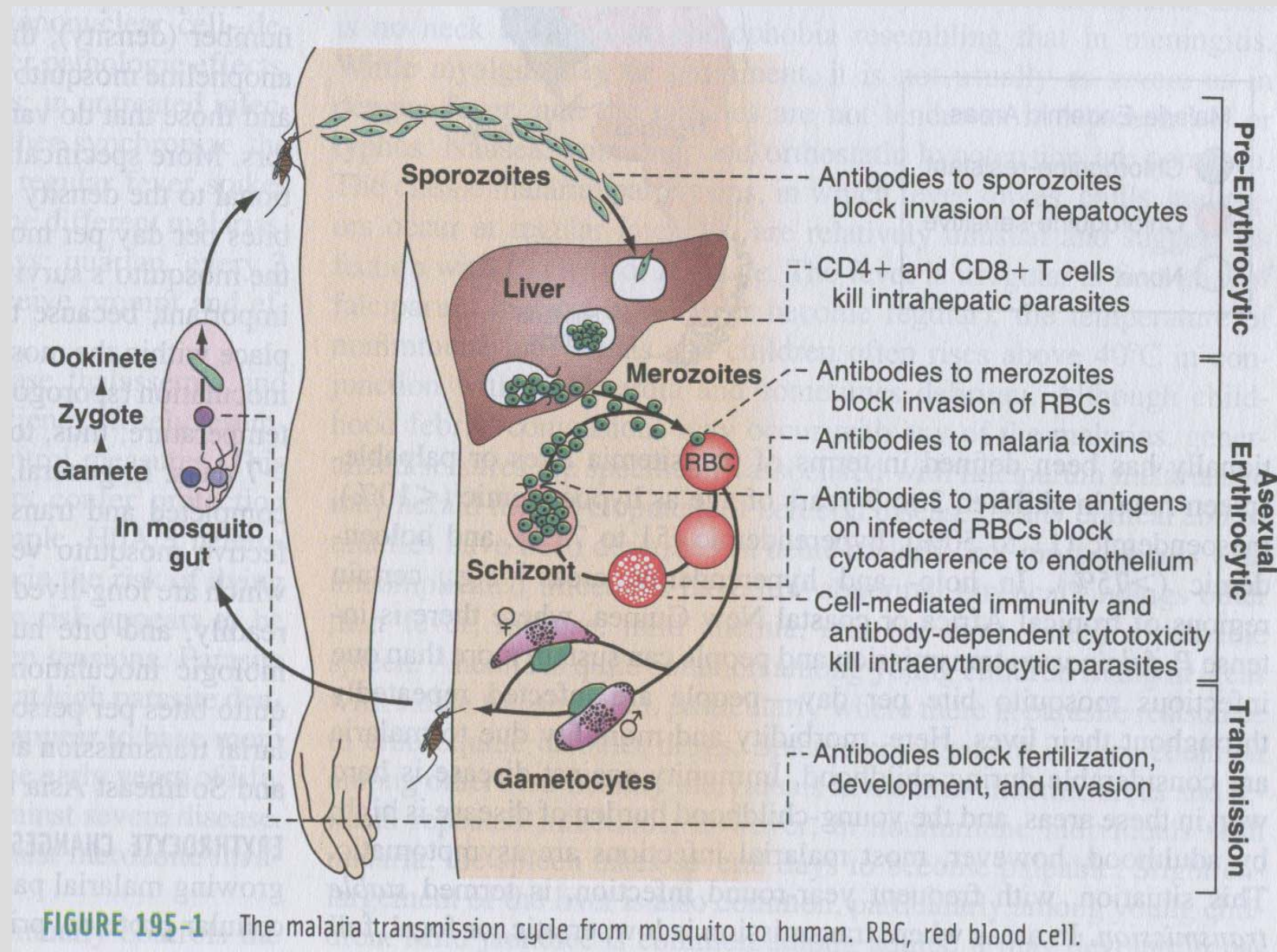


## Malaria humana- agentes

1. *P. falciparum*
2. *P. vivax*
3. *P. ovale*
4. *P. malariae*
5. *P. knowlesi*

**Vector- *Anopheles***



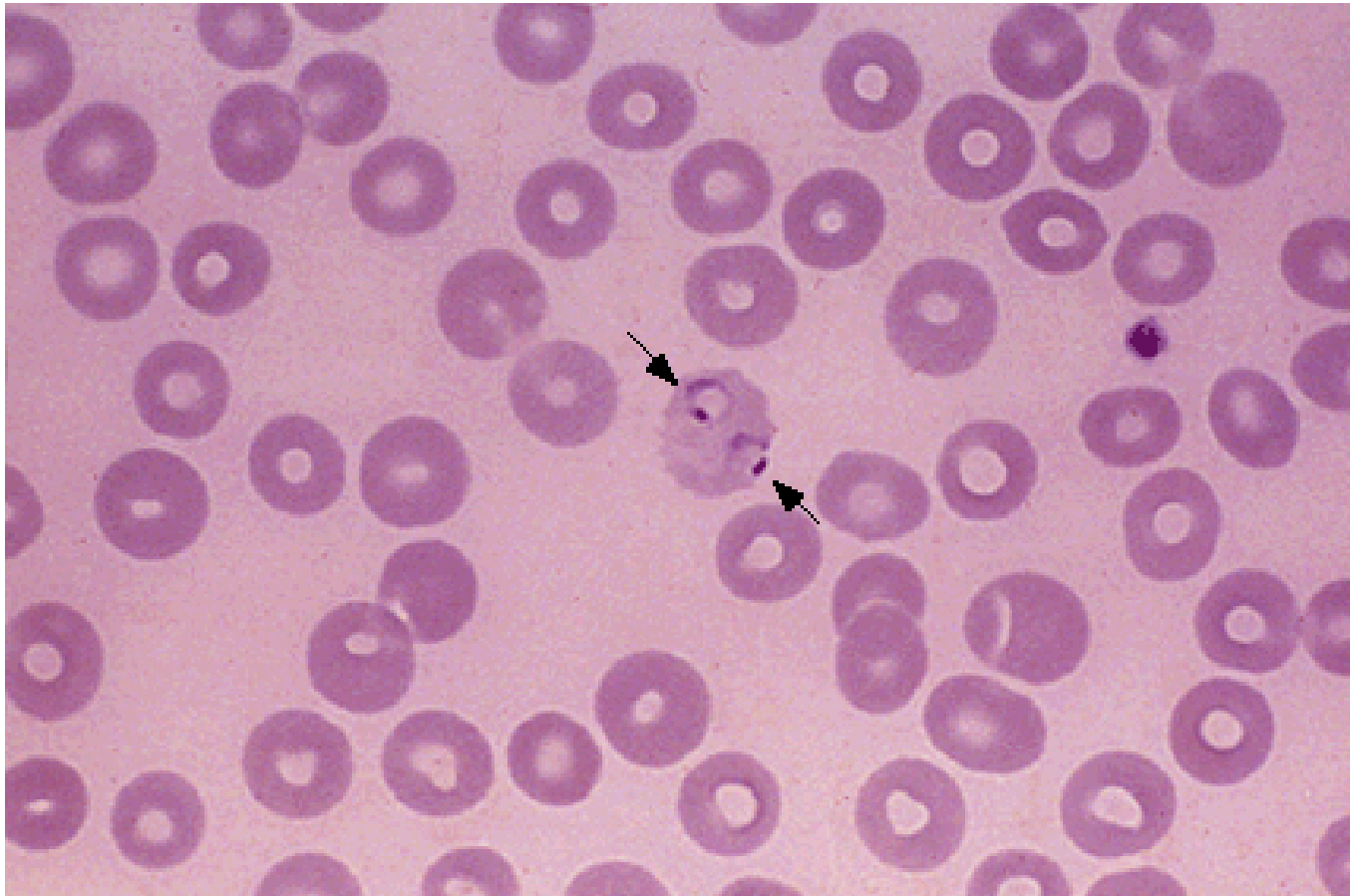


**FIGURE 195-1** The malaria transmission cycle from mosquito to human. RBC, red blood cell.

### Clues to Species Diagnosis Via Thin Smear

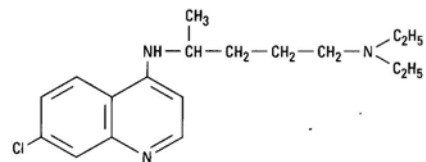
	<b><i>P. falciparum</i></b>	<b><i>P. vivax</i></b>	<b><i>P. ovale</i></b>	<b><i>P. malariae</i></b>
<b>Size of RBCs</b>	Normal size (sometimes distorted and crenated)	Enlarged	Enlarged, and usually oval in shape (with fimbriated ends)	Normal size
<b>Number of parasites per RBC</b>	May be multiple	Usually one	Usually one	Usually one
<b>Typical form of trophozoite</b>	Rings	Amoeboid, often fragmented	Compact and regular	Compact
<b>Other characteristics</b>	Banana-shaped gametocytes; black pigment in RBCs; schizonts rare	Schuffner's granules; often see gametocytes and schizonts	Schuffner's granules; often see gametocytes and schizonts	Often see gametocytes and schizonts

RBC: red blood cell.

