

FEVER IN THE RETURNED TRAVELLER

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

| | |
|-----------------------|--------|
| Serious / very common | Red |
| Common | Orange |
| Rare | Green |

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

Fever in the returned traveller

Fever with rash

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

| | |
|-----------------------|--------|
| Serious / very common | Red |
| Common | Orange |
| Rare | Green |

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Fever in the returned traveller

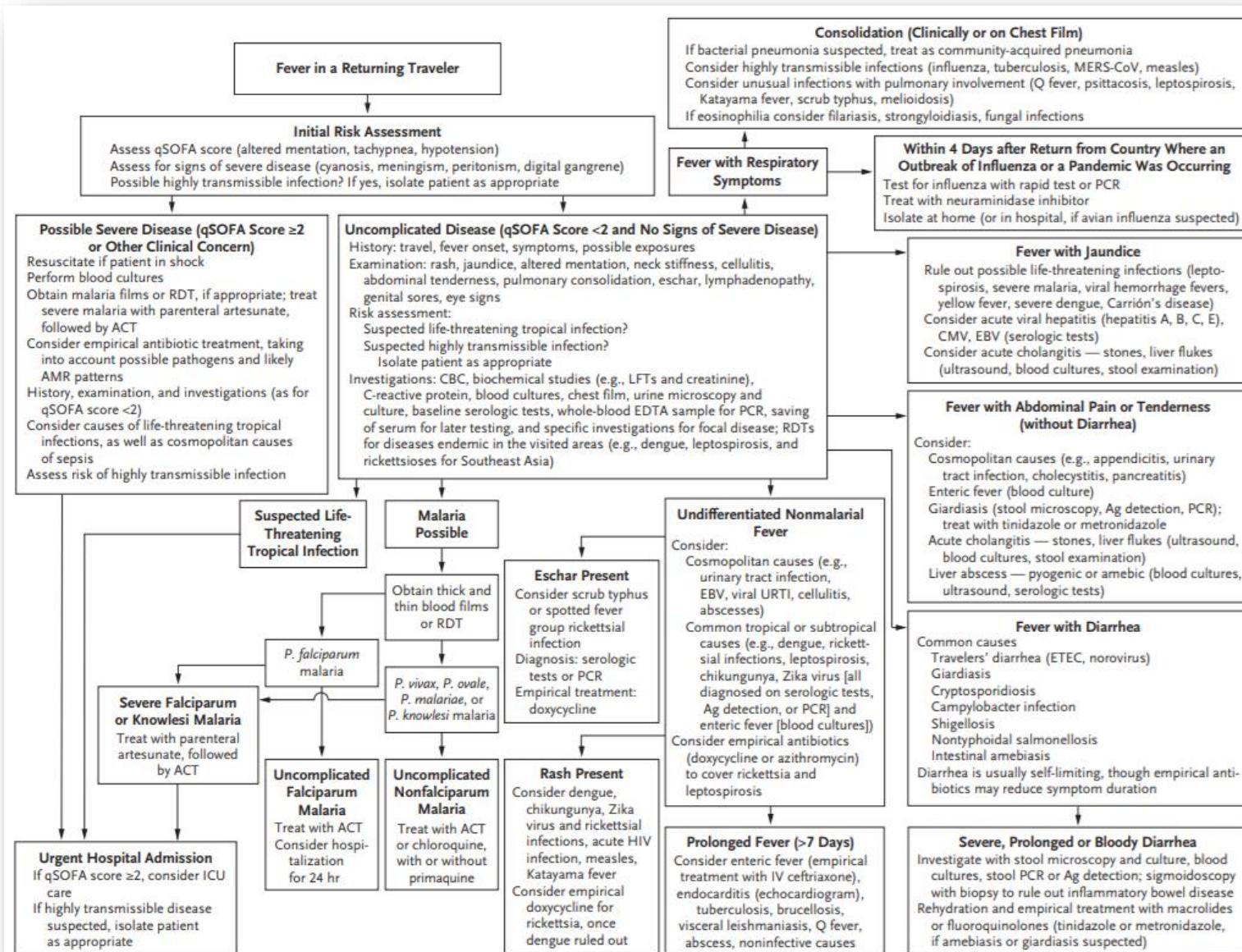
Fever with jaundice

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

| | |
|-----------------------|--------|
| Serious / very common | Red |
| Common | Yellow |
| Rare | Green |

