FEVER IN THE RETURNED TRAVELLER

Luke Moore

FRCPath MRCP(Inf.Dis) PhD MPH MSc DTM&H DipULT FHEA

Consultant Infectious Diseases & Microbiology

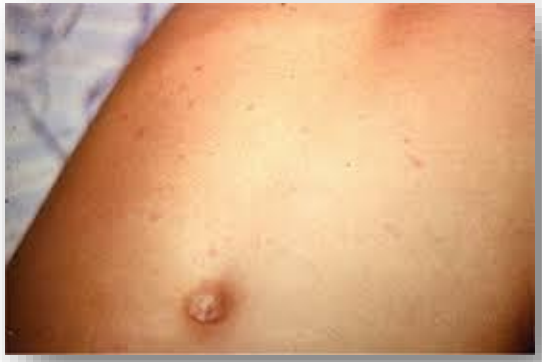
Chelsea & Westminster NHS Trust

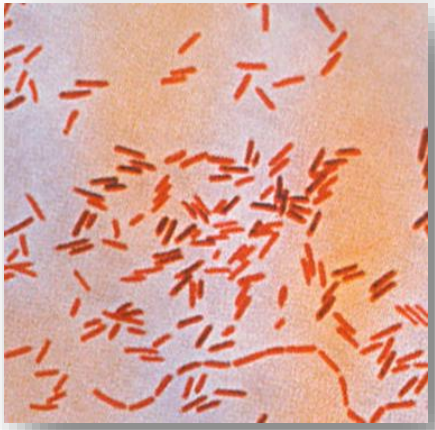
Imperial College Healthcare NHS Trust

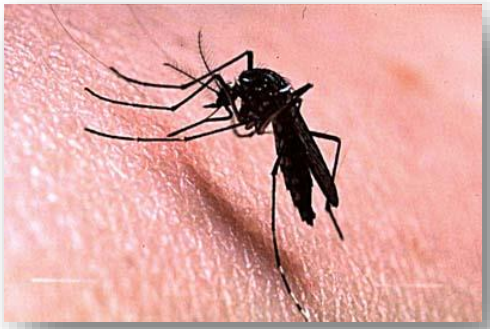
Central London Community Healthcare NHS Trust

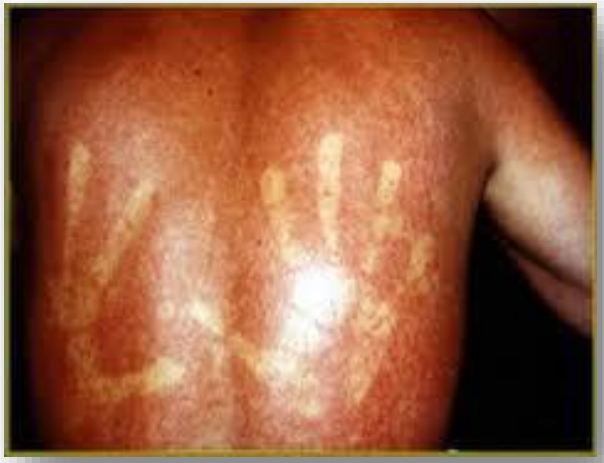
Learning objectives

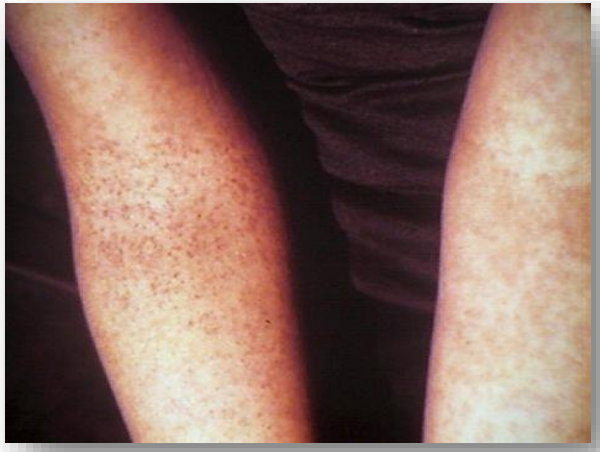
- Recall common tropical infectious diseases
- Optimise approach for fever in the returned traveler
- Review malaria diagnostics and treatment
- Explore resources for dealing with fever in the returned traveler

