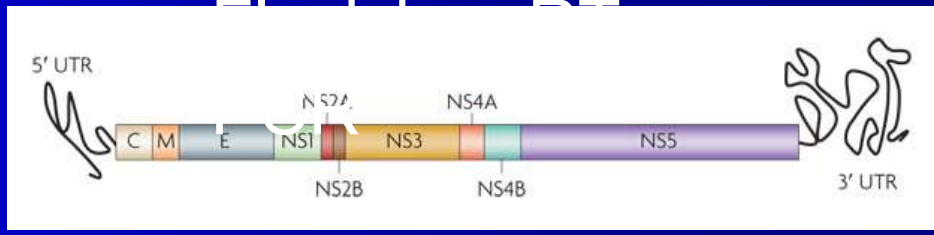
- FBE: 122/14.7/304
- Normal renal function
- Bili 7, GGT 18, ALT 47, AST 83, ALP 47, albumin 21
- CRP 117 INR 1.0
- CK: 944 → 3175 → 1990
- Malaria screen x 3 negative
- Blood cultures x 6 (2 before antibiotics) – no growth
- CT and MRI brain – no intracranial pathology
- EEG – some encephalopathic waves, no epileptic discharges
- Comprehensive diagnostic work-up: bacterial, viral, TB, autoimmune

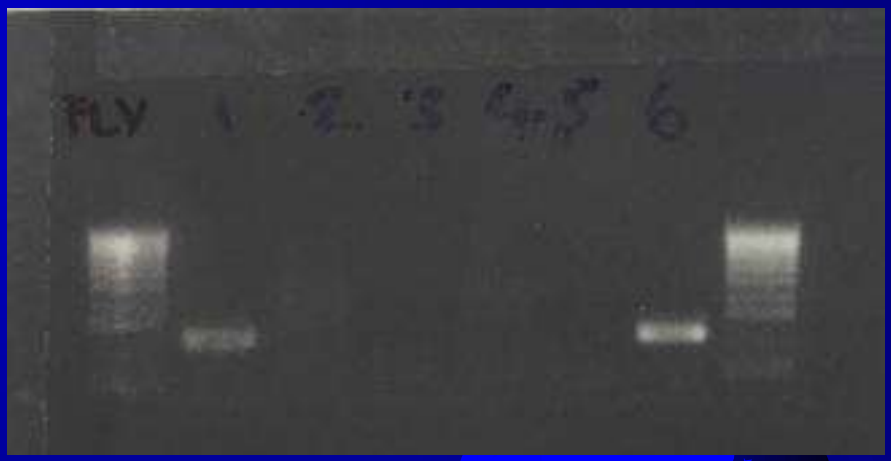
LP Results

	First lumbar puncture (Day 7)	Second lumbar puncture (Day 10)
Glucose (2.2 – 4.2 mmol/L)	3.5	4.2
Protein (0.15 – 0.45 g/L)	1.3	0.92
Erythrocytes (<1 x 10^6/L)	54	5
Polymorphs (<1 x 10^6/L)	280	2
Lymphocytes (<5 x 10^6/L)	87	33
Gram stain	No bacteria seen	No bacteria seen
Culture	No growth	No growth
Opening pressure	Not done	Not done