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Fever in the returned traveller



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

Crimean–Congo fever (Bunyaviridae family)

Widespread area of endemicity, extending across much of Africa, the Middle East and into Asia. Reservoir and the vector: Ixodid (hard) ticks. Ruminants and domesticated animals can serve as amplifying hosts. Person to person transmission has been reported through bodily fluids, including through medical equipment

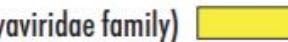
Ebola (Filoviridae family)

Countries reporting current outbreaks include Guinea, Sierra Leone, Liberia and Nigeria.

Historical outbreaks reported in several central African countries and South Africa. Natural reservoir: not yet confirmed, but may be bats. Consumption of bush meat is a risk factor. Person to person transmission is through bodily fluids, including through health-care equipment

Lassa (Arenaviridae family)

Countries reporting endemic disease include Guinea, Sierra Leone, Liberia and Nigeria, with periodic isolation reported in other West African countries. Reservoir: *Mastomys* (a rodent). Transmission is via contact with its urine and droppings or objects/food contaminated with them. Person to person transmission can occur through bodily fluids



Other identified viral haemorrhagic fevers include:

Lujo – South Africa

Chapare and Machupo – Bolivia

Kyasanur forest disease – India

Alkhurma – Saudi Arabia

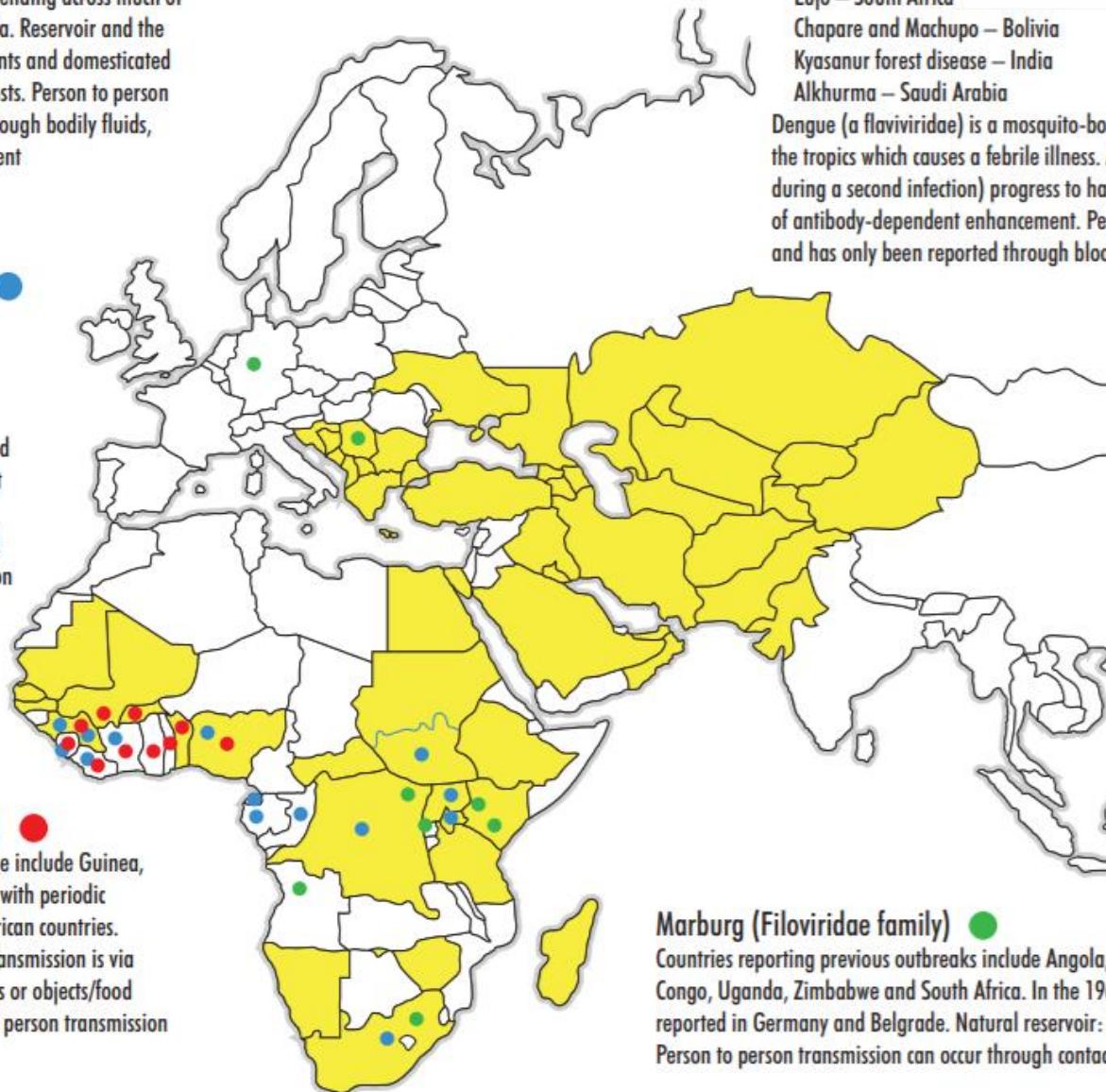
Guanarito – Venezuela

Junín – Argentina

Sabiá - Brazil

Omsk – Russia

Dengue (a flaviviridae) is a mosquito-borne virus prevalent across much of the tropics which causes a febrile illness. A small minority (more frequent during a second infection) progress to haemorrhagic shock through a process of antibody-dependent enhancement. Person to person transmission is rare and has only been reported through blood transfusion and transplantation



Marburg (Filoviridae family)

Countries reporting previous outbreaks include Angola, Democratic Republic of Congo, Uganda, Zimbabwe and South Africa. In the 1960s cases were also reported in Germany and Belgrade. Natural reservoir: animal, most likely bats. Person to person transmission can occur through contact with bodily fluids