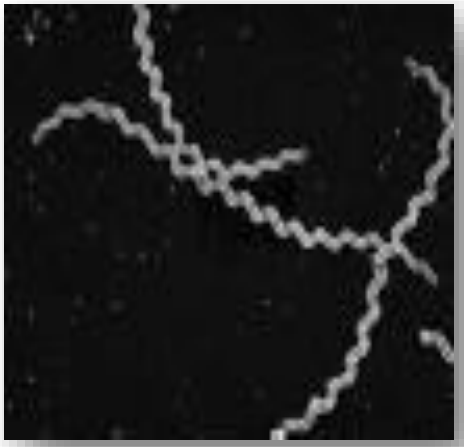


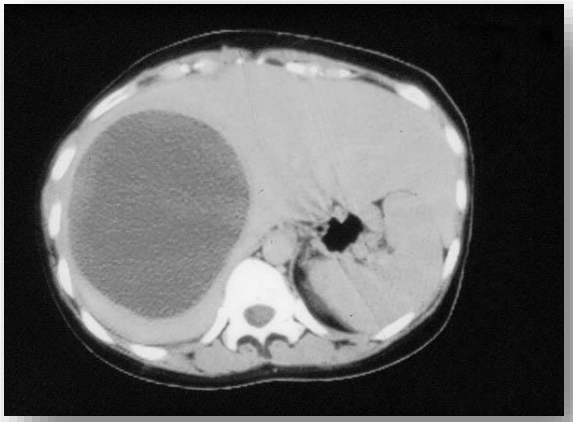


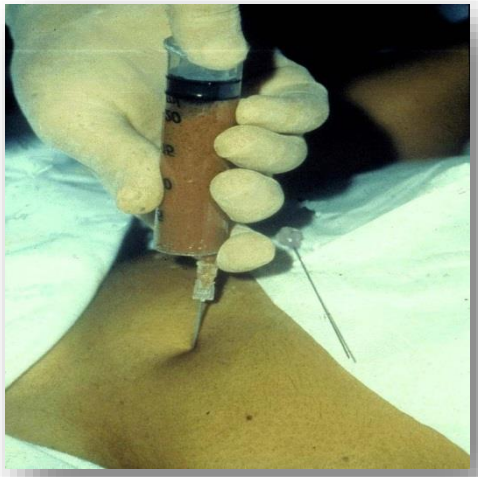


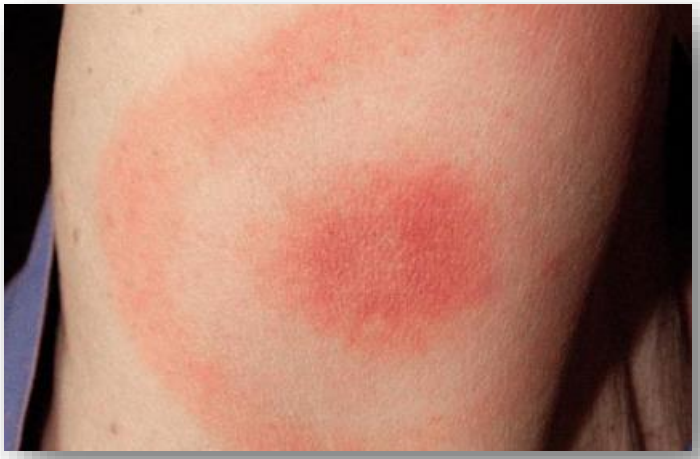












There are a lot of tropical infections…….

Schistosomiasis, filariasis, trichinosis, Hepatitis, Malaria, Onchocerciasis, Buruli Ulcer, Dengue, Chikungunya, Loa loa, tetanus, rabies, japanese encephalitis, Yellow Fever, trypanosomiasis, leishmaniasis, African tick typhus, scrub typhus, leprosy, melioidosis, tuberculosis, leptospirosis, Ebola, Marburg fever, Lassa fever, cholera, polio, dracunculiasis, gnathostomiasis, brucellosis, neurocystercercosis, strongyloides, SARS, avian flu, hantavirus, Rift Valley fever, Paragonimiasis, angiostrongylus cantonensis, amoebic liver abscess, hydatid, shigellosis, typhoid fever ……

Fever in the returned traveller

Undifferentiated fever

	SSA	SEA	SCA	ME/NA	SA	Diagnostics
Amoebic liver abscess						Serology (>92% sensitive at presentation); U/S abdomen
Brucellosis						Extended BC, serology
Chikungunya						PCR (1-4 d) or IgM (>5 days)
Dengue						Dengue PCR (1-8 days post symptom onset) IgM ELISA (>4 days)
Enteric fever (typhoid / paratyphoid)						BC (up to 80% sensitive in 1st wk)
HIV						HIV (antigen and antibody)
Leptospirosis						CSF + BC <5 days EIA IgM >5 days
Rickettsiae						Acute phase + 3-6 wk serum
Schistosomiasis, acute						Not helpful

Serious / very common	
Common	
Rare	

SSA, sub-Saharan Africa ; SEA, South East Asia; SCA, South Central Asia; ME/NA, Middle East, Mediterranean, North Africa; SA, South America, Caribbean

Johnston et al
J Infect
2009;59:1-18.

Fever in the returned traveller

Fever with rash

	SSA	SEA	SCA	ME/NA	SA	Diagnostics
Dengue						Dengue PCR (1-8 days post symptom onset) IgM ELISA (>4 days)
HIV						HIV (antigen and antibody)
Rickettsiae						Acute phase + 3-6 wk serum
Schistosomiasis, acute						Not helpful
VHF						PCR to ref lab

Serious / very common	
Common	
Rare	

SSA, sub-Saharan Africa ; SEA, South East Asia; SCA, South Central Asia; ME/NA, Middle East, Mediterranean, North Africa; SA, South America, Caribbean

Johnston et al J Infect 2009;59:1-18.

