Fever in the returning traveller

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Objectives

- •List the commonest diagnoses causing fever in the returning traveller
- Describe the geography, biology and pathophysiology of malaria
- •Explain the rationale for the clinical management of malaria
- Describe the pathophysiology and treatment of typhoid

Case 1

53 yr male

Owns gold mine in Ghana

Regular traveller

• 3/7 Hx fever, headache & myalgia

Case 2

55 yr male

Thailand 2 wks ago

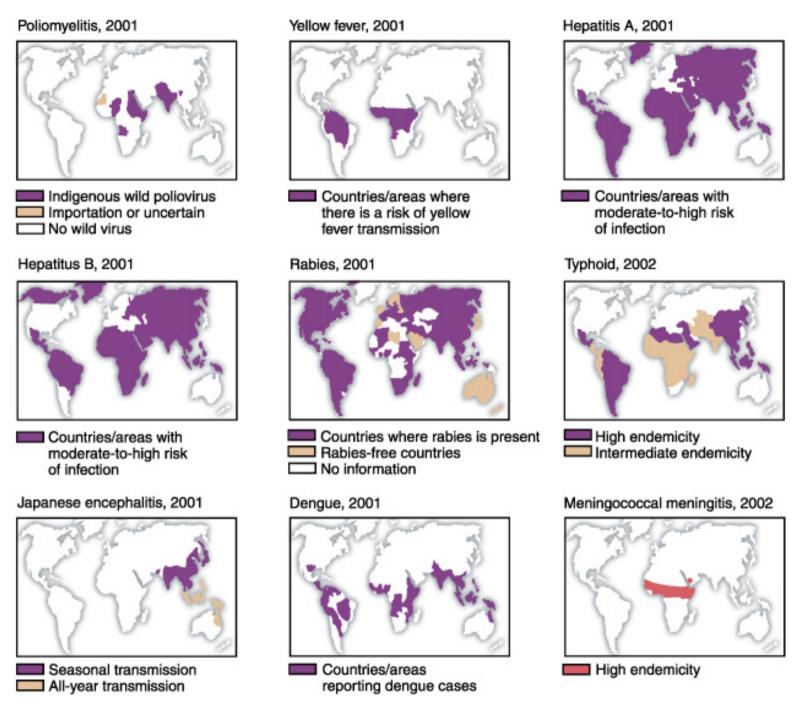
5/7 Hx fever, myalgia

• 1/7 Hx rash on chest & face

Diagnoses in the returning traveller

- Malaria
- Typhoid
- Travellers diarrhoea
- Pneumonia
- HIV Seroconversion

Where?



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When?

Short Incubation (<10 days)	Medium Incubation (10-21 days)	Long Incubation (>21 days)		
Malaria Arboviruses including dengue, yellow fever, Japanese encephalitis Hemorrhagic fevers—lassa, Ebola, South American arenaviruses Respiratory viruses including SARS Typhoid and paratyphoid Bacterial enteritis Rickettsia—spotted fever group: RMSF, African tick typhus, Mediterranean spotted fever, Scrub typhus, Q fever Bacterial pneumonia including Legionella Relapsing fever Amebic dysentery Meningococcemia Brucella (rarely) Leptospirosis Fascioliasis Rabies (rarely) African trypanosomiasis (acute),	Malaria Flaviviruses—tickborne encephalitis and Japanese encephalitis Hemorragic fevers—Lassa, Ebola, Crimean-Congo hemorrhagic fever Acute human immunodeficiency virus Typhoid and paratyphoid Giardia Rickettsia—fleaborne, louse borne, and scrub typhus, Q fever, Spotted fevers (rare). Cytomegalovirus Toxoplasma Amebic dysentery Histoplasmosis Brucella Leptospirosis Babesiosis Rabies African trypanosomiasis (acute), east African Hepatitis A (rarely) Measles	Malaria Schistosomiasis Tuberculosis Acute HIV Viral hepatitis Filariasis Rickettsia—Q fever Secondary syphilis EBV including mononucleosis Amebic liver disease Leishmaniasis Brucella Bartonellosis (chronic) Babesiosis Rabies African trypanosomiasis (chronic Cytomegalovirus		

"Diseases that commonly have variable incubation periods are shown more than once. However, most diseases may rarely have an atypical incubation period and this is not shown here.

SARS, severe acute respiratory syndrome; RMSF, Rocky Mountain Spotted Fever.