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

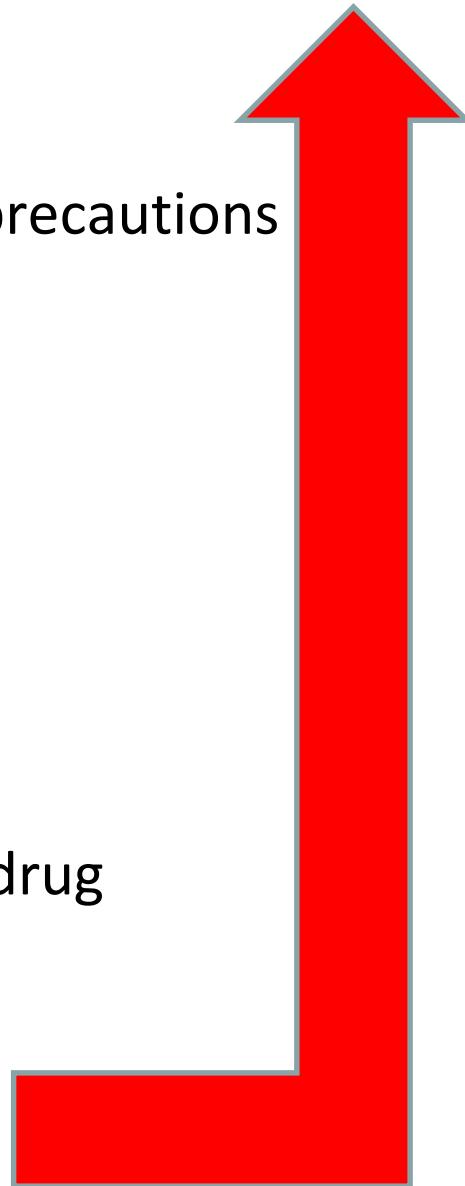


Step 2. Approach

- **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

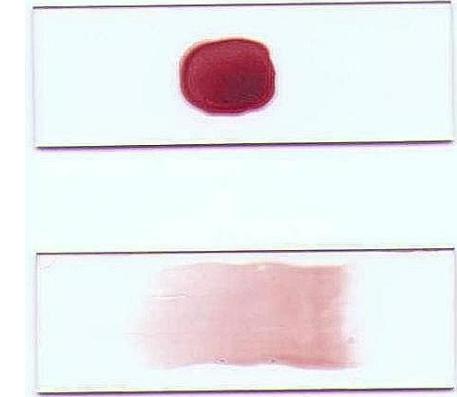
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Step 3.

Adopt a structured
approach to
investigation
pathways

Step 3. General investigations



| | | |
|----------------------|-----------------|---|
| 1. Malaria Film +RDT | | |
| 2. Malaria Film | ↓ Lymph | ? dengue ? viral |
| 3. Malaria Film | ↓ Plts | ? malaria ? DIC |
| 4. FBC/Clotting | ↑ Eosin | ? helminths |
| 5. U&E/LFT/CK | Transaminitis | EBV/CMV/ Enteric fever/Hepatitis viruses/ Leptospirosis/ Relapsing fevers/ Rickettsia/VHF |
| 6. Blood cultures | | |
| 7. Serum Save | | |
| 8. Urinalysis | Proteinuria | Leptospirosis |
| 9. Stool MCS/OCP | Haemoglobinuria | Malaria |
| 10.CXR | | |

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

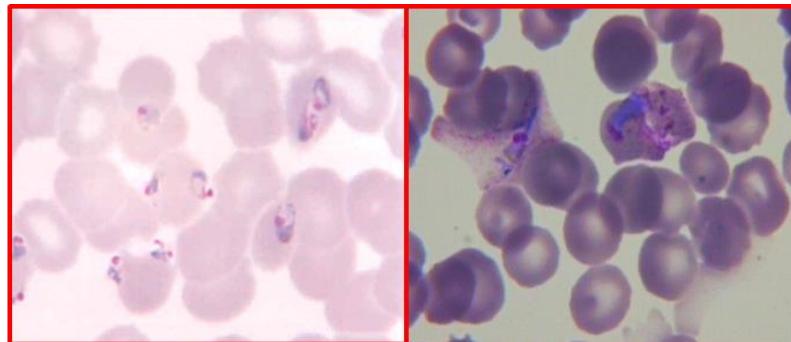
1. Malaria
2. Typhoid
3. Leptospirosis
4. Rickettsiae/Borrelia
5. Amoebiasis