Additional Investigations

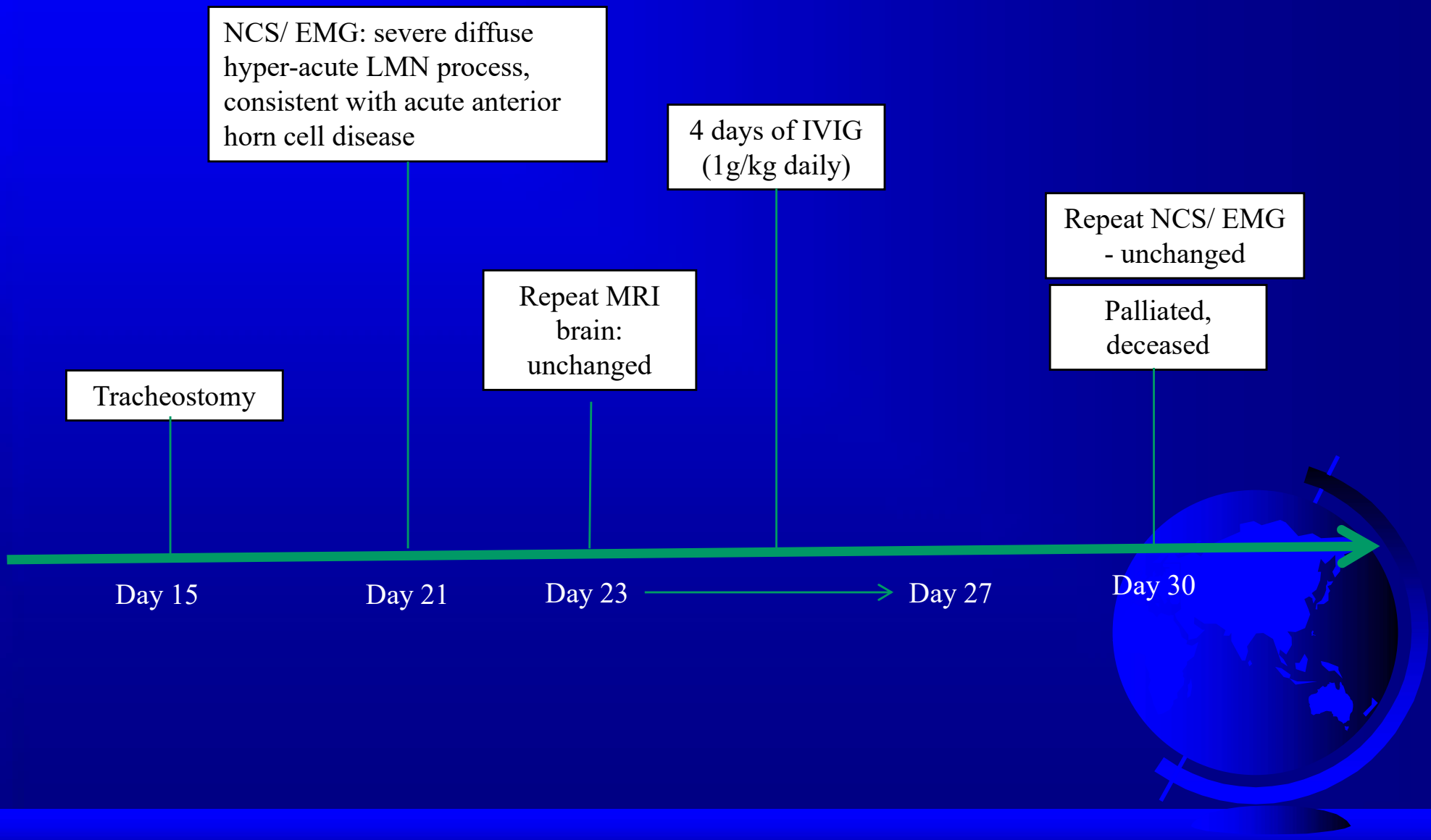
- Japanese encephalitis virus (JEV) serology IgG (Euroimmun)
  - 160 (D7) → 1280 (D12) → >2560 (D13)
  - Murray Valley total Ab weakly pos D7, neg D12 and D13
  - Kunjin total Ab (EIA) neg
  - Dengue: neg IgM, IgG and NS1 antigen
- JEV IgM (IF) pos on CSF; IgG >=10 (D10)
- Pan-flavivirus PCR and JEV real-time PCR
  - Neg PCR serum and CSF
  - Pos PCR urine and whole blood
  - Confirmed by sequencing of the NS5 region



