

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?

Poliomyelitis, 2001



Indigenous wild poliovirus
 Importation or uncertain
 No wild virus

Yellow fever, 2001



Countries/areas where there is a risk of yellow fever transmission

Hepatitis A, 2001



Countries/areas with moderate-to-high risk of infection

Hepatitis B, 2001



Countries/areas with moderate-to-high risk of infection

Rabies, 2001



Countries where rabies is present
 Rabies-free countries
 No information

Typhoid, 2002



High endemicity
 Intermediate endemicity

Japanese encephalitis, 2001



Seasonal transmission
 All-year transmission

Dengue, 2001



Countries/areas reporting dengue cases

Meningococcal meningitis, 2002



High endemicity

When?

TABLE 329-2 Incubation Periods of Common Travel-Related Infections*

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

*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.

Malaria

Malaria

- 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

Malaria

- **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)

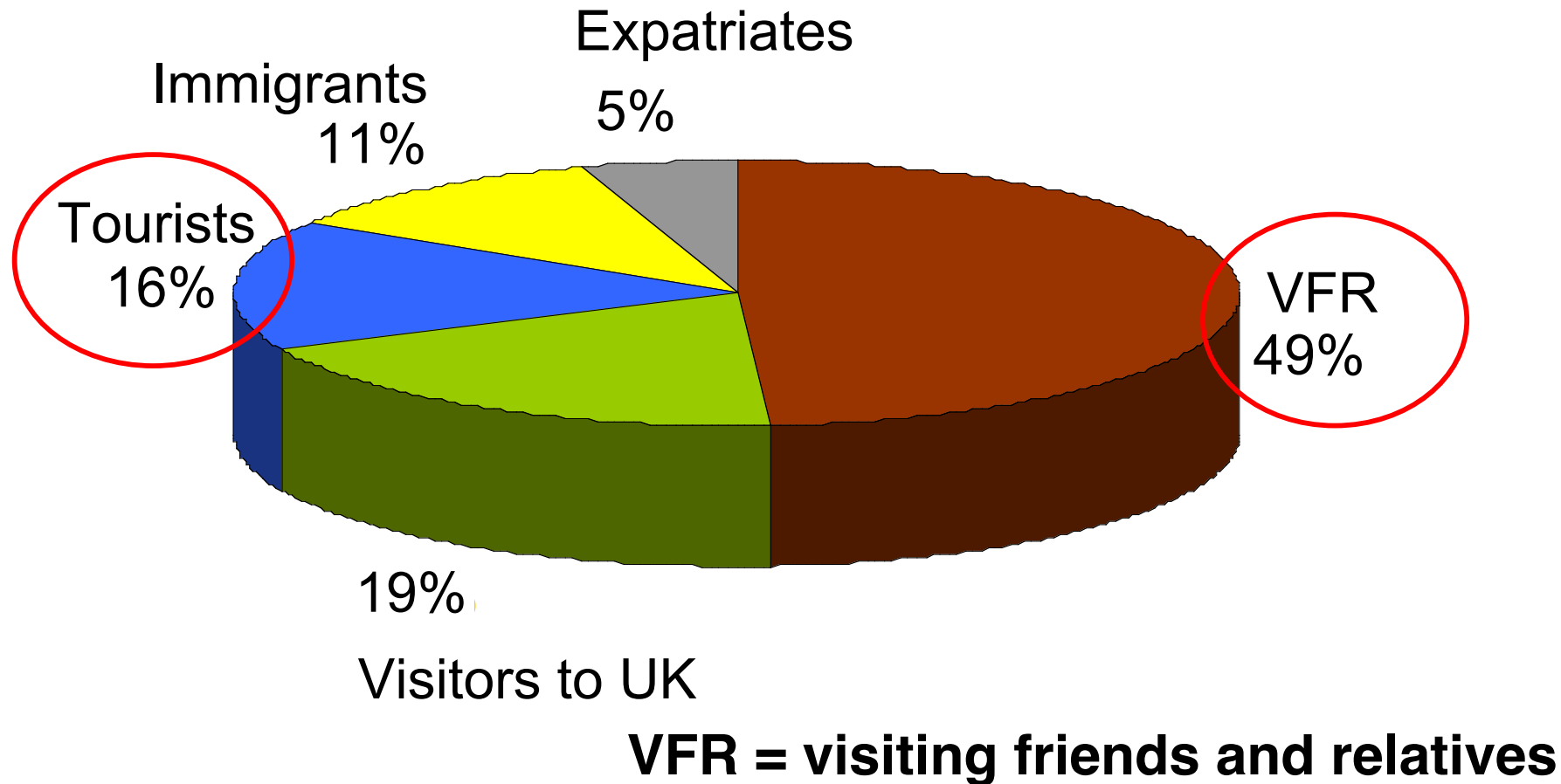
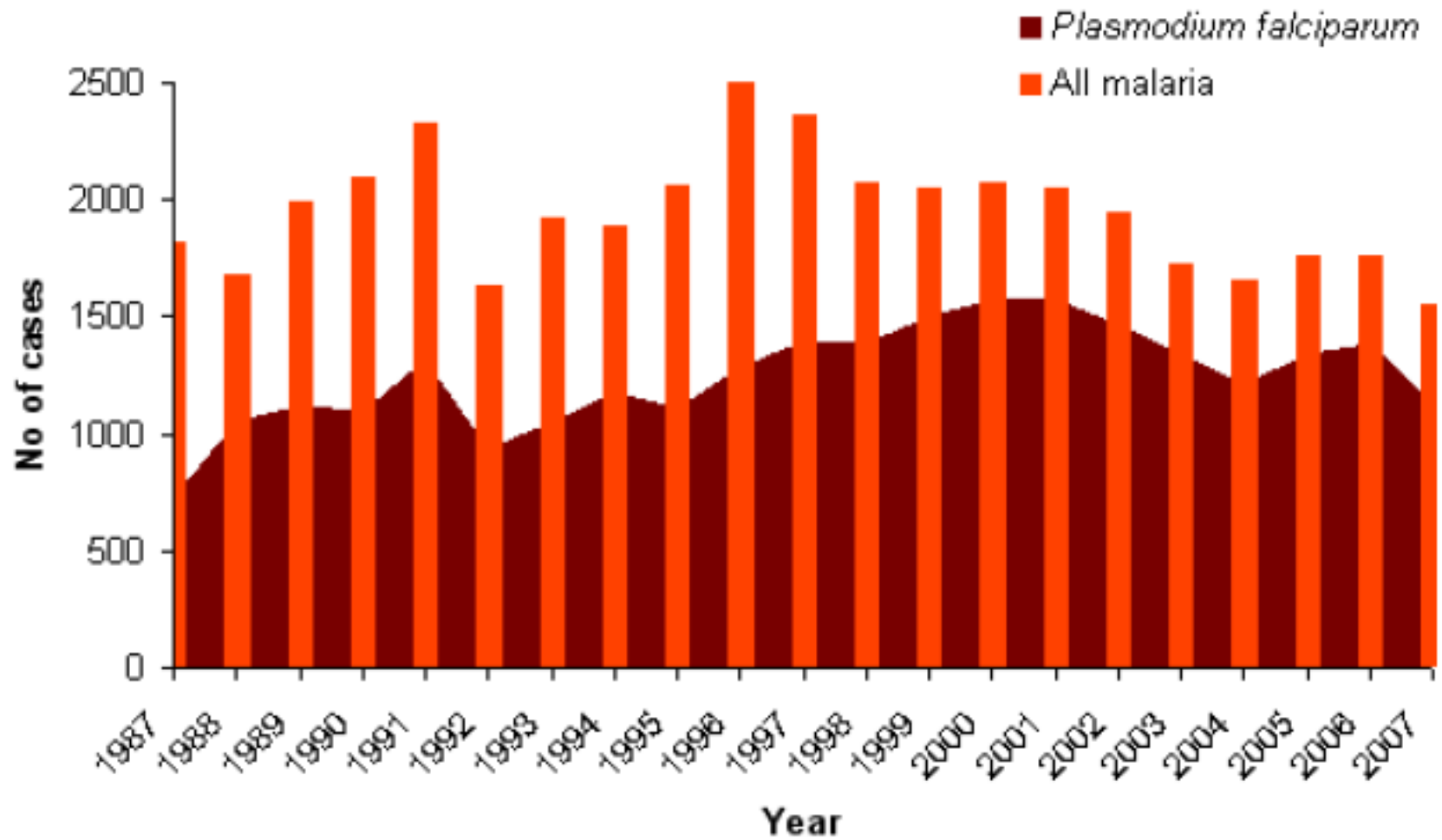