- 2000 cases in UK per annum
- 75% Plasmodium falciparum
- 20 deaths per annum
- There are no typical clinical features!
 - Not even fever

» Journal of Infection (2007) 54: 111-121

• 2 billion cases worldwide per annum

1-2 million deaths

Globally malaria is a disease that kills children



Causes maternal anaemia, LBW, prem



90% of 1 million malarial deaths/yr are African children

Malaria in the UK

UK falciparum malaria is a disease of adults

Data from the Malaria Reference Laboratory, LSHTM, R Behrens, 2002-3 (n=3012)

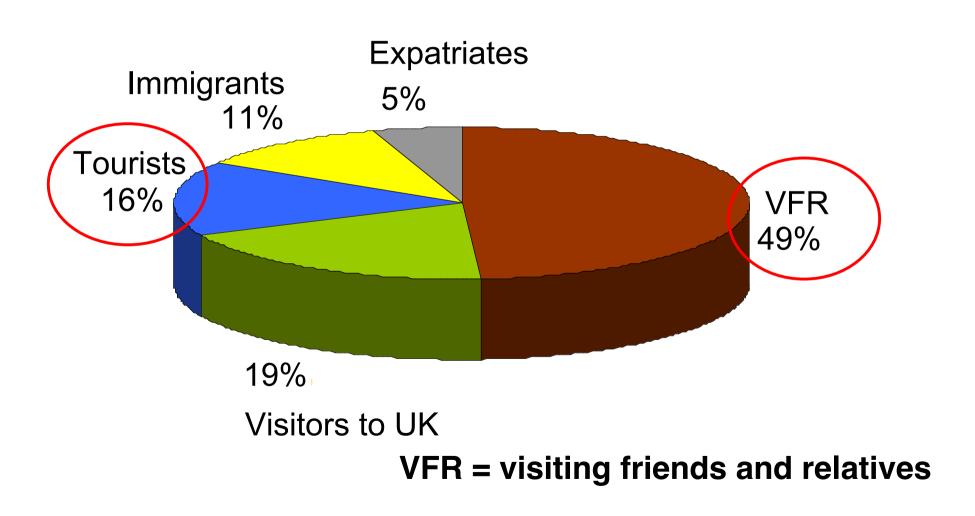
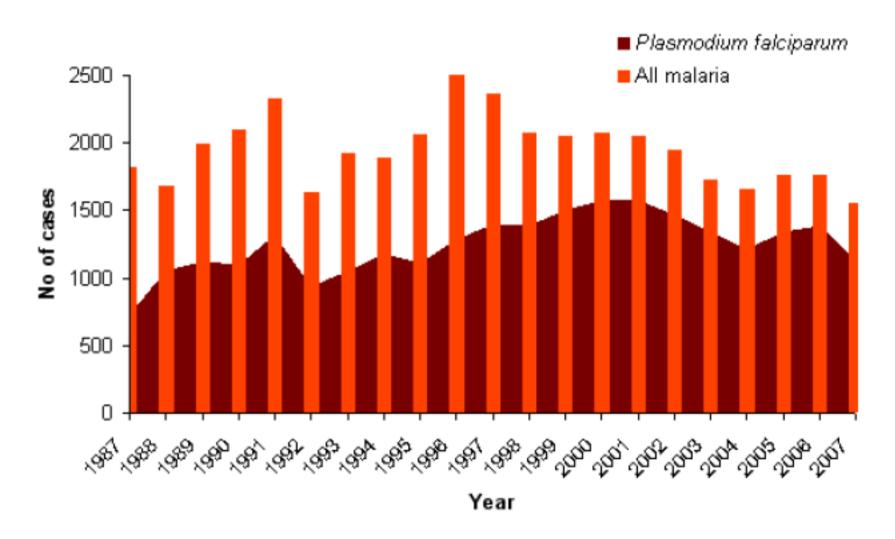


Figure 1. Imported malaria cases (with P. falciparum cases) in the UK: 1987- 2007



There were 1548 cases of malaria reported in 2007, a slight decline on the 1758 cases of malaria reported by this stage in 2006. (It is possible that a few cases have still to be reported).

Geography

Worldwide transmission of malaria

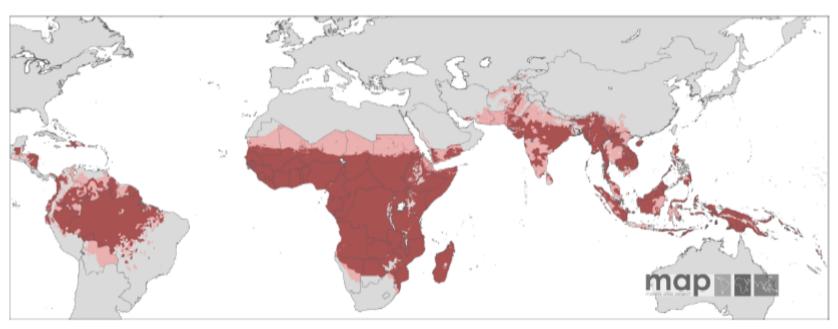


Figure 1. P. falciparum Malaria Risk Defined by Annual Parasite Incidence (top), Temperature, and Aridity (bottom)