Fever in the returned traveller

Fever with jaundice

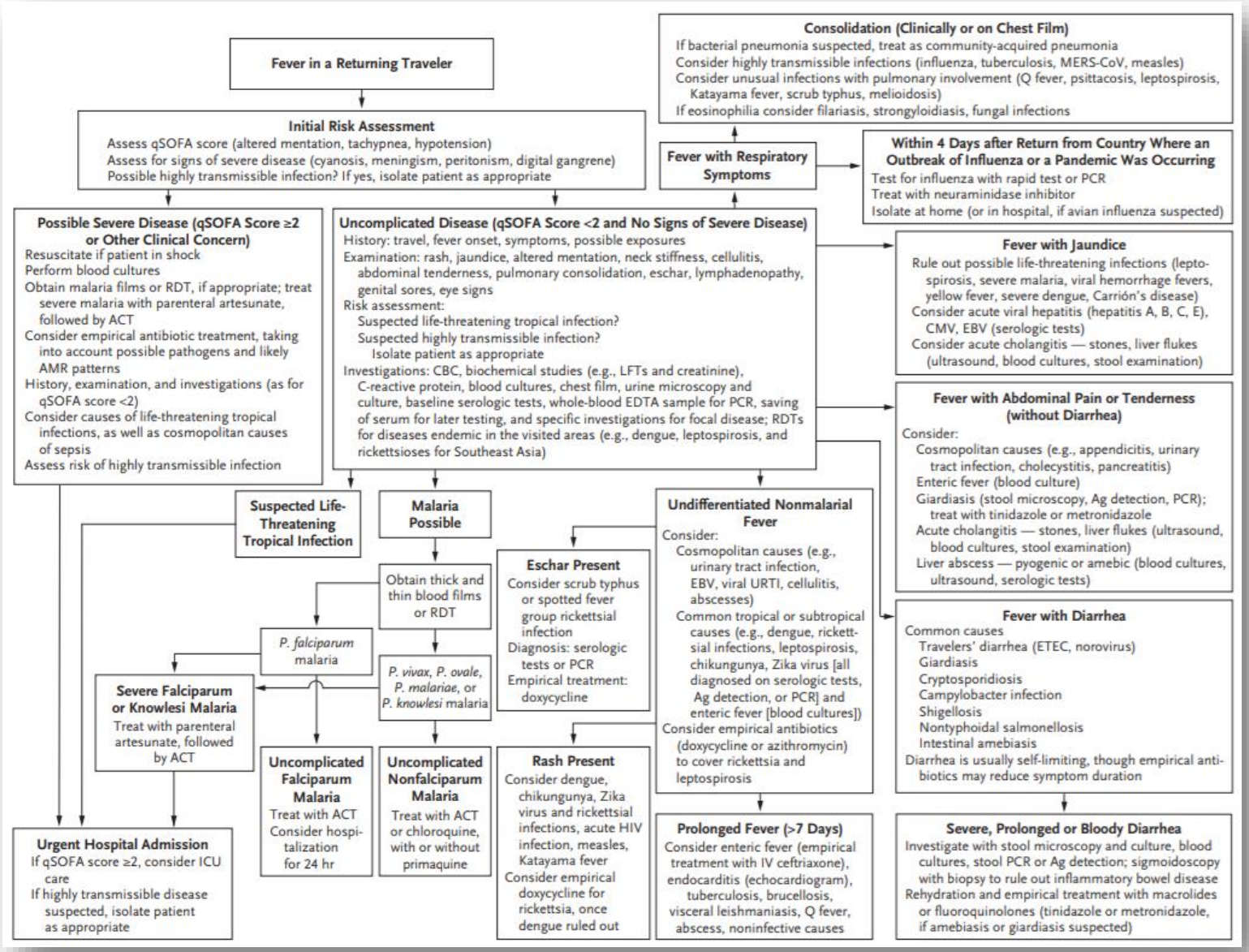
	SSA	SEA	SCA	ME/NA	SA	Diagnostics
Leptospirosis						CSF + BC < 5days EIA IgM >5 days
Viral Hepatitis						Anti-HAV IgM, HBsAg, anti-HEV IgM
VHF						PCR to ref lab
Yellow fever						EDTA (blood) +/- CSF for PCR; IgG / IgM serology

Serious / very common	
Common	
Rare	

SSA, sub-Saharan Africa ; SEA, South East Asia; SCA, South Central Asia; ME/NA, Middle East, Mediterranean, North Africa; SA, South America, Caribbean

Johnston et al J Infect 2009;59:1-18.