Figure 1. Imported malaria cases (with *P. falciparum* cases) in the UK: 1987- 2007



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

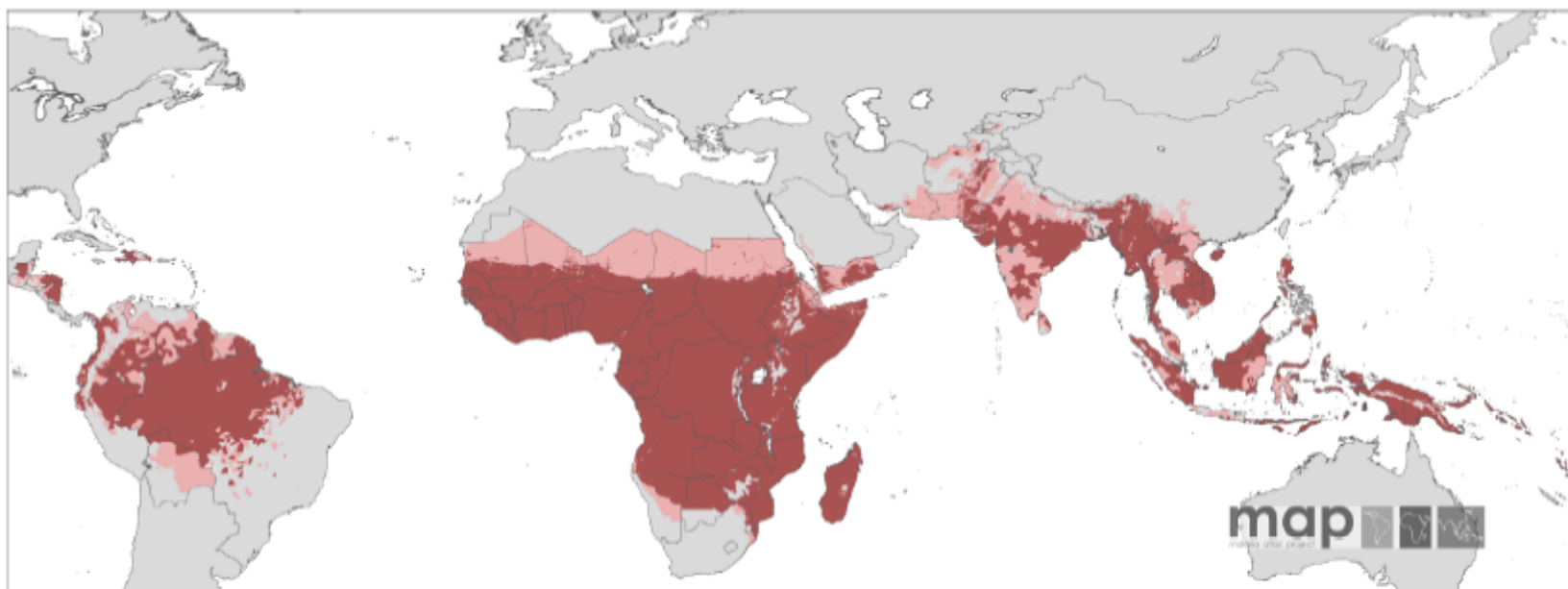


Figure 1. *P. falciparum* Malaria Risk Defined by Annual Parasite Incidence (top), Temperature, and Aridity (bottom)

Areas were defined as stable (dark-red areas, where $PfAPI \geq 0.1$ 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

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
North Africa	-	-	-	-	-	-	-	-	0
Central Africa	23	-	2	2	-	-	-	-	27
East Africa	92	8	10	11	-	1	-	1	123
Southern Africa	31	1	1	1	-	-	-	-	34
West Africa	719	2	11	67	1	3	5	-	808
Africa - unspec.	12	1	-	1	-	-	-	-	14
Middle East	1	-	-	-	-	-	-	-	1
Asia	22	168	-	1	2	-	-	-	193
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
Total	1139	256	30	108	4	5	5	1	1548