Areas were defined as stable (dark-red areas, where $PfAPI \ge 0.1$ per thousand pa), unstable (pink areas, where PfAPI < 0.1 per thousand pa), or no risk (light grey). The few areas for which no PfAPI data could be obtained, mainly found in India, are coloured in dark grey. The borders of the 87 countries defined as P. falciparum endemic are shown. Highland areas where risk was excluded due to temperature appear in light grey. The aridity mask excluded risk in a step-wise fashion, reflected mainly in the larger extents of unstable (pink) areas compared to the top panel, particularly in the Sahel and southwest Asia (southern Iran and Pakistan). doi:10.1371/journal.pmed.0050038.g001

Source: Guerra Plos Med 08

Table 1. Cases of malaria by species of parasite and primary region of travel, United Kingdom: 2007

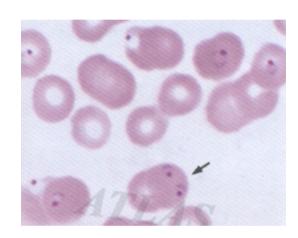
	Geographic Area	P.falciparum.	P.vivax	P.malariae	P.ovale	Pf/Pv	Pf/Pm	Pf/Po	Pm/Pv	Total
I	North Africa	-	-	-	-	-	-	-	-	0
1	Central Africa	23	-	2	2	-	-	-	-	27
$ar{4}$	East Africa	92	8	10	11	-	1	-	1	123
	Southern Africa	31	1	1	1	-	-	-	-	34
abla	West Africa	719	2	11	67	1	3	5	-	808
	Africa - unspec.	12	1	-	1	-	-		-	14
	Middle East	1	-	-	-	-	-	-	-	1
abla	Asia	22	168	-	1	2	-	-	-	193
l	Asia - unspecified	-	1	-	-	-	-	-	-	1
	Far East/SE Asia	1	3	-	-	-	-	-	-	4
	Far East - unspec.	-	1	-	-	-	-	-	-	1
	Central/S. America	2	11	-	1	-	-	-	-	14
	Oceania	1	14	-	-	-	-	-	-	15
	Not given	235	46	6	24	1	1	-	-	313
abla	Total	1139	256	30	108	4	5	5	1	1548

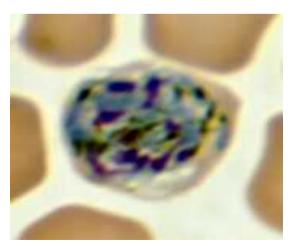
History of discovery

- Sir Ronald Ross
 - Life cycle of malaria in *Culex* mosquito
 - Vector borne disease
 - Nobel Prize 1902
- Charles Laveran
 - Proved that protozoan causes malaria
 - Anopheles mosquito in human disease
 - Nobel Prize 1907

Biology & Pathophysiology

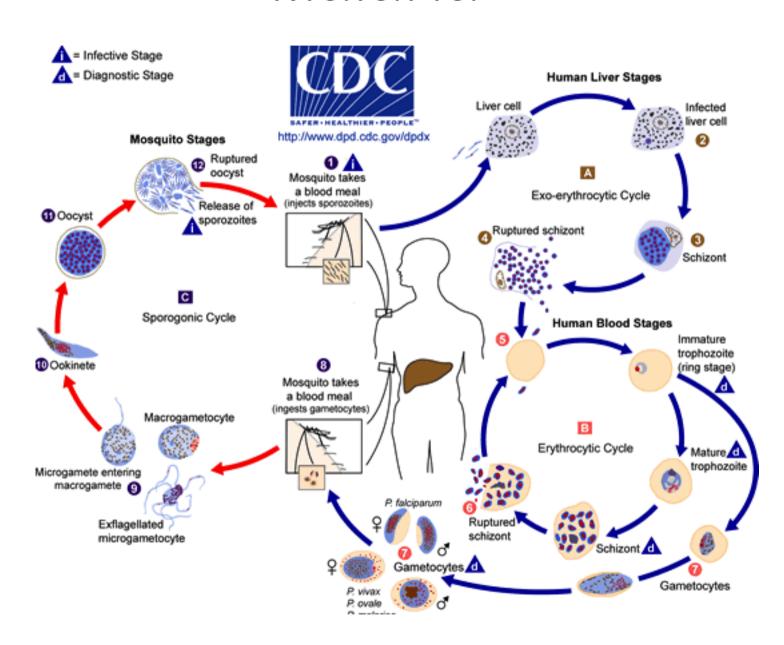
- Protozoan
- Apicomplexa
 - Toxoplasmosis
 - Cryptosporidium
- Plasmodium
 - falciparum
 - malariae
 - ovale
 - vivax