Fever in the returned traveller



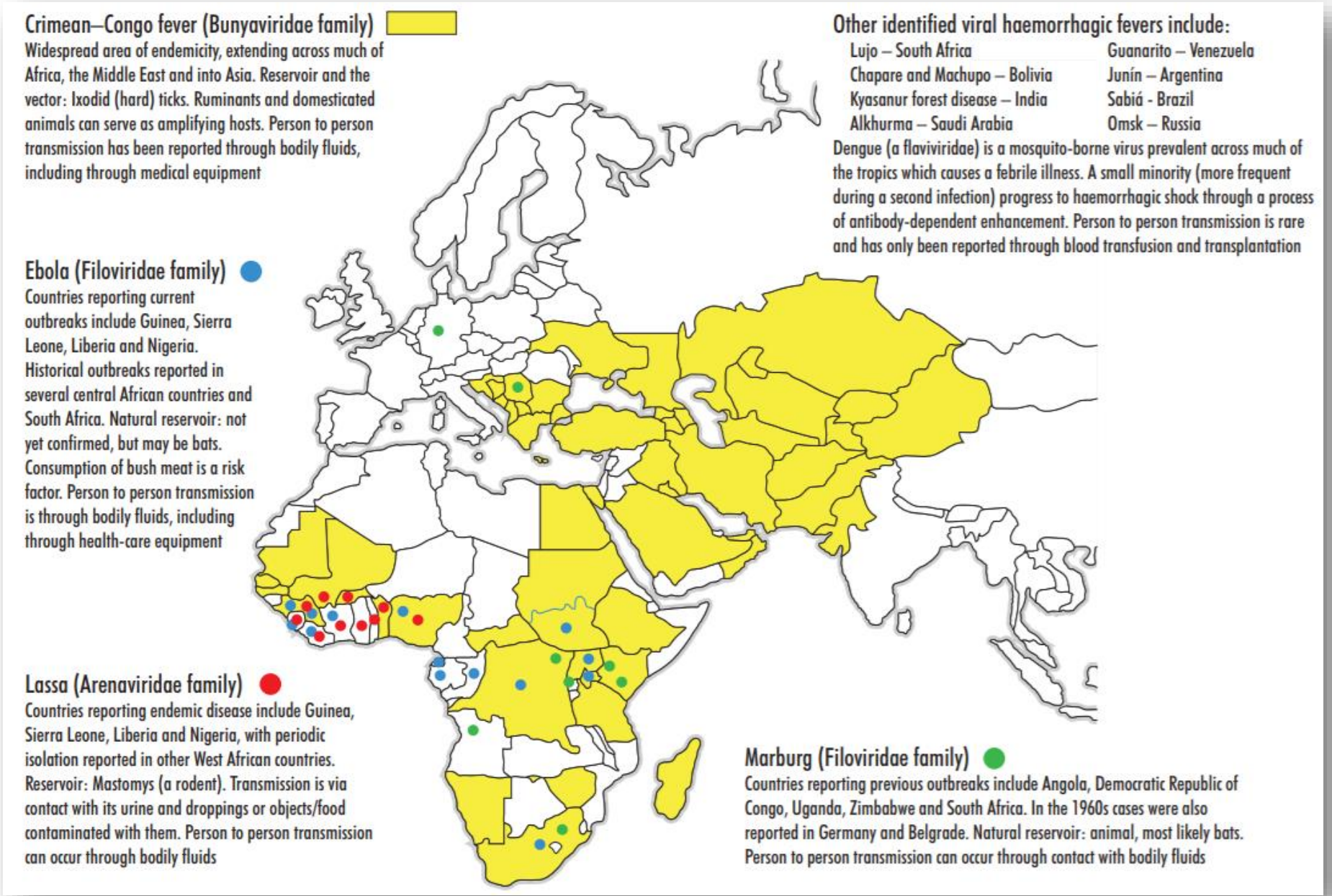
Thwaites, Day
NEJM
2017;376:548-60.

Step 1.

Identify your patient as a returning traveller

Diseases we REALLY don’t want to miss

1. Malaria
2. Malaria
3. VHF e.g. Ebola virus disease



Moore et al
BJHM
2014;75(99):515-522.

Diseases we REALLY don't want to miss

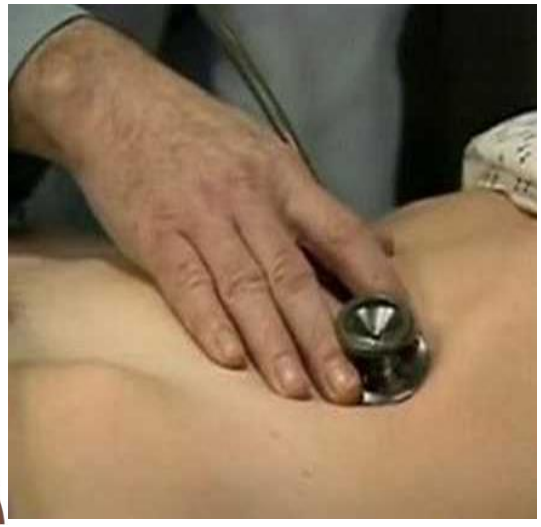
1. Malaria
2. Malaria
3. VHF e.g. Ebola virus disease
4. Typhoid fever
5. Leptospirosis
6. Rickettsial infections
7. Zika virus (in a woman of child-bearing age)
8. Amoebic liver abscess
9. [Tuberculosis]
10. [HIV]

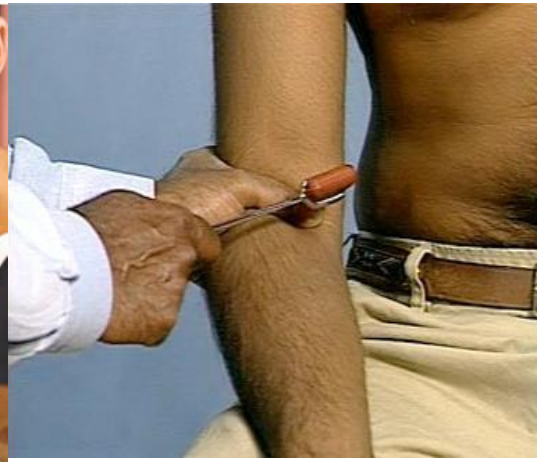
Step 2.

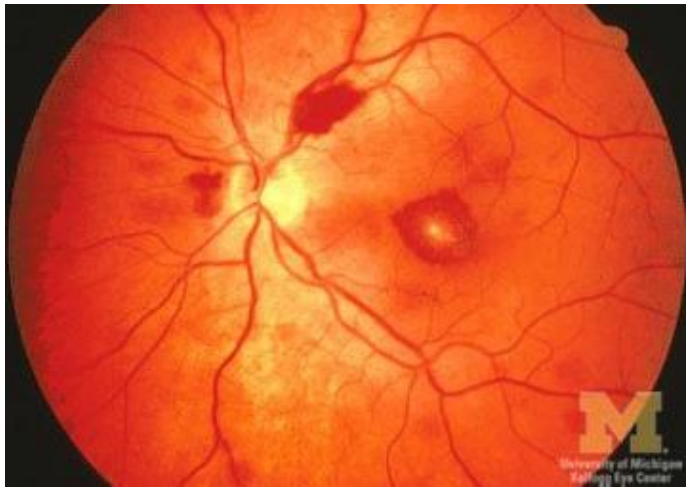
Have a systematic, comprehensive approach