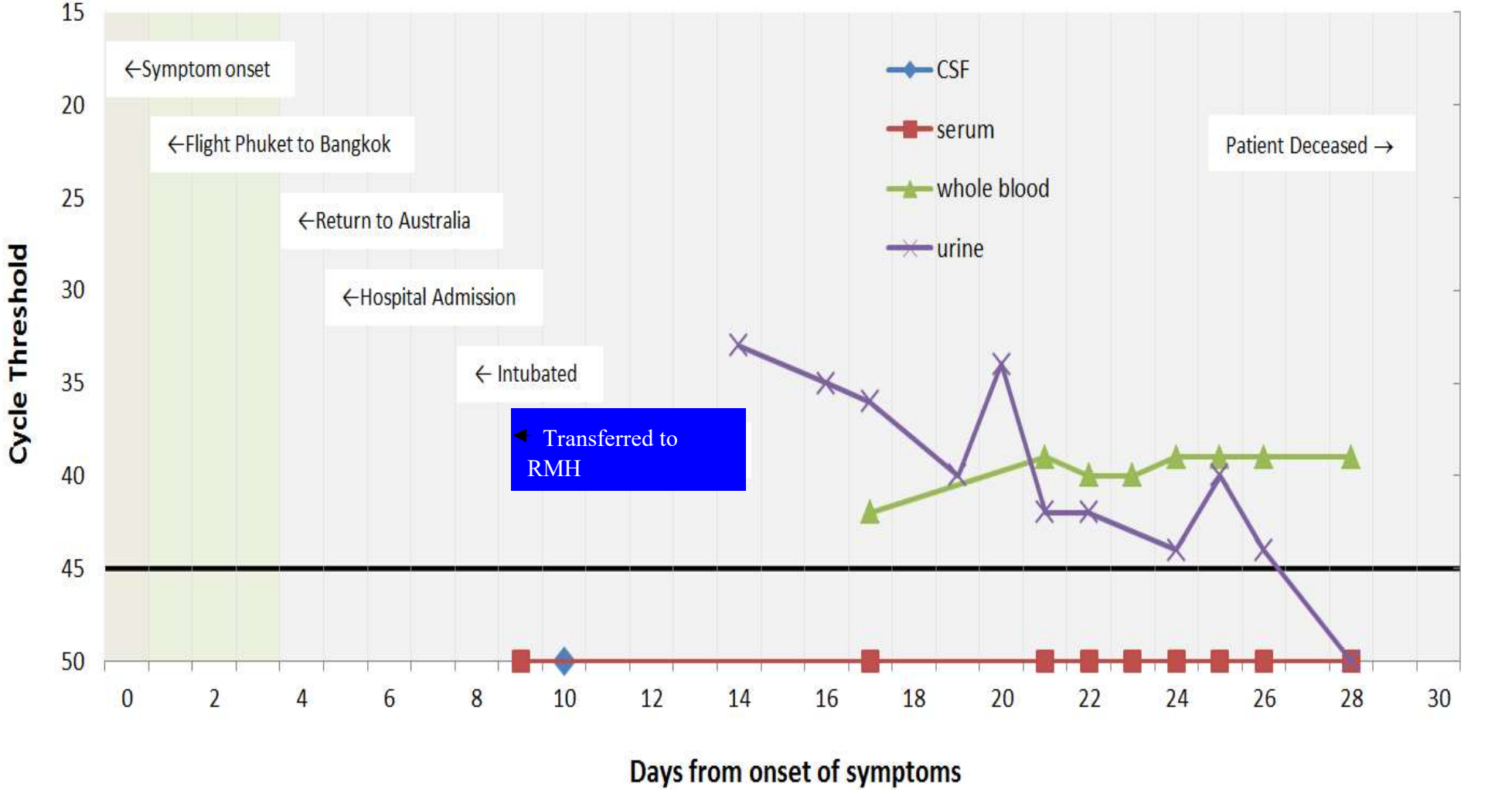


1 – Patient
2-5 Other patient samples
6 – Kokobera positive control

Illness Progression



PCR Results Over Time



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JUNE 22 2017

Victorian man dies after contracting Japanese encephalitis in Phuket, Thailand

ABC NEWS LOCATION: Melbourne, Vic Change

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Australian dies of rare mosquito-borne disea after visiting Thailand

By Anne Barker

Updated 21 Jun 2017, 5:59pm

An Australian man returned from Thailand has died from the rare but potentially fatal mosquito-borne disease, Japanese encephalitis.

It is understood to be only the 10th case of the disease recorded in Australia since 2001 and one of only a handful of deaths in that time, although Japanese encephalitis is endemic in South-East Asia, where it is most commonly found in rural or farming areas.