History of discovery

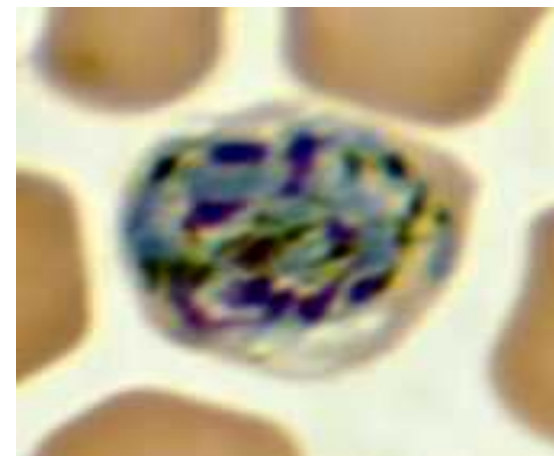
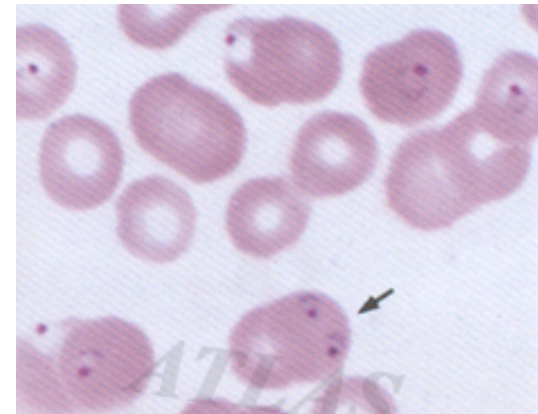
Malaria