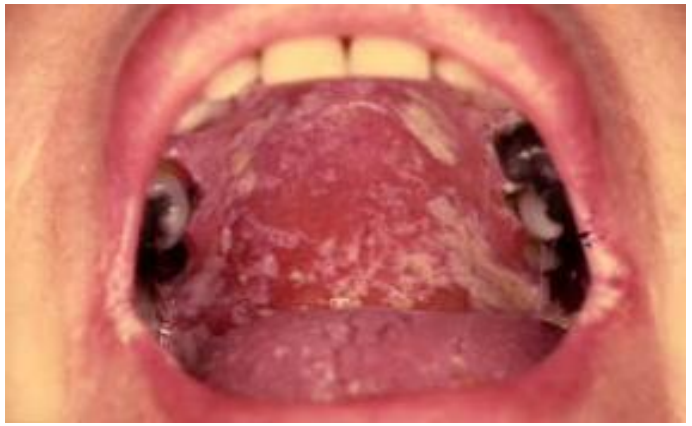
Step 2. History

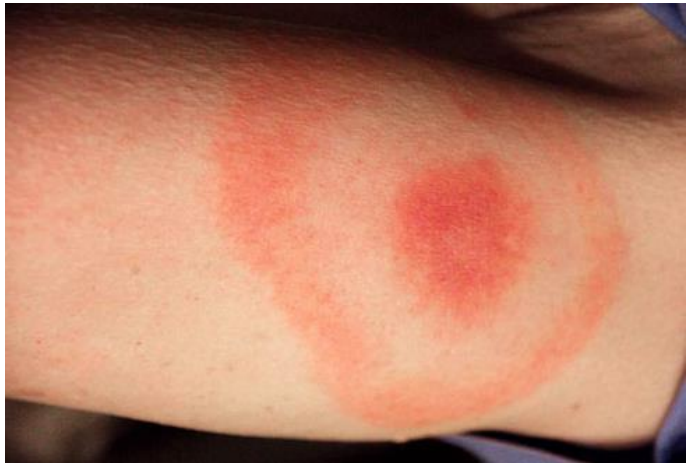
Step 2. Examination









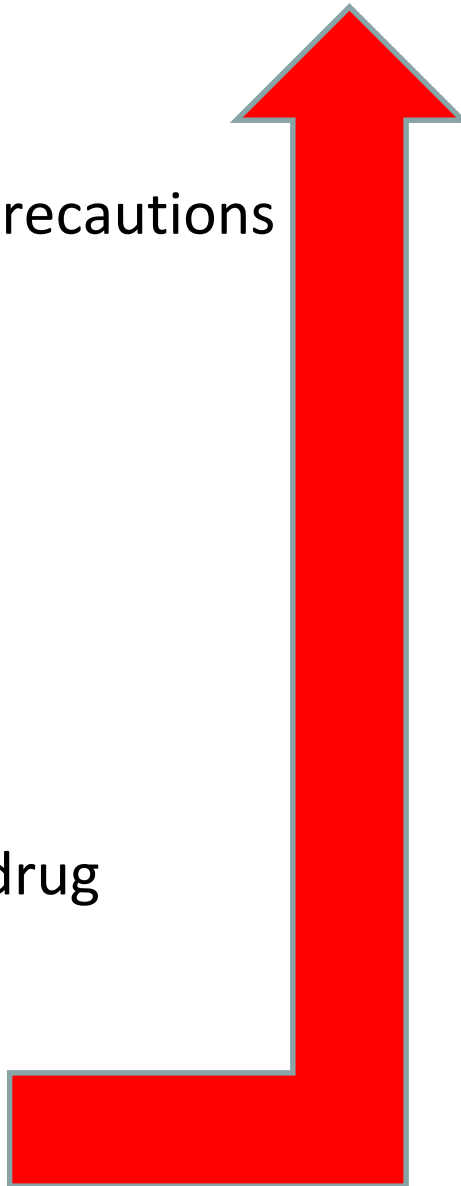


Step 2. Approach

- **Person**
  - backpacker/NGO worker/ businessman,
  - Exposures/behaviours (ask parents to leave), pre travel precautions (vaccination history etc)
- **Place**
  - City/village/forest
  - Hotel/guesthouse
- **Time**
  - Disease incubation vs when left the area
  - Could this be a relapse ? (inadequate Rx abroad/drug resistant infection)
- **History and examination**
- **Infection control issues**

Step 2. Approach

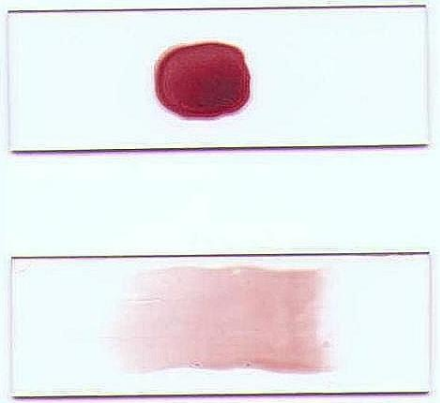
- **Person**
  - backpacker/NGO worker/ businessman,
  - Exposures/behaviours (ask parents to leave), pre travel precautions (vaccination history etc)
- **Place**
  - City/village/forest
  - Hotel/guesthouse
- **Time**
  - Disease incubation vs when left the area
  - Could this be a relapse ? (inadequate Rx abroad/drug resistant infection)
- **History and examination**
- **Infection control issues**



Step 3.