Herald Sun

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The man's death is only the 10th reported case in Australia and only Victoria's second AUNG THU

VIC News

Melbourne man dies from Japanese encephalitis after returning from Thailand

JE Diagnostics

- Traditional teaching: Serology on serum or CSF mainstay of diagnosis, JE virus only detectable very early in illness
- Extending window of detection
  - Virus detected in urine for other *Flaviviridae* family: WNV, dengue, YF, Zika
  - Testing of whole blood also prolongs detection for Zika and WNV
- Case is first description of prolonged detection of JEV in urine (26 days) and whole blood (28 days)
  - Only one prior case of detection of JEV in urine by WGS in early 2017

JE Risk for Travelers

- Vector: *Culex* mosquitoes
- Risk: Rural areas, long-term travel
  - Tropical: year round;
  - Temperate: May-Oct
- Incidence in endemic populations
  - 1.8 cases/100,000 population (68000 cases/year globally)
  - <1% with symptomatic meningo-encephalitis
  - 1/3 recover, 1/3 severe sequelae, 1/3 die
- 79 cases reported among travelers or expatriates from non-endemic countries 1973 to 2015
  - 60% tourists, age 1 - 91 (median: 34 y)
  - Travel duration: 65% >1 month
  - Destinations: Thailand and Bali most common (non-urban areas)
  - Poor outcome: 18% died, 44% neurologic sequelae
- **Overall JE risk: <1 case/ 1 million travelers to endemic countries**
- **Rare but potentially devastating**

Balancing Benefits and Risks of JE Vaccine

- Risk of disease difficult to assess due to immunization of local population and rapidly changing epidemiology
- Allergic adverse events associated with JEVax; may be more common in those with history of allergic reactions and allergy to gelatin
- Some protective measures available but may be incomplete (bed nets, repellents)

Japanese Encephalitis Vaccines

- *Ixiaro:* Vero-cell derived
  - 2 doses (0, 28 days)
  - Boost at 1 years and then 10 years
- *JEVax*
  - 3 dose series (Days 0, 7, 30)
  - Allergic reactions include angioedema
  - No longer available in the US
- *Imojev: (not available in the US)*
  - Live attenuated recombinant JE virus (chimeric), licensed > 9 months, single dose for adults, lasts >5 years

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  - Khai H…
  - Shio Y…
  - Leon C…
  - Sueller…
  - Irani T…
  - Gina P…

Open Forum Infectious Diseases

BRIEF REPORT

Prolonged Detection of Japanese Encephalitis Virus in Urine and Whole Blood in a Returned Short-term Traveler

G. Khai Lin Huang,[1,*] Shio Yen Tio,[2,*] Leon Caly,[1,*] Suellen Nicholson,[1] Irani Thevarajan,[2] Georgina Papadakis,[1] Mike Catton,[1] Steven Y. C. Tong,[2,3,] and Julian Druce[1,**]**

[1]Victorian Infectious Diseases Reference Laboratory, The Royal Melbourne Hospital, and The University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Victoria, Australia; [2]Victorian Infectious Disease Service, The Royal Melbourne Hospital, and The University of Melbourne, at the Peter Doherty Institute for Infection and Immunity, Victoria, Australia; [3]Menzies School of Health Research, Darwin, Australia

Somnolent Zambian Hunter

- 35 year old man from near Siavonga (Lake Zambezi)
- Fishes and hunts in rural forested areas near lake
- Presents to UTH with a 3 month history of fever and increasing confusion
- Hospitalized and treated one month ago for malaria at a district hospital