- **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**

Malaria

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

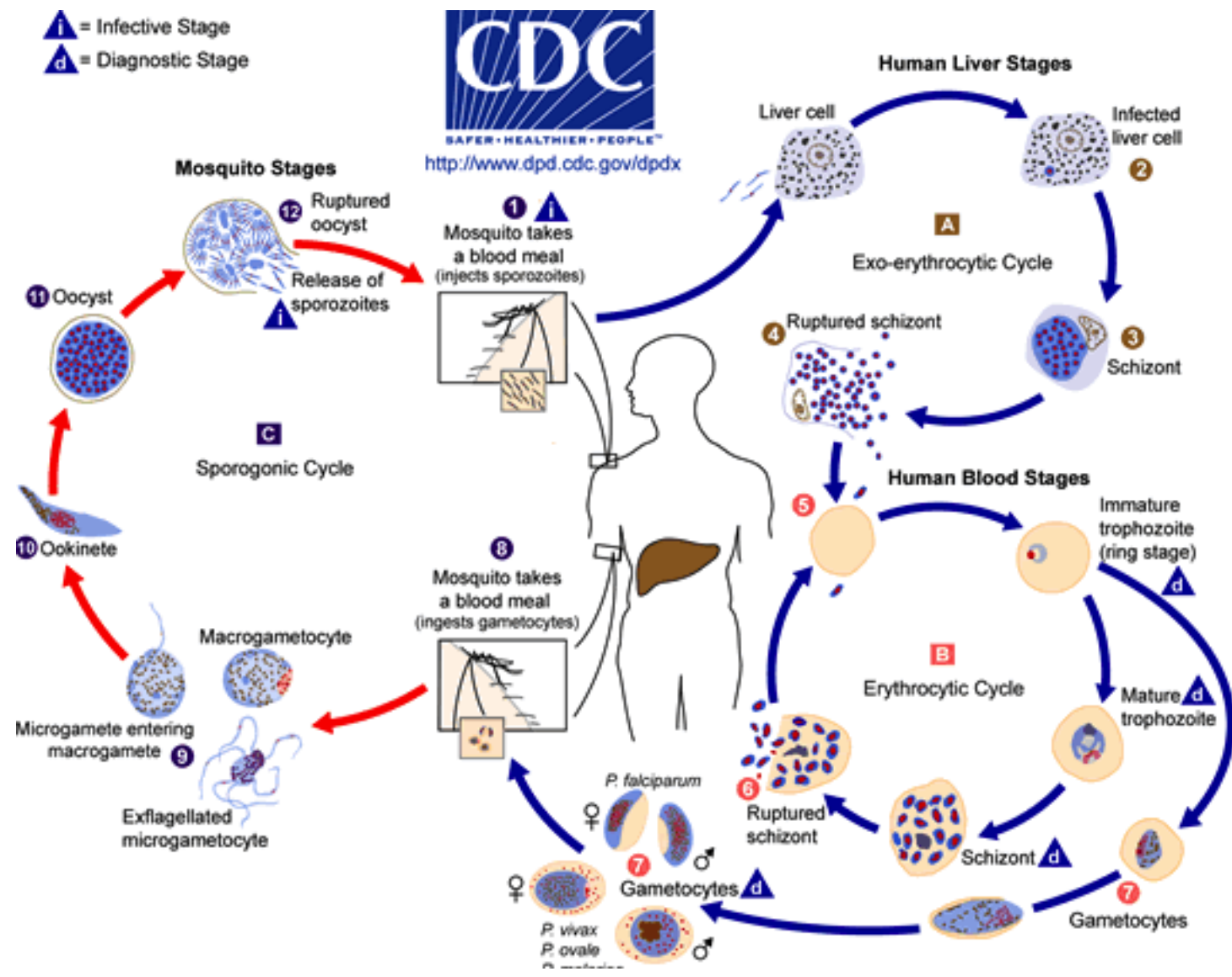


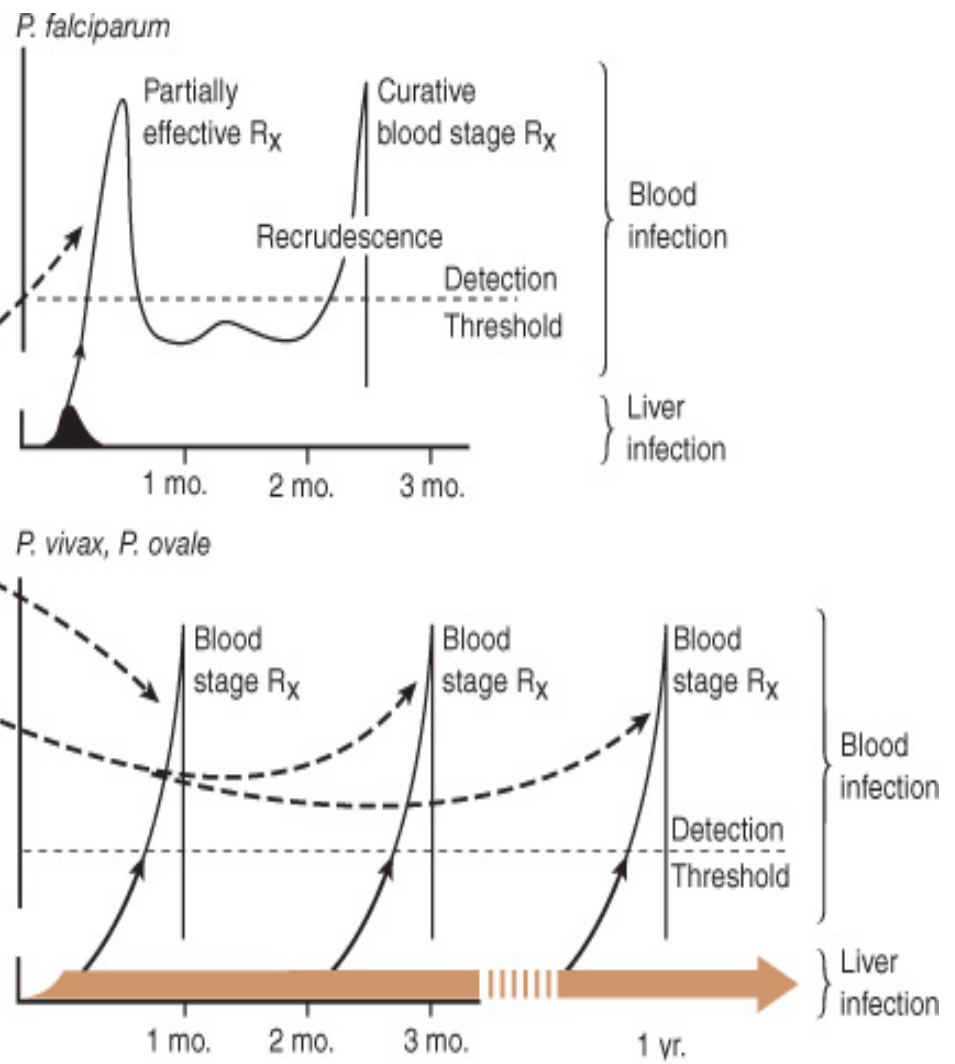
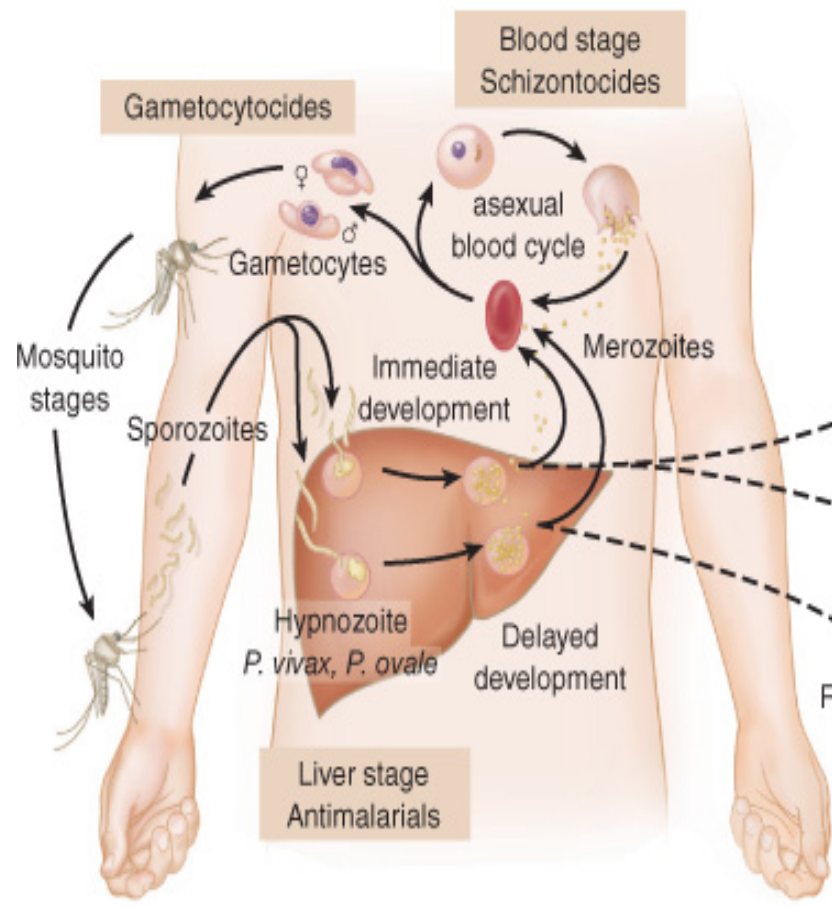
Malaria