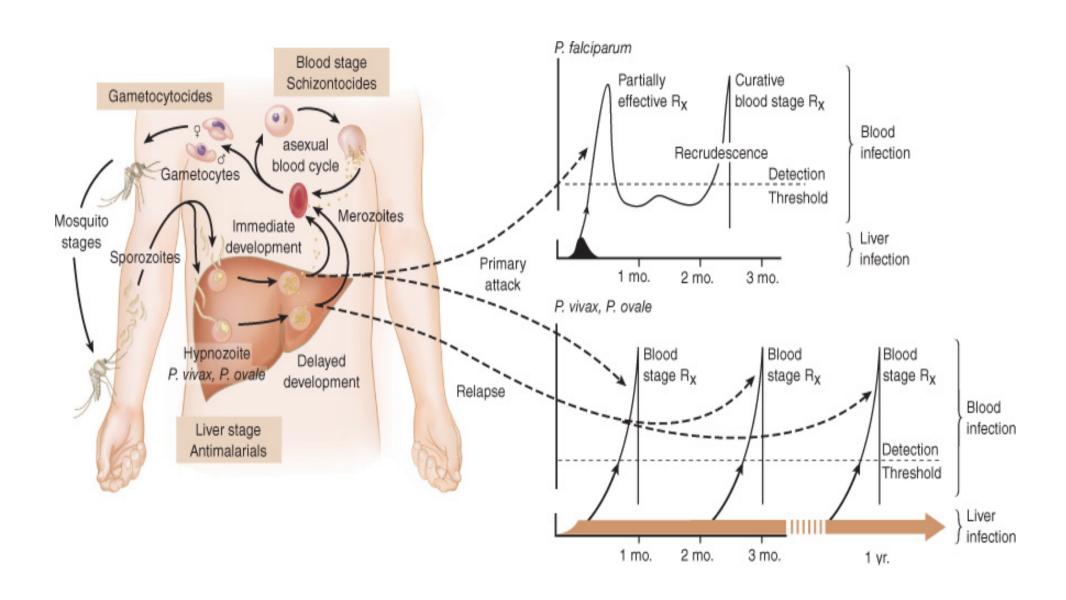




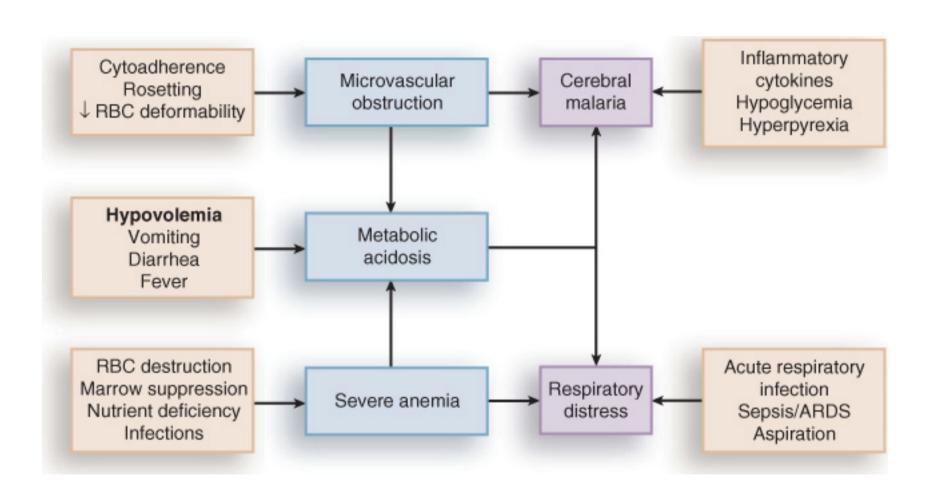
- Anopheles mosquito (vs Culex)
 - Definitive host
- Night time
- Heat & CO₂ sensors
- Female mosquito
 - Blood proteins for egg