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- No foc
- No ne
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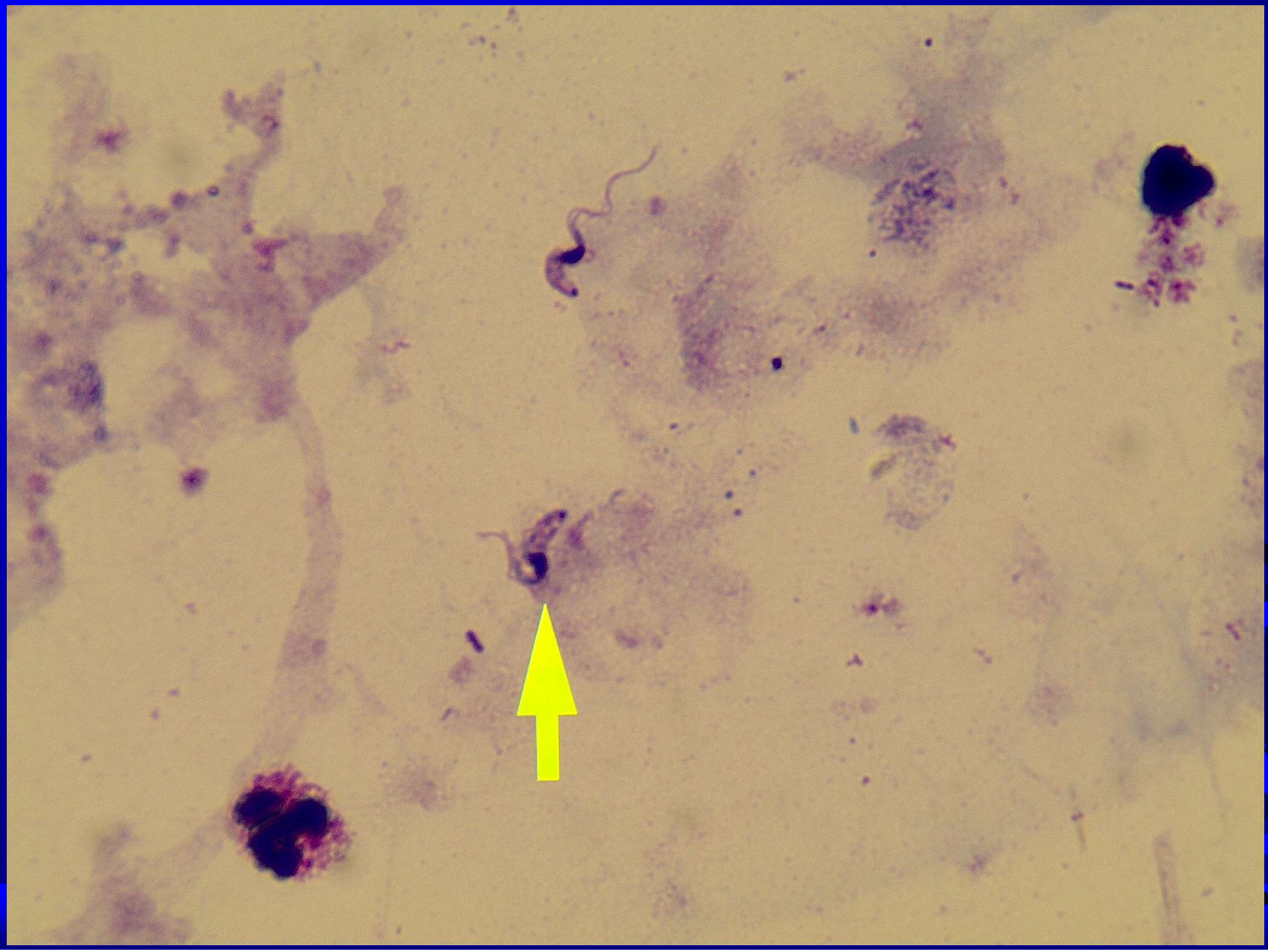
Differential Diagnosis?

- Cerebral malaria
- CNS OI associated with HIV (toxoplasmosis, lymphoma, etc.)
- Viral encephalitis (HSV)
- Typhoid fever
- East African trypanosomiasis

Blood Smear Results



Additional Work-up?

- Head CT scan negative
- LP results:
  - 2 WBC (lymphs)
  - Normal protein
  - PCR + Trypanosoma brucei rhodesiense

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Human African Trypansomiasis (Sleeping Sickness)