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



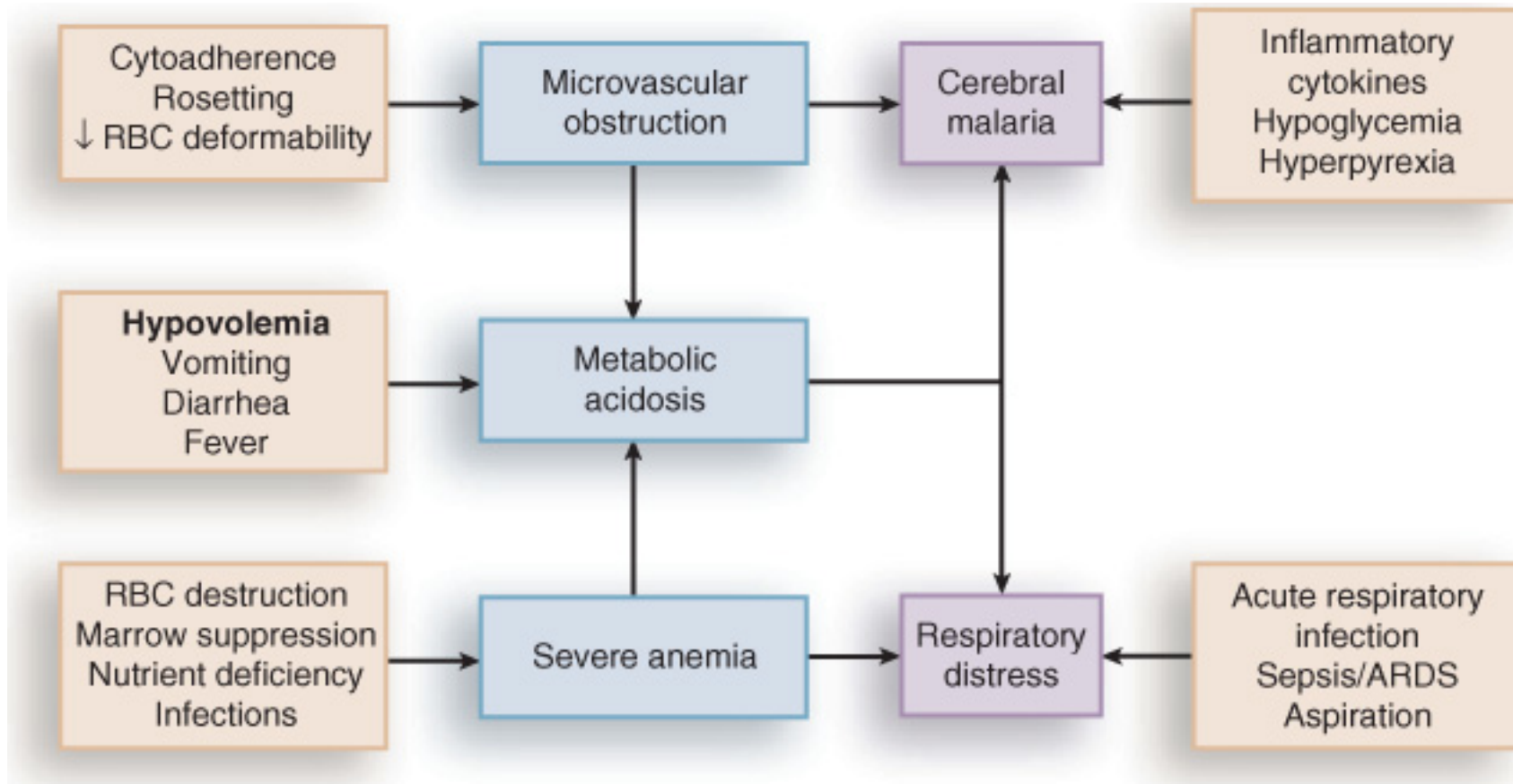
Malaria





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

Malaria



Diagnosis of Malaria

Clinical symptoms

Common

Fever
Flu like illness
Headache
Back pain
Myalgia

Nausea

Vomiting

Rigors

Uncommon

Diarrhoea
Abdominal
cramps
Cough

Dark urine

Confusion

Clinical signs

Common

Fever

Nothing

Splenomegaly

Uncommon

Focal neurology

Reduced

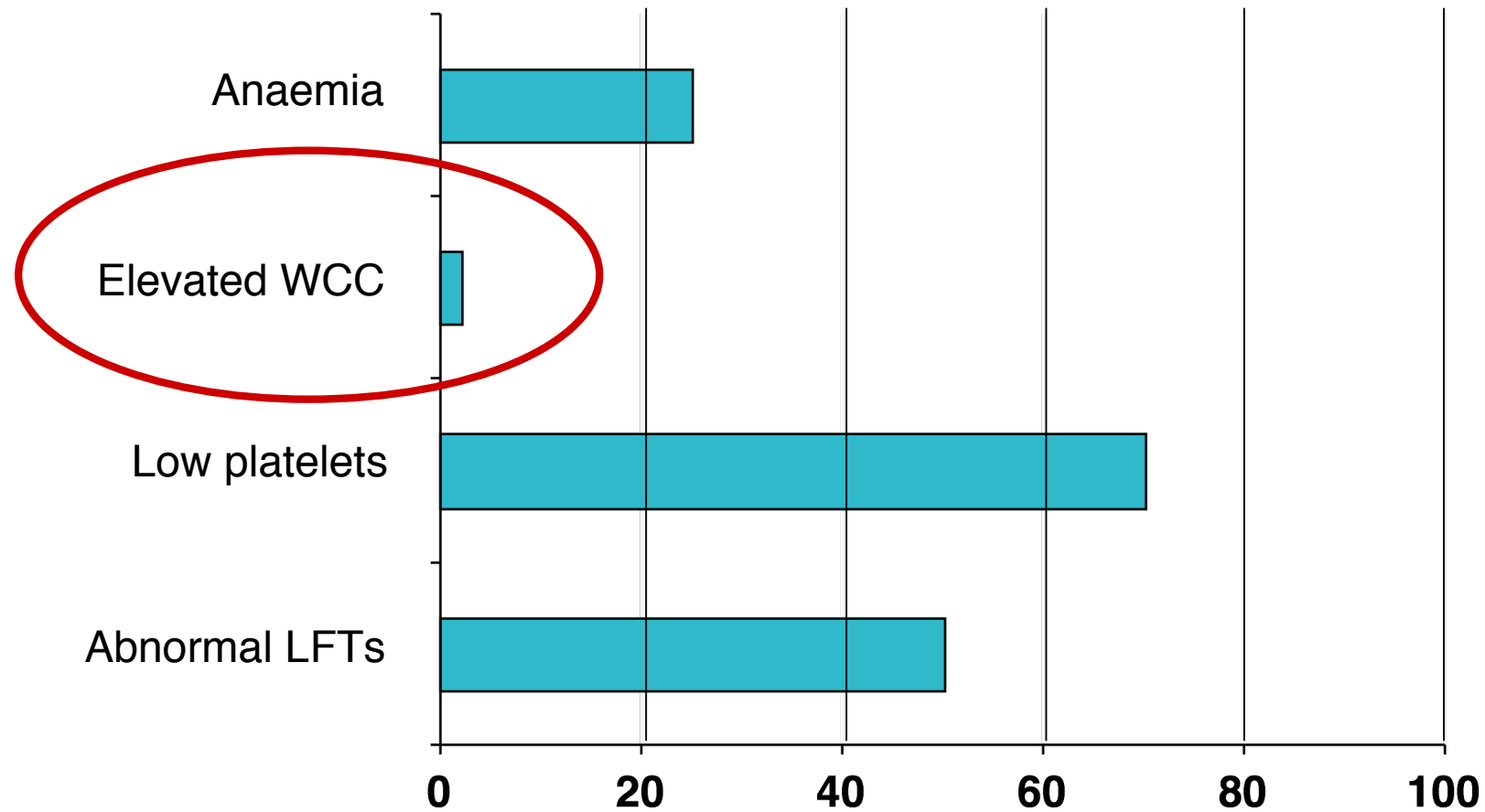
GCS/coma

Shock

Hepatomegaly

Uncomplicated falciparum malaria at presentation

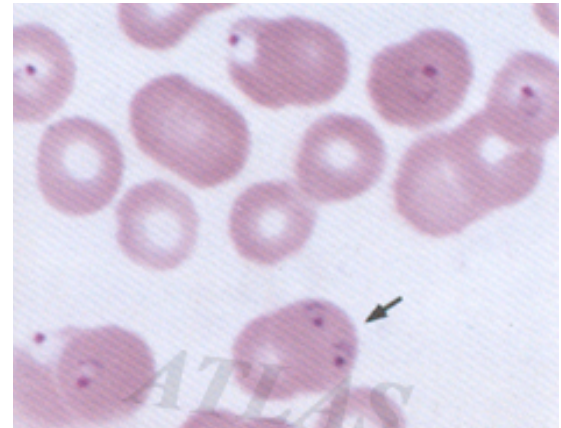
Froude JR et al *Clin Infect Dis* 1992;**15**:774