Mandell, Principles & Practice of Infectious Diseases. Elsevier, 2004



Diagnosis of Malaria

Clinical symptoms

Common

Uncommon

Fever

Flu like illness

Headache

Back pain

Myalgia

Nausea

Vomiting

Rigors

Diarrhoea

Abdominal

cramps

Cough

Dark urine

Confusion

Clinical signs

Common Uncommon

Fever Focal neurology

Nothing

Reduced

GCS/coma

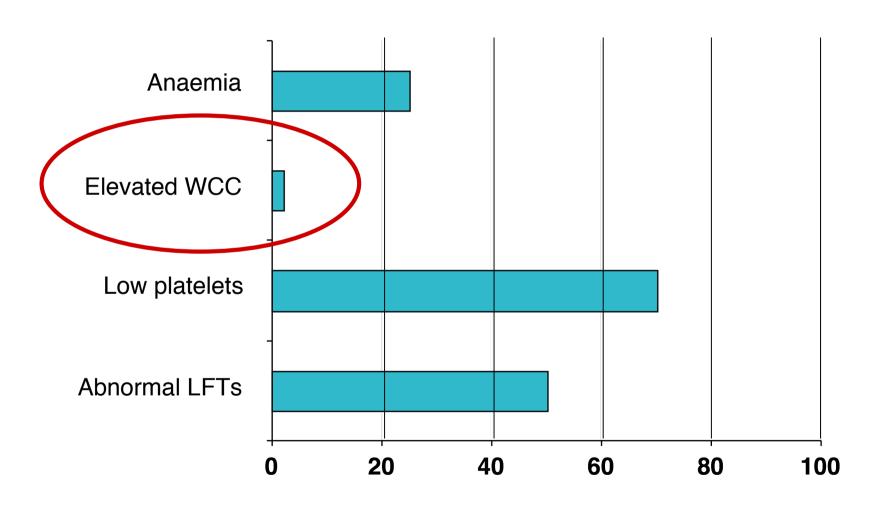
Shock

Splenomegaly

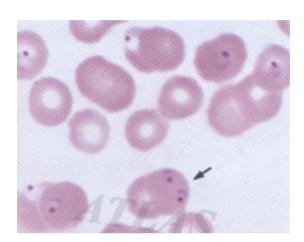
Hepatomegaly

Uncomplicated falciparum malaria at presentation

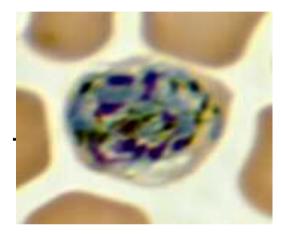
Froude JR et al Clin Infect Dis 1992;15:774



- Thin film
 - parasitaemia
- Antigen test
- falciparum vs non-falciparum
- Severe vs non-severe / uncomplicated

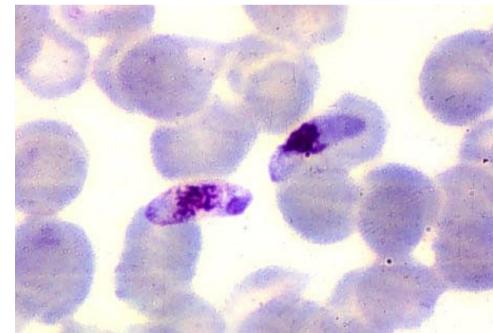


Thin film



Schizonts





Features of severity

Box 2. Major features of severe or complicated falciparum malaria in adults

- Impaired consciousness or seizures
- Renal impairment (oliguria < 0.4 ml/kg bodyweight per hour or creatinine > 265µmol/l)
- Acidosis (pH < 7.3)
- Hypoglycaemia (<2.2 mmol/l)
- Pulmonary oedema or acute respiratory distress syndrome (ARDS)
- Haemoglobin ≤ 8 g/dL
- Spontaneous bleeding/disseminated intravascular coagulation
- Shock (algid malaria BP < 90/60 mmHg)
- Haemoglobinuria (without G6PD deficiency)

Other indications for parenteral therapy; High parasitaemia >2%, pregnancy, vomitting

Source: BIS guidelines 2008

Management of *P.falciparum*

Management

Malaria - Algorithm for Initial Assessment and Management in Adults

Important information

- Malaria occurs in the tropics and sub-tropics
- Adherence to chemoprophylaxis does not exclude malaria
- All cases should be discussed with a specialist with current experience of managing malaria
- Notify all cases to the local health protection unit, send blood films to reference laboratories

Triage

- All febrile or ill patients with a history of travel to a malaria area in the prior 6 months should be assessed urgently (Incubation for non-falciparum infection may occasionally be greater than 6 months)
- For those within 3 weeks of return, discuss infection control requirements (eg viral haemorrhagic fever (VHF), avian influenza or SARS) with the duty microbiologist but do NOT delay blood film

Early diagnosis and assessment of severity is vital to avoid malaria deaths

Expert Advice

Local infectious disease unit or Liverpool 0151 706 2000 London 0845 155 5000 Ask for duty tropical doctor

Useful information

British National Formulary UK malaria treatment guidelines Lalloo DG et al. J Infect 2007; 54: 111-21 from www.hpa.org.uk or www.britishinfectionsociety.org

Key points in history and examination - no symptoms or signs can accurately predict malaria

- Symptoms are non-specific, but may include: fever/sweats/chills, malaise, myalgia, headache, diarrhoea, cough, jaundice, confusion and seizures
- Consider country of travel, including stopovers, and date of return; falciparum malaria is most likely to occur within 3 months of return, but this may be longer in those who have taken chemoprophylaxis or partial treatment. The incubation period for malaria is at least 6 days
- Consider what malaria prophylaxis was taken (ie drug, dose & adherence): Correct prophylaxis with full adherence does not exclude malaria
- Consider other travel-related infections: eg typhoid fever, hepatitis, dengue fever, avian influenza, SARS, HIV, meningitis/encephalitis and VHF
- Examination findings are non-specific