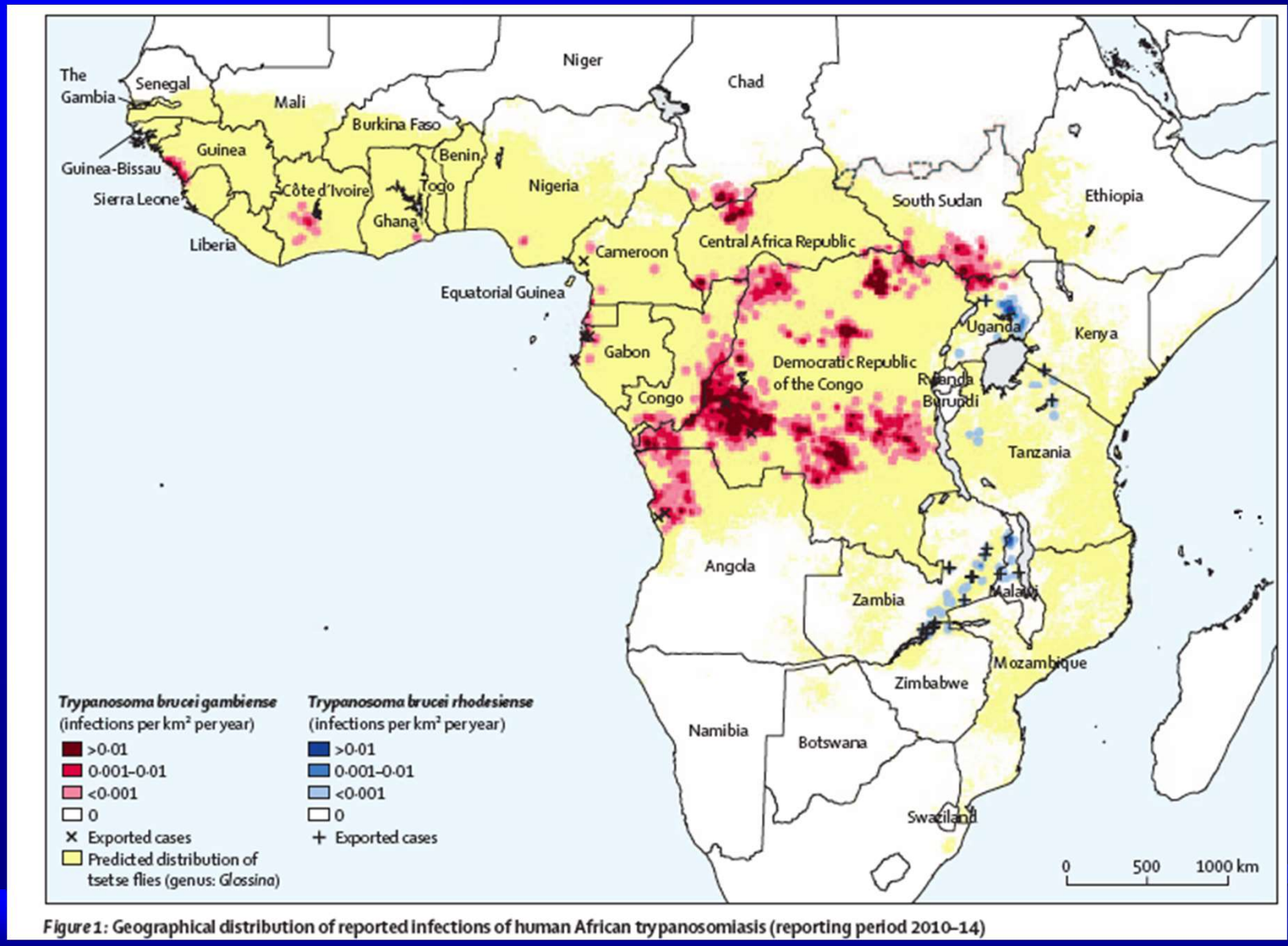


Figure 1: Geographical distribution of reported infections of human African trypanosomiasis (reporting period 2010–14)