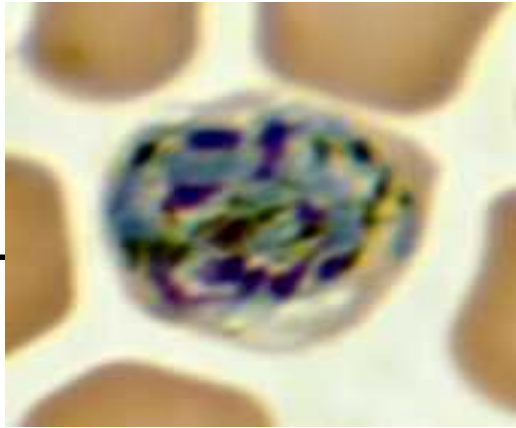
Malaria

- **Thin film**
 - parasitaemia
- **Antigen test**
- **falciparum vs non-falciparum**

- **Severe vs non-severe / uncomplicated**

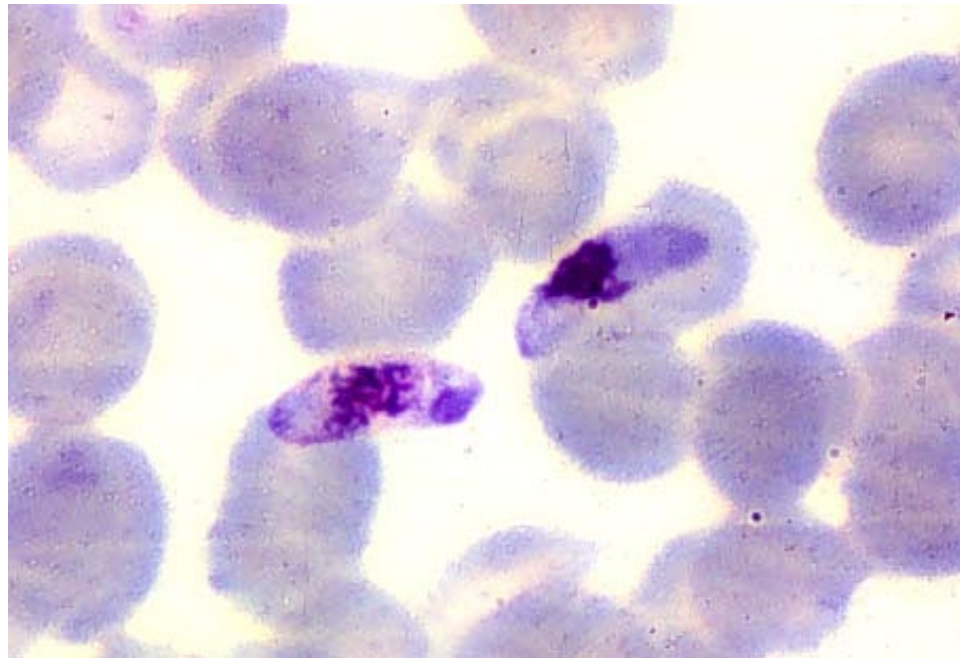


Thin film



Schizonts

Gametocytes



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 body-weight per hour or creatinine > 265 μ mol/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)

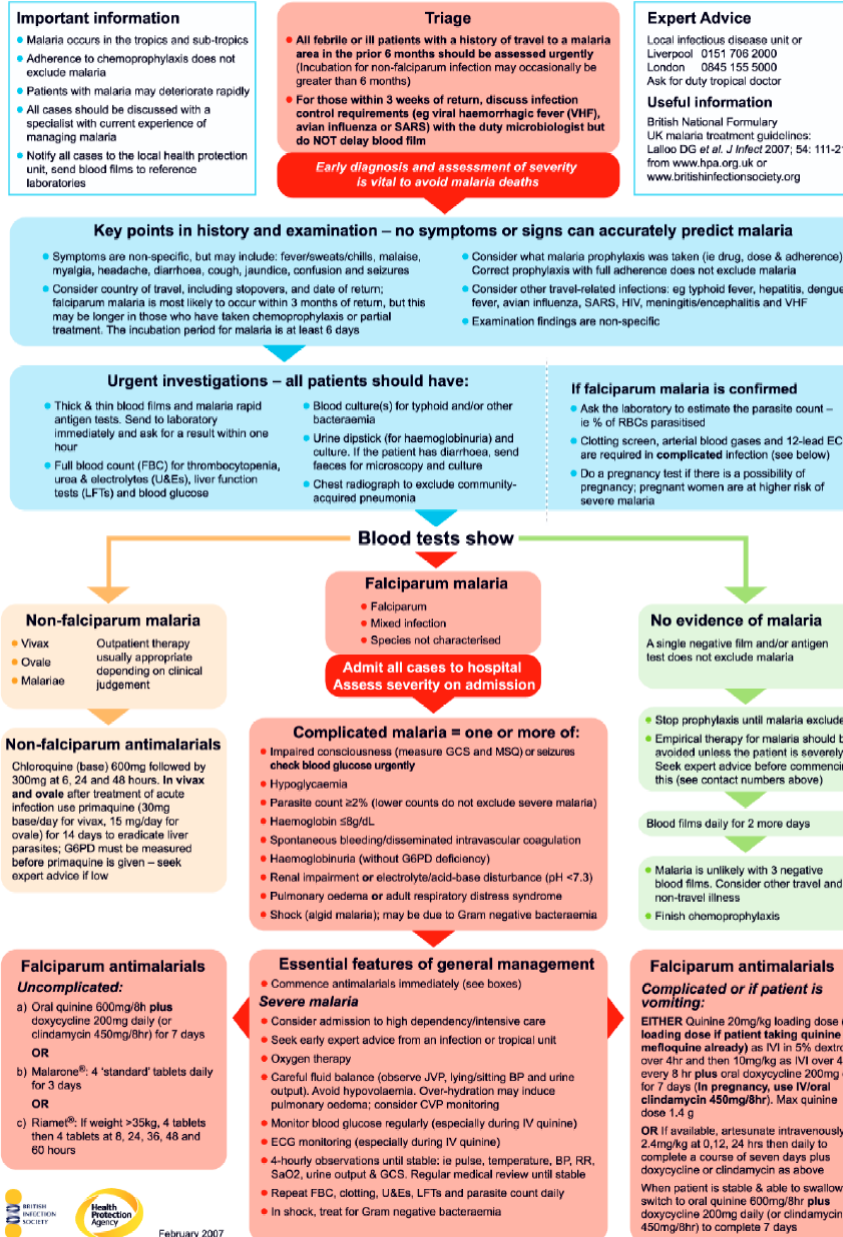
Other indications for parenteral therapy ;High parasitaemia $> 2\%$, pregnancy, vomiting

Source: BIS guidelines 2008

Management of *P.falciparum*

Management

Malaria - Algorithm for Initial Assessment and Management in Adults



For more detail:
BIA/HPA website

Treatments

Mild

Quinine+ doxy
Atovoquone/
Proguanil

ACT

co-artem- artemether/lumefantrine)