Urgent investigations - all patients should have:

- Thick & thin blood films and malaria rapid immediately and ask for a result within one
- Full blood count (FBC) for thrombocytopenia, urea & electrolytes (U&Es), liver function tests (LFTs) and blood glucose
- Blood culture(s) for typhoid and/or other
- Urine dipstick (for haemoglobinuria) and culture. If the patient has diarrhoea, send faeces for microscopy and culture
- Chest radiograph to exclude community-

If falciparum malaria is confirmed

- Ask the laboratory to estimate the parasite count ie % of RBCs parasitises
- Clotting screen, arterial blood gases and 12-lead ECG are required in complicated infection (see below)
- Do a pregnancy test if there is a possibility of pregnancy; pregnant women are at higher risk of

Blood tests show

Non-falciparum malaria

Non-falciparum antimalarials

Chloroquine (base) 600mg followed by 300mg at 6, 24 and 48 hours. In vivax

and ovale after treatment of acute

ovale) for 14 days to eradicate liver parasites; G6PD must be measured

Falciparum antimalarials

b) Malarone®: 4 'standard' tablets daily

c) Riamet®: If weight >35kg, 4 tablets

then 4 tablets at 8, 24, 36, 48 and

before primaquine is given – seek expert advice if low

infection use primaguine (30mg base/day for vivax, 15 mg/day for

- Vivax
- Outpatient therapy usually appropriate
- Malariae
- depending on clinical judgement

Falciparum malaria

- Falciparum
- Mixed infection Species not characterise

Admit all cases to hospital Assess severity on admission

No evidence of malaria

A single negative film and/or antigen test does not exclude malaria

Stop prophylaxis until malaria excluded

Empirical therapy for malaria should be

Seek expert advice before commencing

Complicated malaria = one or more of:

- Impaired consciousness (measure GCS and MSQ) or seizures check blood glucose urgently
- Hypoglycaemia
- Parasite count ≥2% (lower counts do not exclude severe malaria).
- Spontaneous bleeding/disseminated intravascular coagulation
- Haemoglobinuria (without G6PD deficiency)
- Renal impairment or electrolyte/acid-base disturbance (pH <7.3)
- Pulmonary oedema or adult respiratory distress syndrome
- Shock (algid malaria): may be due to Gram negative bacteraemia
- this (see contact numbers above) Blood films daily for 2 more days
- Malaria is unlikely with 3 negative blood films. Consider other travel and non-travel illness
- Finish chemoprophylaxis

Essential features of general management

- Commence antimalarials immediately (see boxes) Uncomplicated: Severe malaria a) Oral quinine 600mg/8h plus doxycycline 200mg daily (or clindamycin 450mg/8hr) for 7 days
 - Consider admission to high dependency/intensive care
 - Seek early expert advice from an infection or tropical unit.

 - Careful fluid balance (observe JVP, lying/sitting BP and urine) output). Avoid hypovolaemia. Over-hydration may induce pulmonary oedema; consider CVP monitoring
 - Monitor blood glucose regularly (especially during IV quinine)
 - ECG monitoring (especially during IV guinine).
 - 4-hourly observations until stable: ie pulse, temperature, BP, RR, SaO2, urine output & GCS. Regular medical review until stable
 - Repeat FBC, clotting, U&Es, LFTs and parasite count daily
 - In shock, treat for Gram negative bacteraemia

Falciparum antimalarials

Complicated or if patient is

EITHER Quinine 20mg/kg loading dose (no loading dose if patient taking quinine or mefloquine already) as IVI in 5% dextrose over 4hr and then 10mg/kg as IVI over 4h every 8 hr plus oral doxycycline 200mg daily for 7 days (In pregnancy, use IV/oral clindamycin 450mg/8hr). Max quinine dose 1.4 g

OR If available, artesunate intravenously complete a course of seven days plus

When patient is stable & able to swallow switch to oral quinine 600mg/8hr plus doxycycline 200mg daily (or clindamycin 450mg/8hr) to complete 7 days