Step 4. Infections managed supportively

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

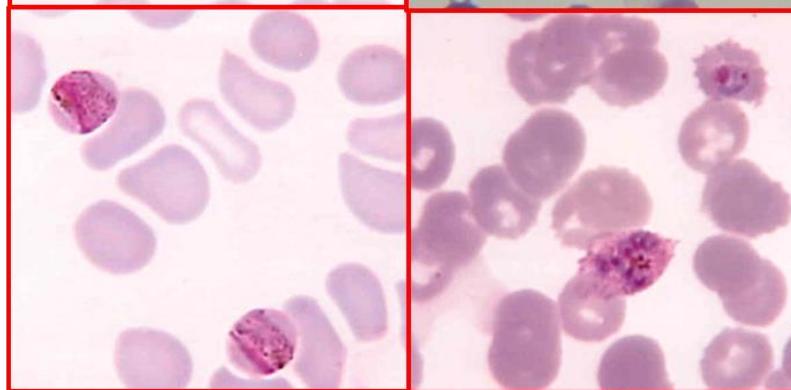
Malaria species cause human disease

P. falciparum



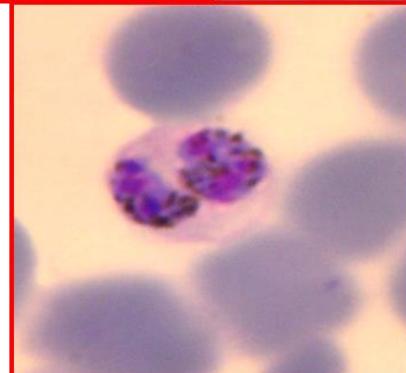
P. vivax

P. malariae



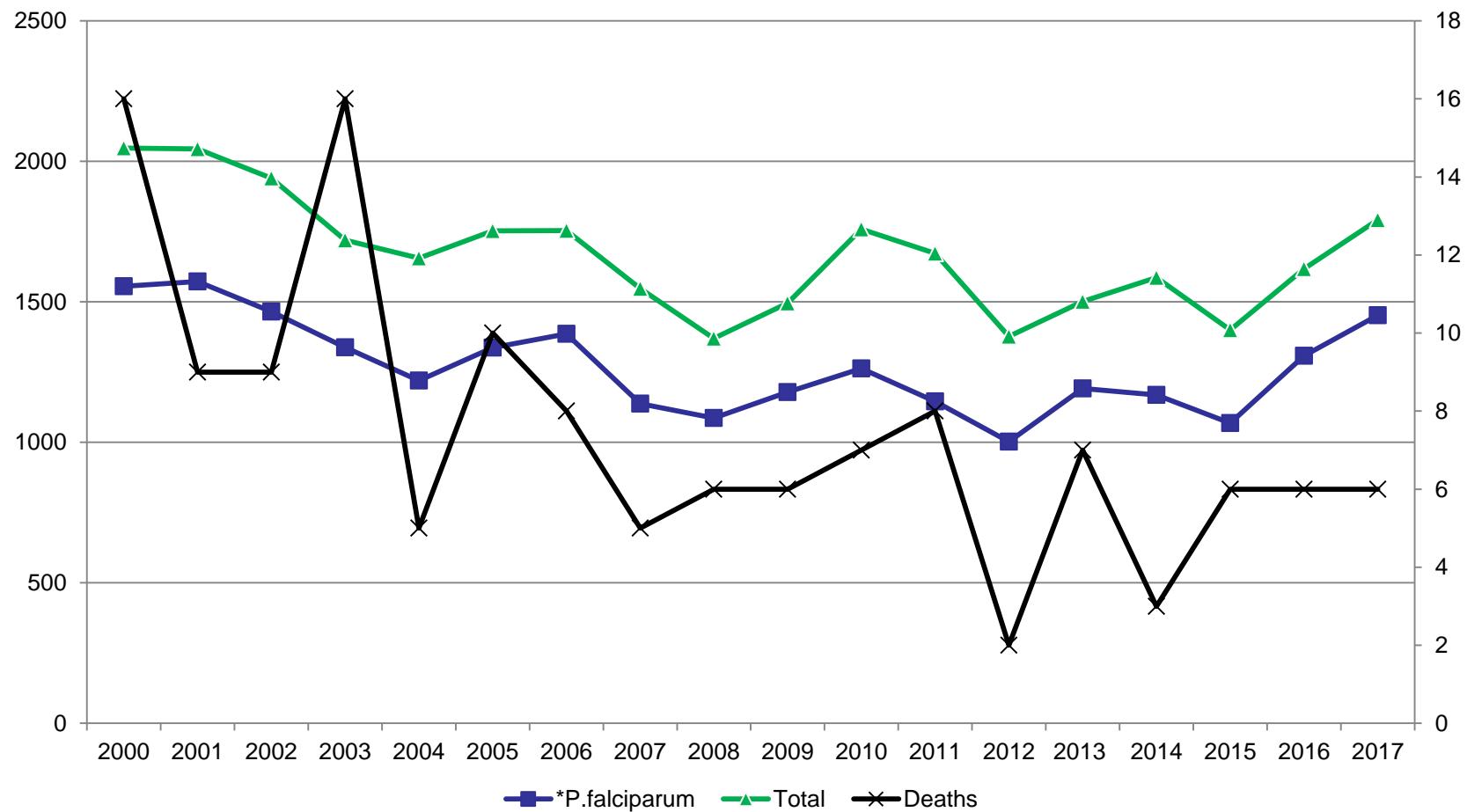
P. ovale

P. knowlesi



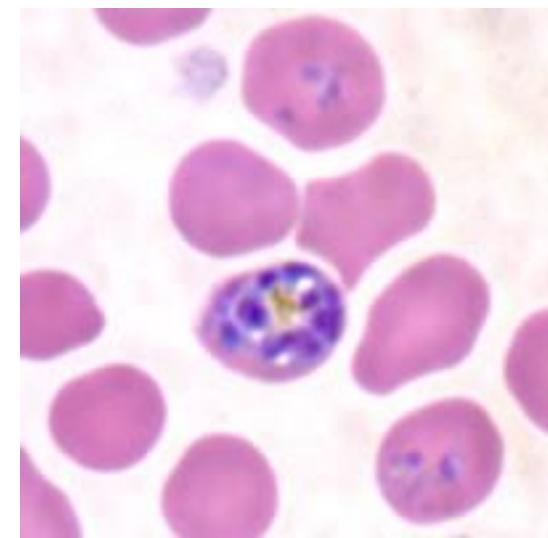
Courtesy: Dr Kesinee Chotivanich

UK Malaria cases & deaths



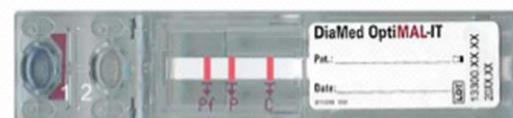
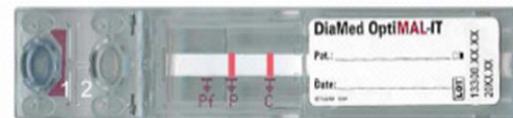
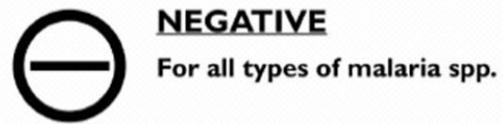
Clinical presentation of malaria

- 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



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.

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.

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.

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.

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 | |

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/>



The screenshot shows the ProMED-mail website. At the top, there is a header with a back and forward button, a search icon, and the URL 'www.promedmail.org'. Below the header is the ProMED-mail logo, which includes a globe icon and the text 'ProMED-mail' with 'INTERNATIONAL SOCIETY