Severe

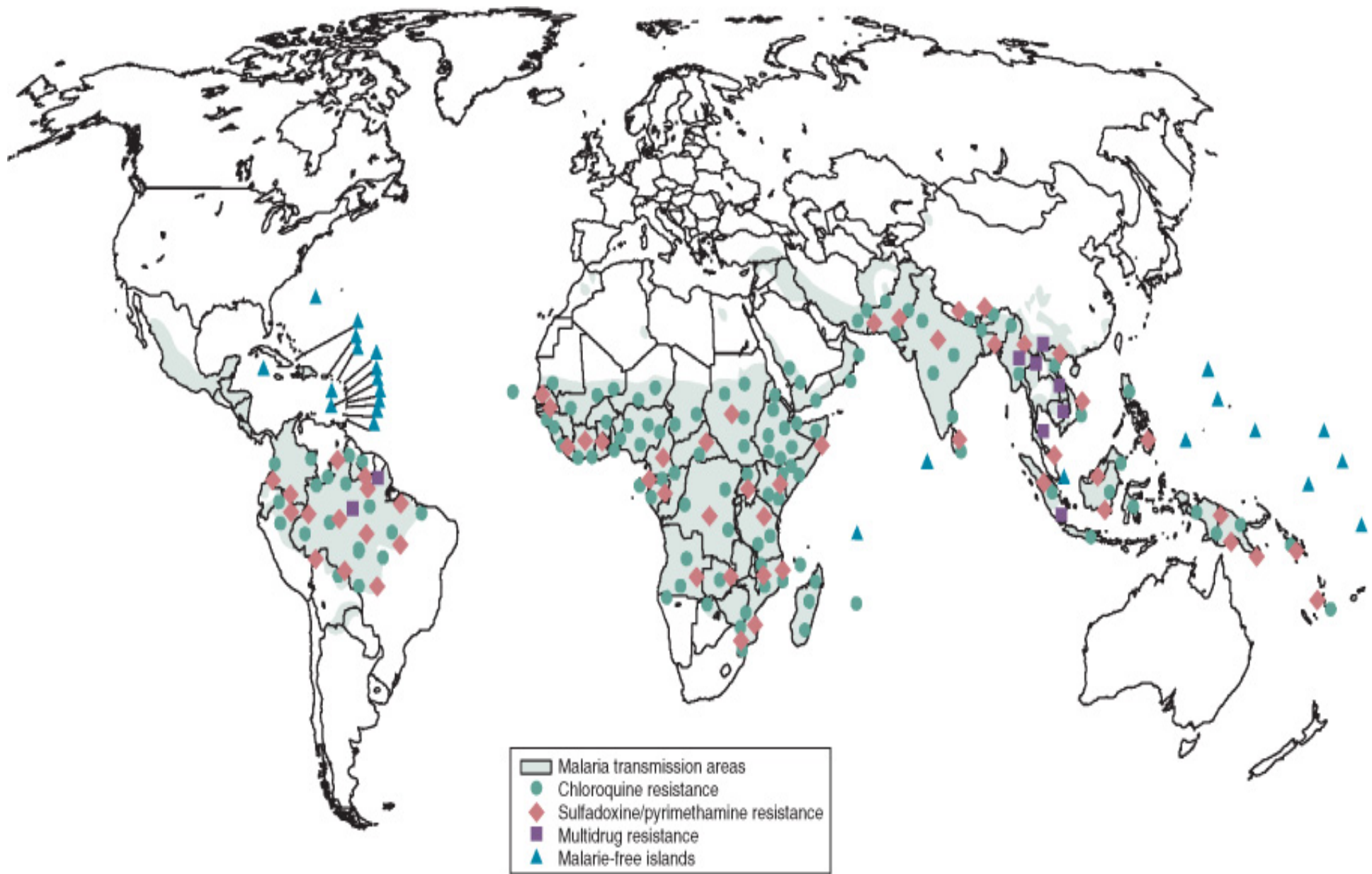
Quinine

Artemisinin

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



SEAQUAMAT

Deaths

Artesunate 15%

107 / 730

Quinine 22%

164 / 731

Odds Ratio = 0.60

(0.45 – 0.79) p = 0.0002

RRR 35%

ARR 7%

NNT 14 (11 – 20)