For more detail: **BIA/HPA** website



60 hours

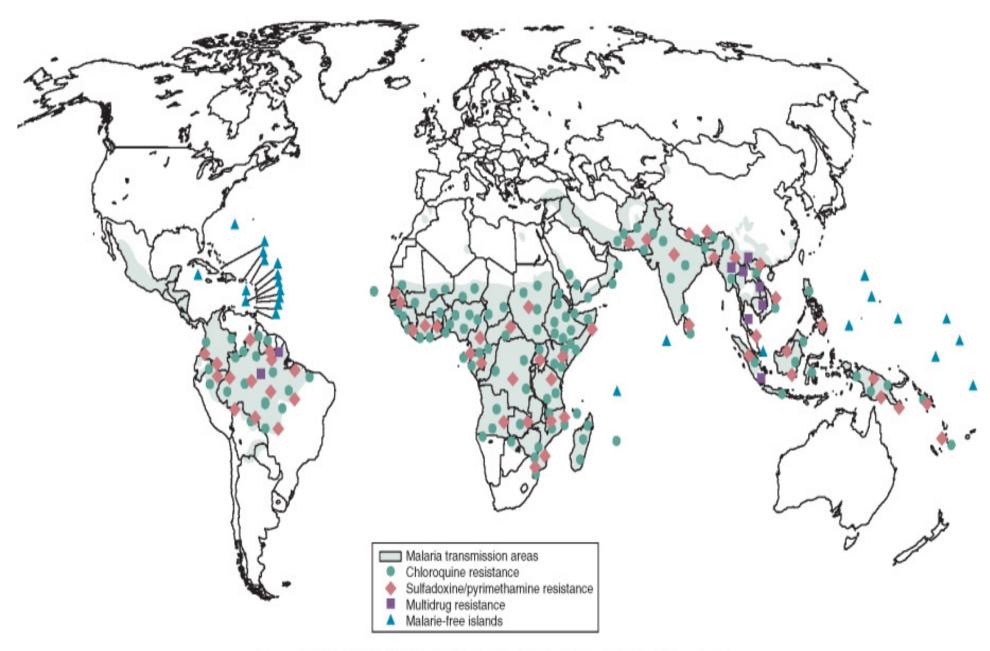


Treatments

Mild	Severe			
Quinine+ doxy Atovoquone/ Proguanil	Quinine			
ACT	Artemisinins			
co-artem- artemether/lumefantrine)	With Doxycycline			

Malaria

- Call HTD or local ID unit
- ECG +/- cardiac monitor
- Quinine sulphate
 - iv 20mg/Kg loading
 - iv 10mg/Kg TDS (HOURLY GLU)
 - 600mg TDS PO
- Daily parasitaemia, FBC, U&E
- Doxycycline



Mandell, Principles & Practice of Infectious Diseases. Elsevier, 2004

Artesunate v quinine for severe falciparum malaria

- Declining efficacy of quinine in SE Asia
- Rapid parasite clearance with artesunate
- Prospective open label RCT
- 1461 adults & children (15%)
- Bangladesh (453); India (142);
- Indonesia (289); Myanmar (577)
- Severe malaria
- IV therapy plus routine care



Source: Dondorp-A et al SEAQAMAT group, Lancet 2005; 366: 717-25

SEAQUAMAT

Deaths

Artesunate 15%

107 / 730

Odds Ratio = 0.60

(0.45 - 0.79) p = 0.0002

RRR 35%

ARR 7%

NNT 14 (11 – 20)