FOR INFECTIOUS DISEASES' underneath. The main navigation bar has links for 'ProMED-mail', 'Português', 'Español', and a language icon. The page features a 'Latest Posts on ProMED-mail' section with a list of recent health news items. The 'wellcome' trust logo is visible on the right side of the page.

Latest Posts on ProMED-mail

- 05 Aug 2015 Rabies - Ukraine: (KK) human, feline exposure
- 05 Aug 2015 Anthrax - Armenia: ex Georgia, human
- 05 Aug 2015 Legionellosis - USA (D5): (New York City) fatal, update
- 05 Aug 2015 NDM-1 carrying Gram-negative bacillus - France: (MR) poss ex Viet Nam, RFI
- 05 Aug 2015 Anthracnose, chili - Fiji
- 05 Aug 2015 Foot & mouth disease - Botswana (D4): (North West) bovine, st pending, OIE
- 05 Aug 2015 Undiagnosed disease, coconut palm - Guyana: (ES)
- 04 Aug 2015 MERS-CoV (100): Saudi Arabia, South Korea
- 04 Aug 2015 Hantavirus update - Americas (33): USA (IN)
- 04 Aug 2015 Rabies - Viet Nam, Indonesia: failing control
- 04 Aug 2015 Invasive mosquito - USA (D7): (AZ) comment
- 04 Aug 2015 Malaria vaccine: pediatric, positive opinion, EMA
- 04 Aug 2015 Anthrax - Uzbekistan (D2): (SA) human, NOT

Learning objectives

- Recall common tropical infectious diseases
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