Adopt a structured approach to investigation pathways

Step 3. General investigations



1. Malaria Film +RDT
2. Malaria Film
3. Malaria Film
4. FBC/Clotting
5. U&E/LFT/CK
6. Blood cultures
7. Serum Save
8. Urinalysis
9. Stool MCS/OCP
10. CXR

↓ Lymph	? dengue ? viral
↓ Plts	? malaria ? DIC
↑ Eosin	? helminths
Transaminitis	EBV/CMV/ Enteric fever/Hepatitis viruses/ Leptospirosis/ Relapsing fevers/ Rickettsia/VHF
Proteinuria	Leptospirosis
Haemoglobinuria	Malaria

Step 3. Specific Investigations

- Rare & Imported Pathogens Laboratory (RIPL)
  - PCR
  - Serology
- Respiratory virus swab +/- MERS CoV
- USS abdomen

Step 4.

Provide supportive and/or specific therapy

Step 4. Treatable common tropical infections

1. Malaria
2. Typhoid
3. Leptospirosis
4. Rickettsiae/Borrelia
5. Amoebiasis

Step 4. Infections managed supportively

1. Dengue
2. Chikungunya
3. MERS/SARS
4. Zika
5. VHFs (e.g. Ebola)

Malaria species cause human disease

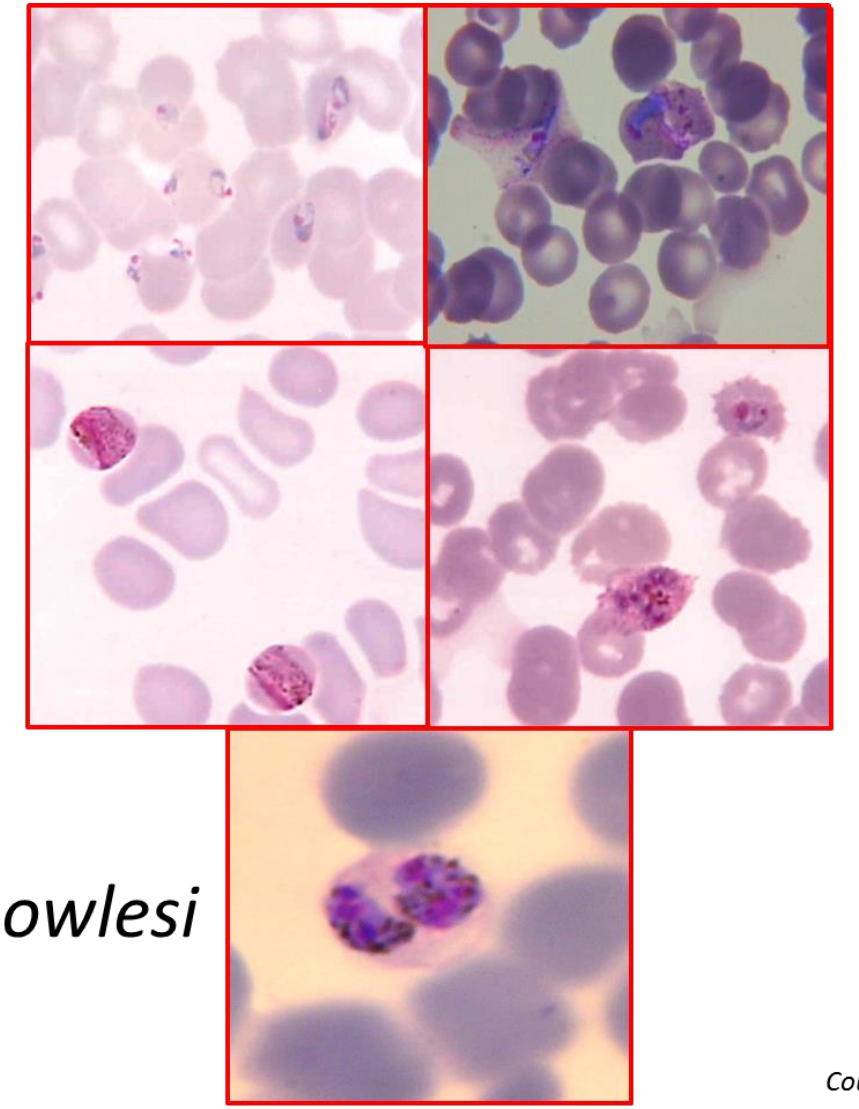
P. falciparum

P. vivax

P. malariae

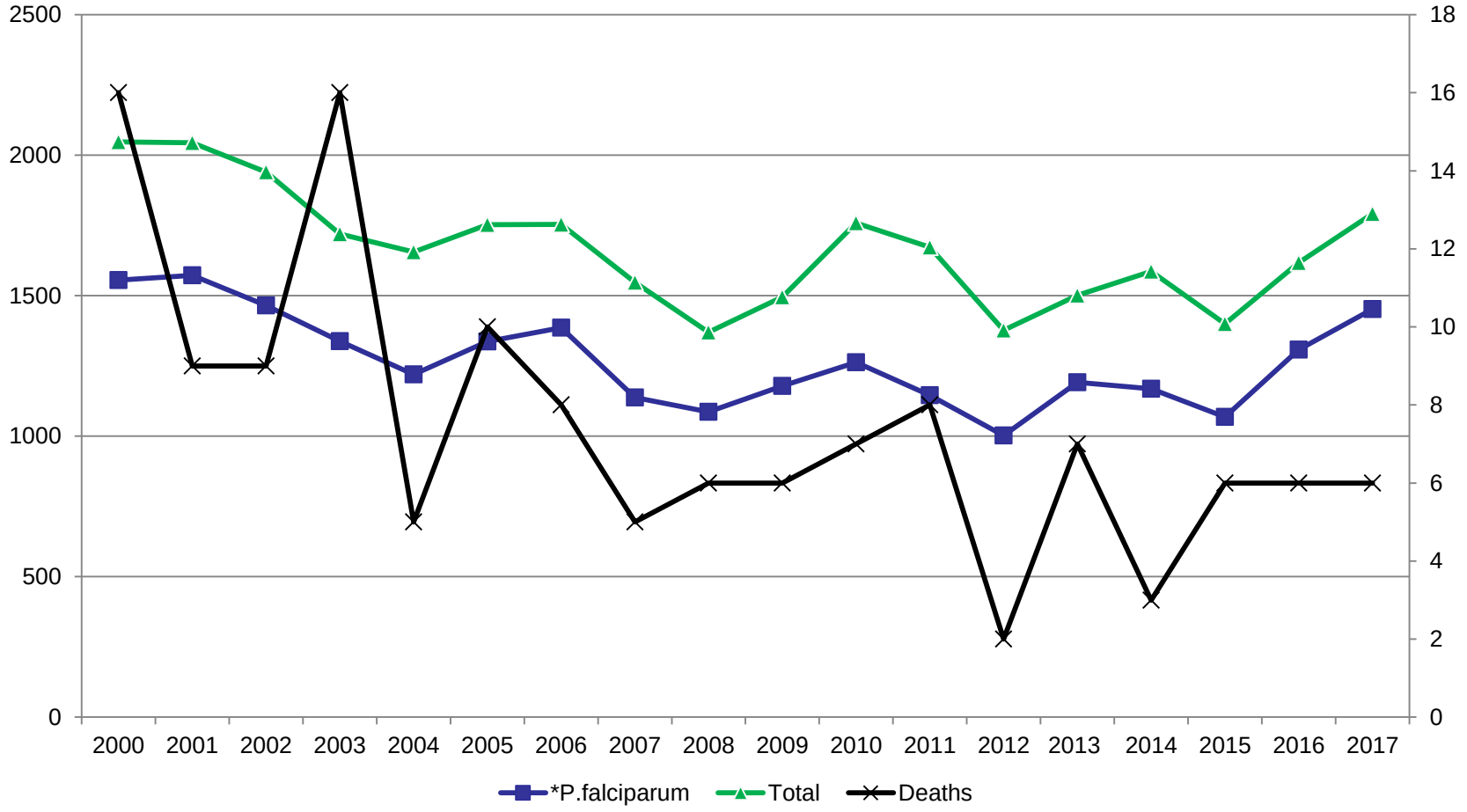
P. ovale

P. knowlesi



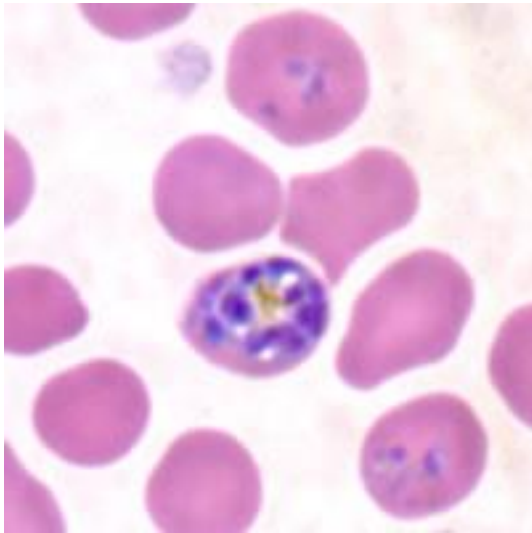
Courtesy: Dr Kesinee Chotivanich

UK Malaria cases & deaths



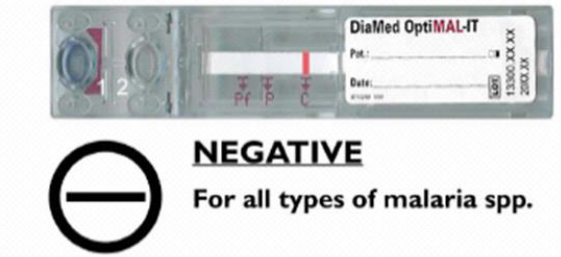
Clinical presentation of malaria

- Undifferentiated fever
- Severe
  - Clinical signs of severity
    - prostration
    - jaundice
    - Acidosis
  - Parasitaemia >2%, or schizonts



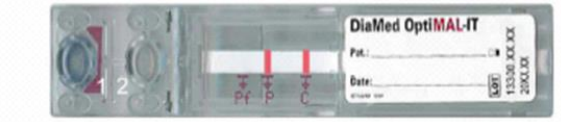
Diagnosis: Malaria slide vs RDTs

- Rapid Diagnostic Test
  - Accuracy reduced at low parasitaemia
  - Occasionally negative with very high parasitaemia ('prozone')
  - May remain positive for a few weeks following a recent treatment



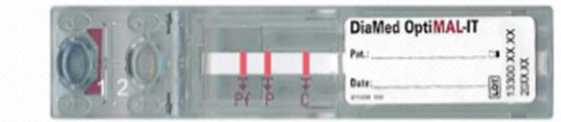
NEGATIVE

For all types of malaria spp.