Quinine 22% 164 / 731



Source: Dondorp-A et al SEAQAMAT group, Lancet 2005; 366: 717-25

Prevention

- Avoid being bitten
 - Repellant
 - Bed nets
- Prophylaxis
- Vaccine

UK falciparum malaria is a disease of adults

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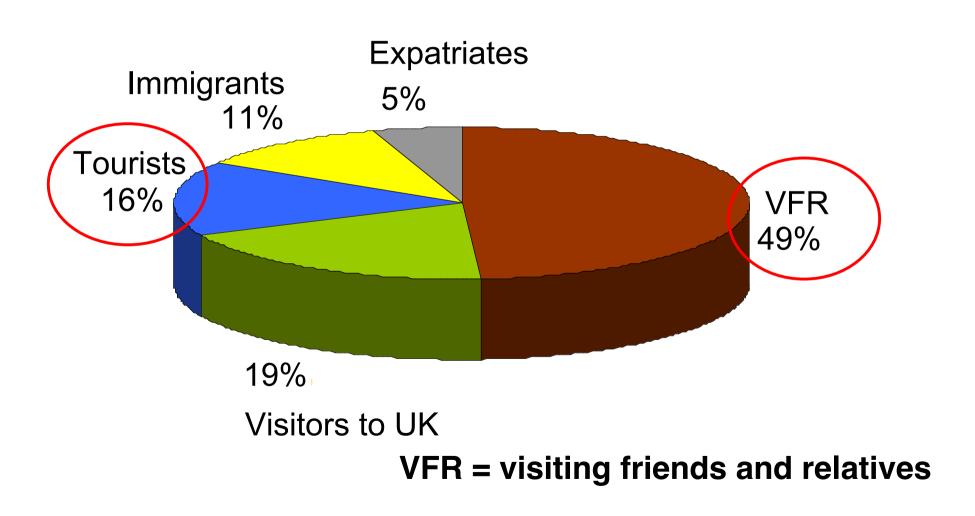
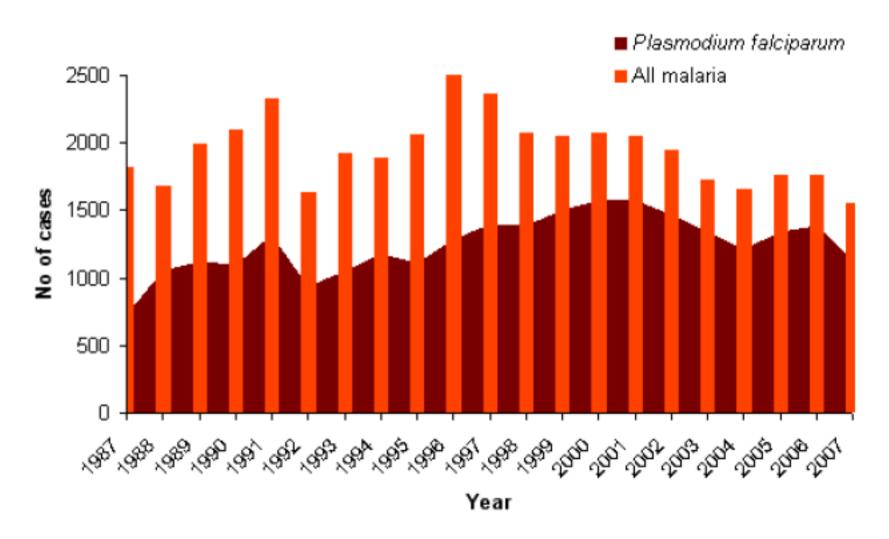


Figure 1. Imported malaria cases (with P. falciparum cases) in the UK: 1987- 2007



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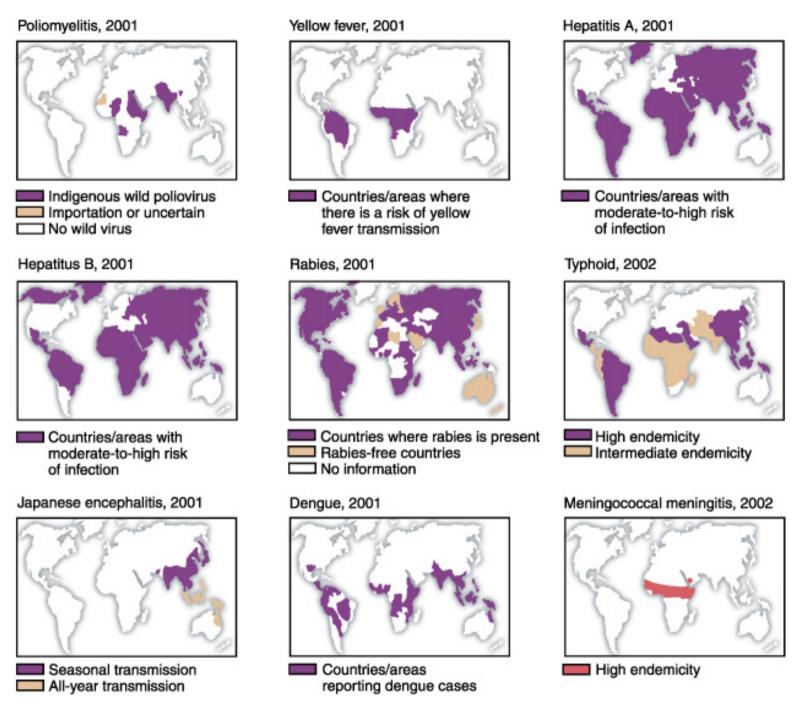
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abla	Total	1139	256	30	108	4	5	5	1	1548

- Enteric fever
- Salmonella species
 - typhi
 - Paratyphi
- 16 million cases worldwide
- 600,000 deaths

Transmitted in food & water

- Gram neg bacillus
 - TLR 4
- Anaerobic
- S.typhi & paratyphi only infect humans
- Infects Peyers patches



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- Clinically
 - Fever
 - Headache
 - Abdominal pain
 - Diarrhoea or constipation
 - Rose spots (30%)
 - Relative bradycardia (non-specific & <50%)
 - Hepatosplenomegaly (50%)
- Chronic carriage
 - Gallstones
 - Immunosuppression

- Diagnosis
 - Hx
 - Blood cultures
 - Stool
- Management
 - i.v fluids
 - Oral or iv antibiotics
 - Ciprofloxacin resistance
 - Cephalosporins
- Infection control
- Notifiable disease

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- •Explain the rationale for the clinical management of malaria
- Describe the pathophysiology and treatment of typhoid