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

Prevention

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

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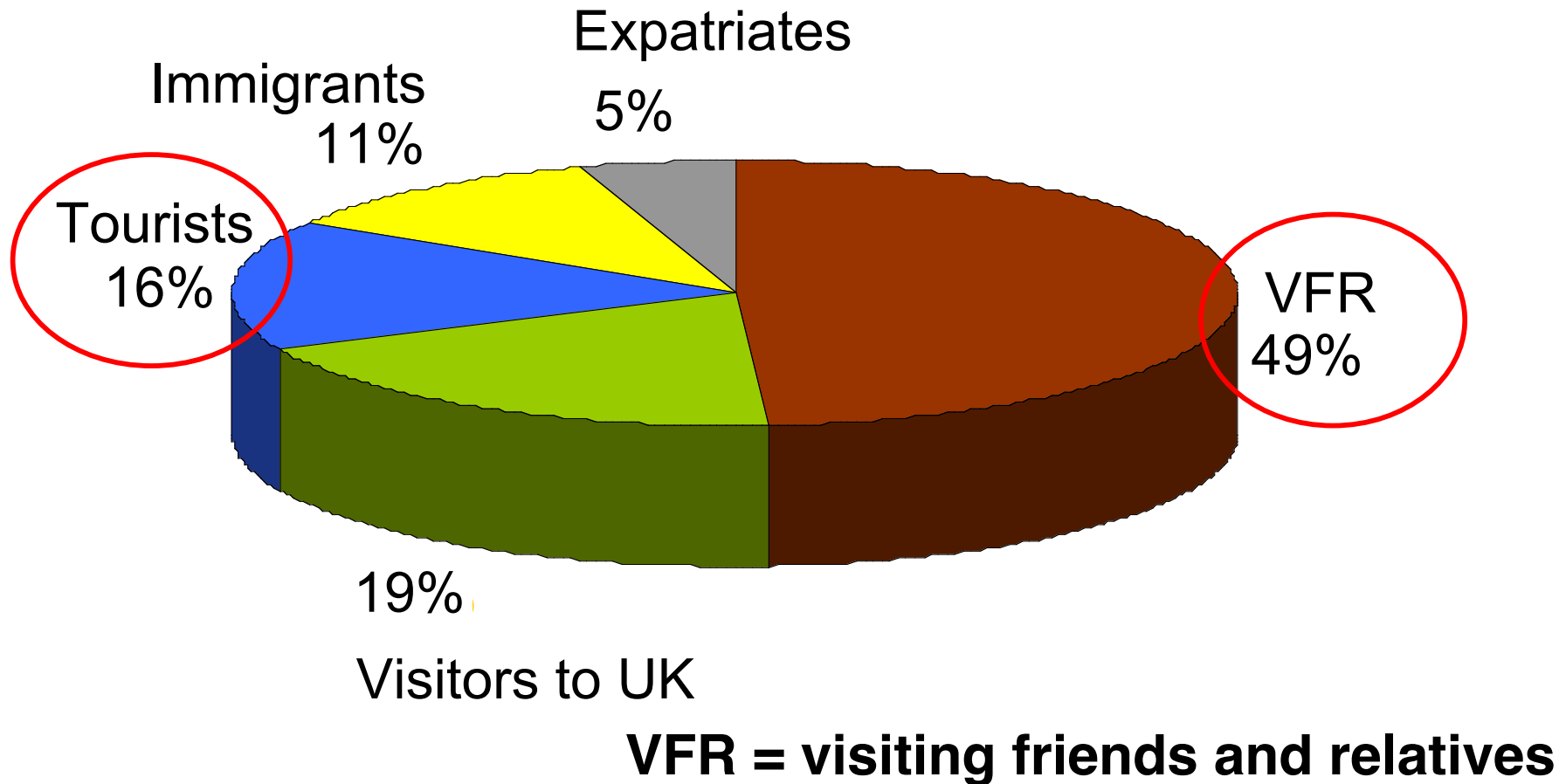
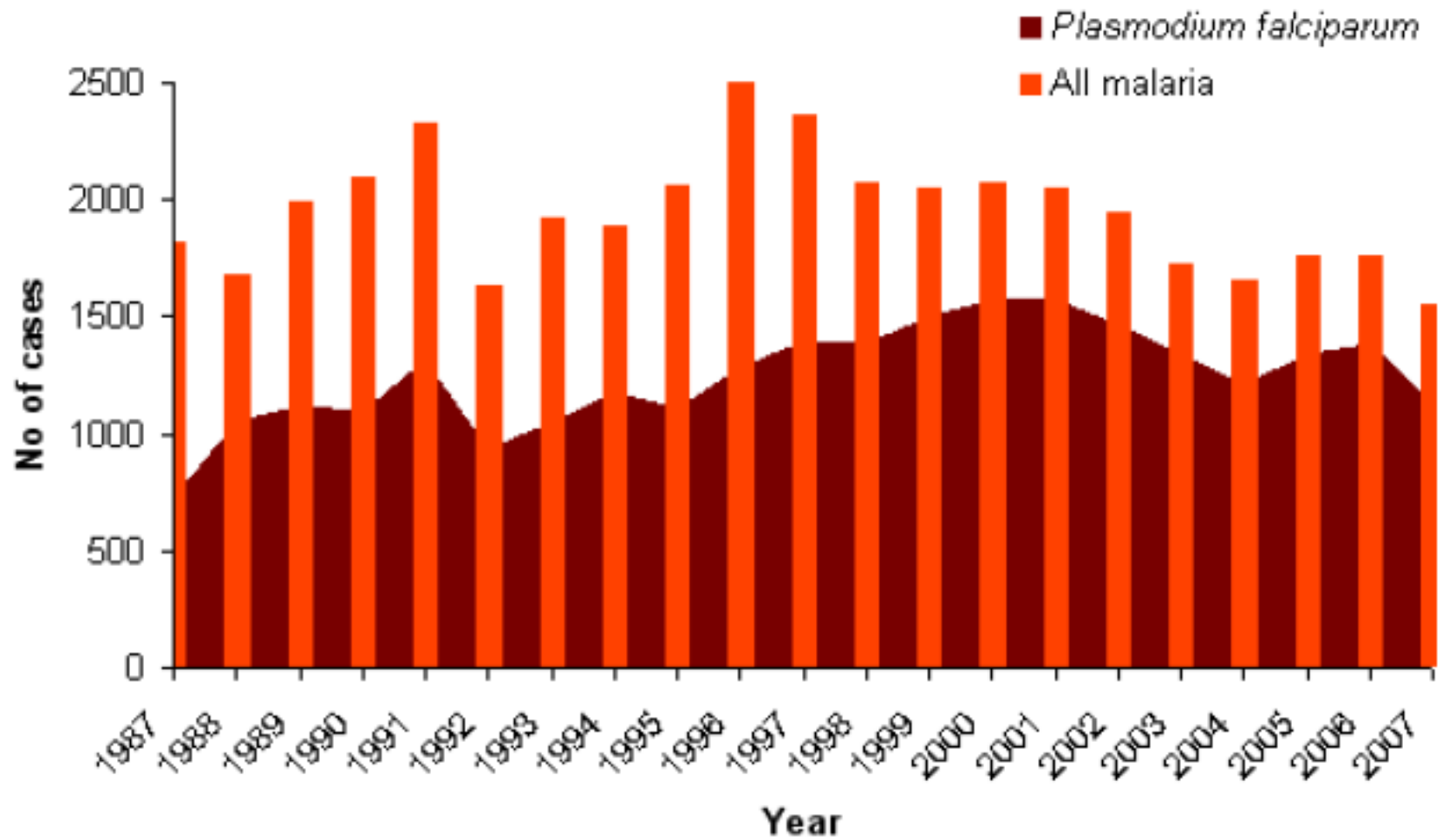


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Typhoid

Typhoid

- Enteric fever
- *Salmonella* species
 - *typhi*
 - *Paratyphi*
- 16 million cases worldwide
- 600,000 deaths
- Transmitted in food & water

Typhoid

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

Poliomyelitis, 2001



Indigenous wild poliovirus
 Importation or uncertain
 No wild virus

Yellow fever, 2001



Countries/areas where there is a risk of yellow fever transmission

Hepatitis A, 2001



Countries/areas with moderate-to-high risk of infection

Hepatitis B, 2001



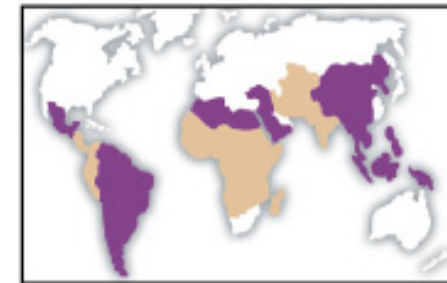
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Typhoid, 2002



High endemicity
 Intermediate endemicity

Japanese encephalitis, 2001



Seasonal transmission
 All-year transmission

Dengue, 2001



Countries/areas reporting dengue cases

Meningococcal meningitis, 2002



High endemicity

Typhoid

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

Typhoid

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

Case 1

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Summary

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