POSITIVE

For Plasmodium sp.
(P. vivax / P. ovale / P. malariae)



POSITIVE

Plasmodium falciparum.
+/- (P. vivax / P. ovale / P. malariae)

Treating malaria

- Malaria is a medical emergency and patients with suspected malaria should be evaluated immediately.
- Symptoms of malaria are often non-specific: fever/sweats/chills, malaise, myalgia, headache, diarrhoea, and cough.
- Falciparum malaria is most likely to occur within 3 months of return from an endemic area. The incubation period for malaria is at least 6 days.
- Malaria caused by other species may present more than a year after return from an endemic area.

- A careful exposure history is necessary: country and area of travel, including stopovers, and date of return.
- Consider what malaria prophylaxis was taken (i.e. drug, dose & adherence, premature cessation); appropriate prophylaxis with full adherence does not exclude malaria.
- Consider other travel-related infections: e.g. typhoid, hepatitis, dengue or other arboviruses, avian influenza, MERS-CoV, HIV, meningitis/encephalitis and viral haemorrhagic fevers (VHF).[18]
- Three negative diagnostic samples over a period of 24—48 h are necessary to exclude malaria.

Lalloo et al
J Infect
2016;72:635-649.

Treating malaria – uncomplicated infection

- Artemether–lumefantrine: If weight >35 kg, 4 tablets then 4 tablets at 8, 24, 36, 48 and 60 h (Recommended).
- DHA-piperaquine: 36–60 kg 3 tablets daily for three days >60 kg 4 tablets daily for three days.
- Atovaquone–proguanil: 4 'standard' tablets daily for 3 days.
- Oral quinine sulphate 600 mg 8 hourly for 5–7 days **plus** doxycycline 200 mg daily (or clindamycin 450 mg 8 hourly for pregnant women) for 7 days.

Lalloo et al
J Infect
2016;72:635-649.

Treating malaria – severe infection

- Artesunate regimen: 2.4 mg/kg given as an intravenous injection at 0, 12 and 24 h then daily thereafter. After completion of a minimum of 24 h therapy (maximum five days), a full course of an oral ACT should be taken when the patient can tolerate oral medication.

- Careful management of fluid balance to optimise oxygen delivery and prevent pulmonary oedema.
- Regular monitoring for hypoglycemia.
- Consider broad spectrum antibiotics if evidence of shock or secondary bacterial infection.
- Haemofiltration for renal failure or control of acidosis or fluid/electrolyte imbalance.
- Consider medication to control seizures.

- Quinine: loading dose of 20 mg/kg quinine dihydrochloride in 5% dextrose or dextrose saline over 4 h. Followed by 10 mg/kg every 8 h for first 48 h (or until patient can swallow). Frequency of dosing should be reduced to 12 hourly if intravenous quinine continues for more than 48 h.
- Parenteral quinine therapy should be continued until the patient can take oral therapy when quinine sulphate 600 mg should be given three times a day to complete five to seven days of quinine in total.
- Quinine treatment should always be accompanied by a second drug: doxycycline 200 mg (or clindamycin 450 mg three times a day for children or pregnant women), given orally for total of seven days from when the patient can swallow.

Lalloo et al
J Infect
2016;72:635-649.

Mis-treating malaria

- Delayed patient presentation.
- Failure of health care worker to take a travel history or consider diagnosis of malaria.
- Belief that chemoprophylaxis prevents all malaria.
- Belief that malaria is unlikely if patient does not remember being bitten by mosquitoes.
- Belief that malaria presents with a classical fever pattern.
- Failure to recognise nonspecific clinical presentations of malaria.
- Failure to obtain immediate blood films or RDT.
- Failure to repeat diagnostic tests if first tests are negative.
- Failure to prescribe adequate and appropriate chemotherapy immediately.
- Failure to anticipate or treat complications.

Lalloo et al
J Infect
2016;72:635-649.

Treating non-falciparum malaria

Acute treatment			
Chloroquine	Adult	Initial dose 620 mg (*) 310 mg 6—8 h later 310 mg on days 2 and 3	Treatment of acute vivax, ovale, malariae and knowlesi malaria
	Child	Initial dose 10mg/base then 5 mg/kg base 6—8 h later and on days 2 and 3	
Artemether—lumefantrine OR DHA-PPQ		As for uncomplicated falciparum	Treatment of acute vivax, ovale, malariae and knowlesi malaria; dual infection with falciparum or uncertain species Treatment of resistant vivax malaria
Parenteral artesunate (or quinine)		As for complicated falciparum	Complicated single or dual infection
Preventing relapse			
Primaquine	Adult	15 mg (0.25 mg/kg) as a single daily dose for 14 days	Prevention of relapse in ovale malaria
	Child	0.25 mg/kg as a single daily dose for 14 days	
Primaquine	Adult	30 mg (0.5 mg/kg) as a single daily dose for 14 day	Prevention of relapse in vivax malaria
	Child	0.5 mg/kg as a single daily dose for 14 days	
Primaquine	Adult	0.75 mg/kg as a single weekly dose for 8 weeks	Prevention of relapse in vivax or ovale malaria in patients with mild- moderate G6PD deficiency
	Child	0.75 mg/kg (max 45 mg) as a single weekly dose for eight weeks	

Lalloo et al
J Infect
2016;72:635-649.

Seeking support

- Imperial *or* Chelsea & Westminster
  - Infectious Diseases
  - Medical Microbiology

- Hospital for Tropical Diseases UCLH
- Royal Free ID (High security isolation)
- Public Health England (PHE)

Web-based resources

- http://www.nathnac.org/
- http://www.promedmail.org/

Learning objectives

- Recall common tropical infectious diseases
- Optimise approach for fever in the returned traveler
- Review malaria diagnostics and treatment
- Explore resources for dealing with fever in the returned traveler