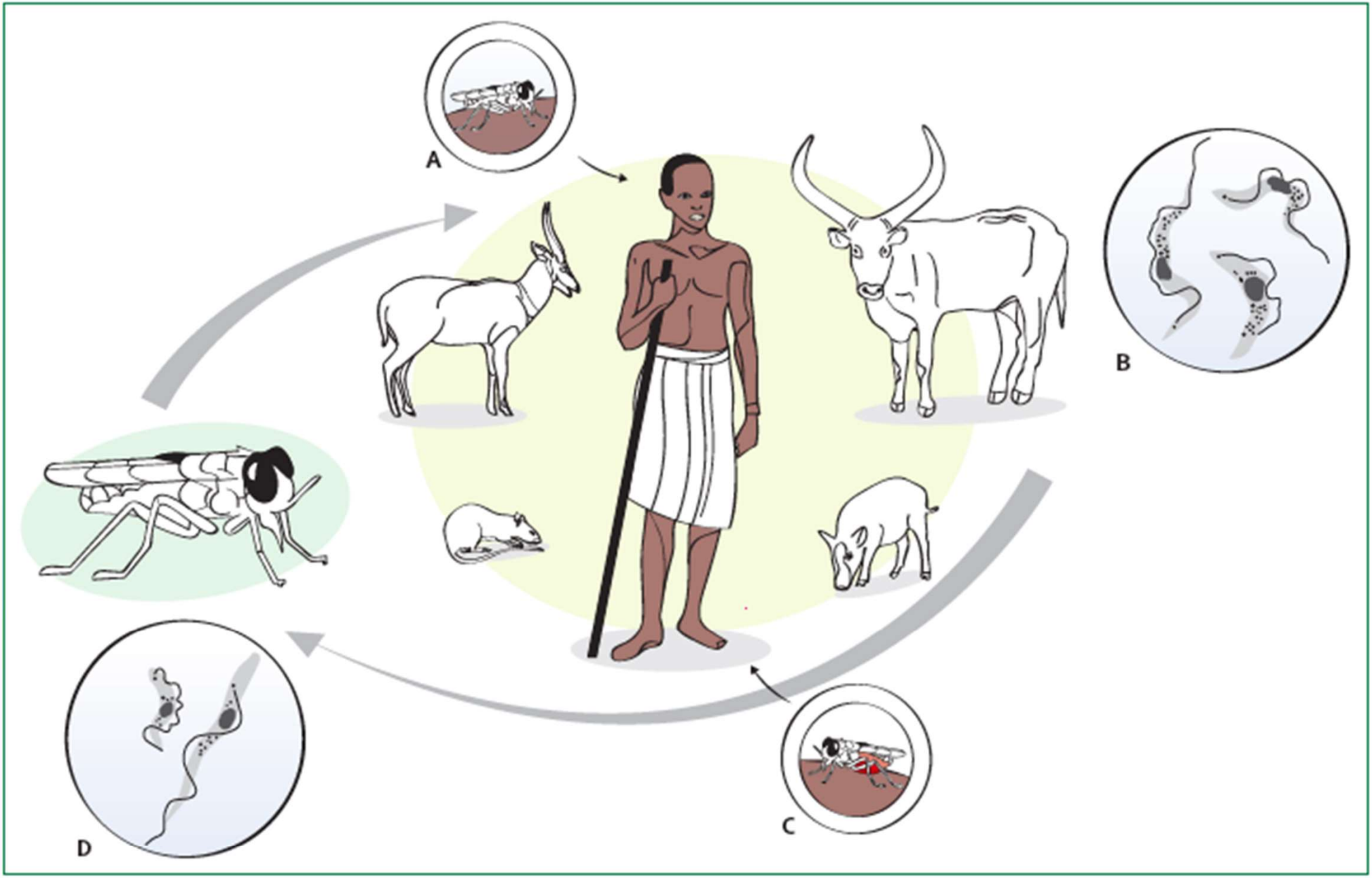
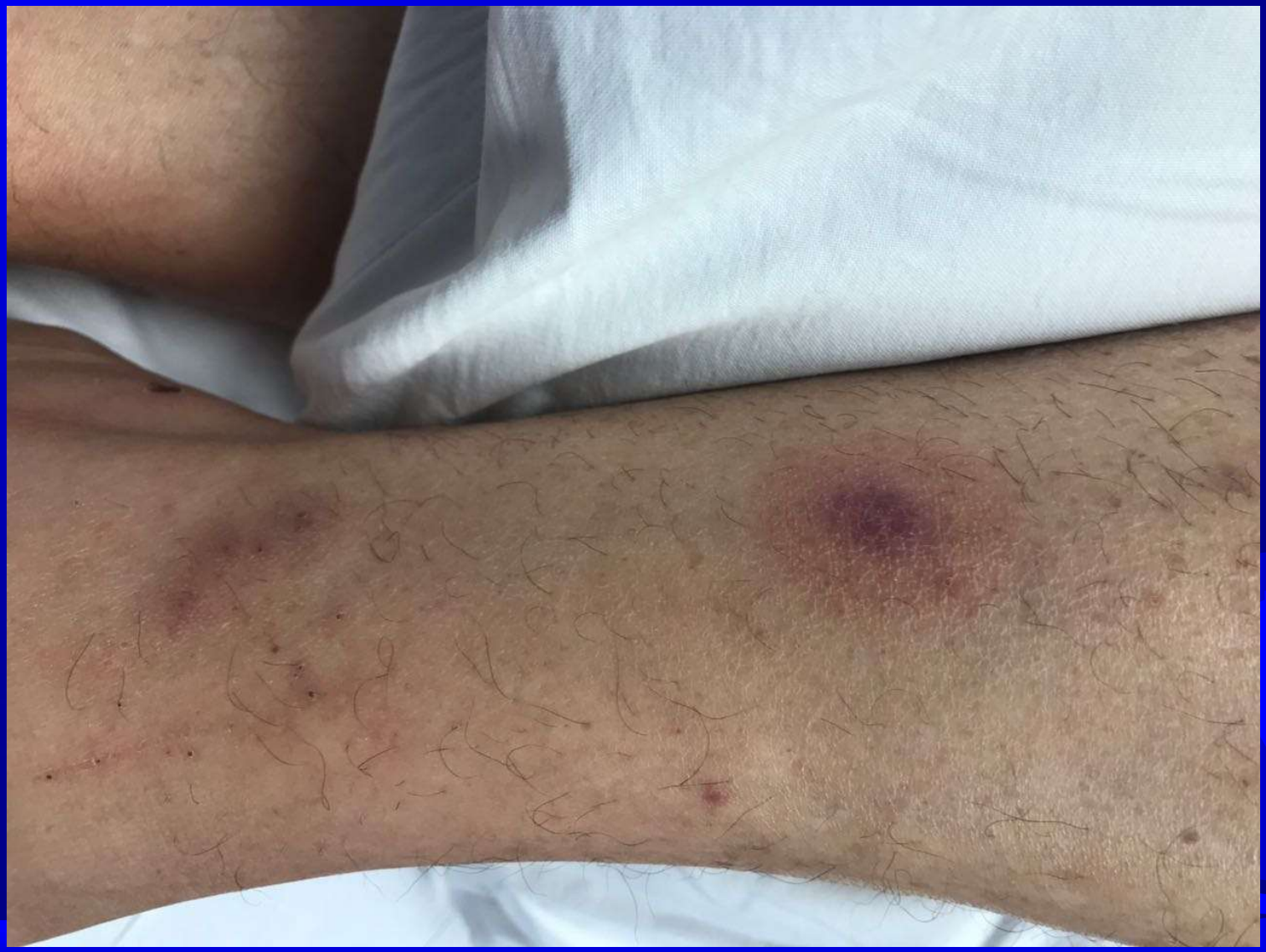


Figure 3: **Lifecycle of *Trypanosoma brucei***

(A) Metacyclic trypanosomes are injected into the skin of a mammalian host, together with saliva containing anticoagulant factors. (B) Once in the mammalian host, trypanosomes transform into dividing long slender forms that, via lymph and blood, can infiltrate tissues and organs, including the brain parenchyma. Some transform into a non-dividing short stumpy form. (C) A tsetse fly is infected by taking blood from a human being or other mammal that contains stumpy trypanosomes. (D) After about 2 weeks, trypanosomes might have colonised the salivary glands, producing free-swimming metacyclic trypanosomes that can then be transmitted to the next mammalian host. Source: © Food and Agriculture Organization of the United Nations. Reproduced with permission.

Tryps chancre Jan 2018 ex South Luangwa



	First-line treatment	Dosage	Alternative treatment and dosage
Trypanosoma brucei gambiense			
First stage	Pentamidine	4 mg/kg per day intramuscularly or intravenously (diluted in saline, in 2-h infusions) × 7 days	..
Second stage	Nifurtimox–eflornithine combination therapy	Nifurtimox 15 mg/kg per day orally in three doses × 10 days; eflornithine 400 mg/kg per day intravenously in two 2-h infusions (each dose diluted in 250 mL of water for injection)* × 7 days	Eflornithine 400 mg/kg per day intravenously in four 2-h infusions (each dose diluted in 100 mL of water for injection)* × 14 days; third-line (eg, treatment for relapse) is melarsoprol 2·2 mg/kg per day intravenously × 10 days
Trypanosoma brucei rhodesiense			
First stage	Suramin	Test dose of 4–5 mg/kg intravenously (day 1), then 20 mg/kg intravenously once per week × 5 weeks (maximum 1 g/injection—eg, days 3, 10, 17, 24, and 31)	Pentamidine 4 mg/kg per day intramuscular or intravenously (diluted in normal saline, in 2-h infusions) × 7 days
Second stage	Melarsoprol	2·2 mg/kg per day intravenously × 10 days	..

*Children weighing <10 kg: dilute in 50 mL of water for injection. Children weighing 10–25 kg: dilute in 100 mL of water for injection. If water for injection is unavailable, eflornithine can be diluted in 5% dextrose or saline.

Table: **Standard treatment for human African trypanosomiasis by form and stage**

Buscher P et al. Lancet 2017

Thank You for Your Attention!