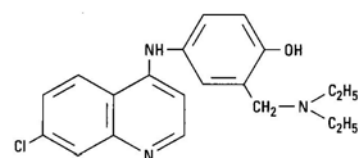


**Malaria** Peripheral smear from a patient with malaria shows intraerythrocytic ring forms (trophozoites) (arrows). Courtesy of Carola von Kapff, SH (ASCP).

#### 4-AMINOQUINOLINES

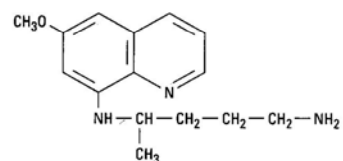


**Chloroquine**



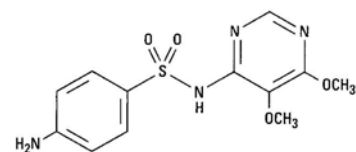
**Amodiaquine**

#### 8-AMINOQUINOLINE

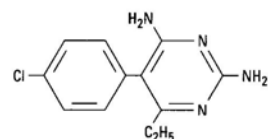


**Primaquine**

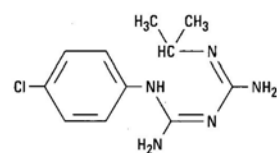
#### FOLATE ANTAGONISTS



**Sulfadoxine**

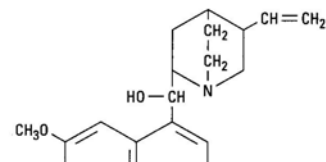


**Pyrimethamine**

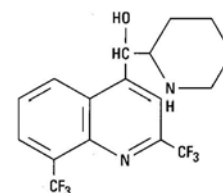


**Proguanil**

#### QUINOLINE METHANOLS

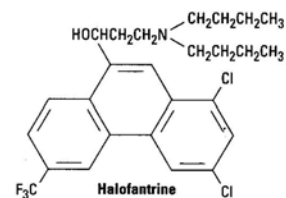


**Quinine**



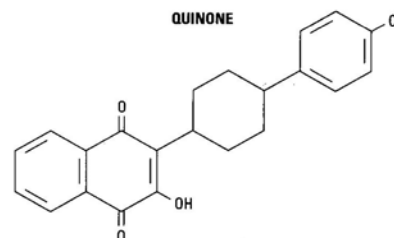
**Mefloquine**

#### PHENANTHRENE METHANOL



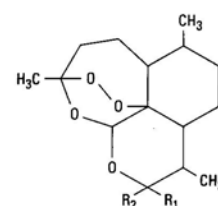
**Halofantrine**

#### QUINONE



**Atovaquone**

#### ENDOPEROXIDES



**Artemisinin**  
(multiple structures)

# Antimaláricos I

<b>Fármacos</b>	<b>Estrutura química</b>	<b>Mecanismo de acção</b>
<b>Cloroquina</b> <b>Amodiaquina</b>	4-aminoquinoleínas	Inibição da polimerização do heme em hemozoina ?
<b>Primaquina</b>	8-aminoquinoleínas	desconhecido
<b>Quinina</b> <b>Quinidina</b> <b>Mefloquinina*</b>	Quinolinas (alcaloides da Cinchona) Derivado sintético*	desconhecido

## Antimaláricos II

<b>Fármacos</b>	<b>Estrutura química</b>	<b>Mecanismo de acção</b>
<b>Halofantrina</b>	Fenantreno-metanol	desconhecido
<b>Proguanil<sup>a</sup></b>	biguanida	Inib. reduct. ac. dihidrofólico
<b>Pirimetamina+</b>	diaminopirimidina	Inib. reduct. ac. dihidrofólico
<b>Sulfadiazina</b> <b>Sulfadoxina+</b>	sulfonamidas	Ant. PABA
<b>Doxiciclina</b>	tetraciclina	Inib. síntese proteica (30s)
<b>Atovaquona<sup>a</sup></b>	hidroxinaftoquinona	Inib. Transporte de electrões na mitocôndria

**Fansidar+**

**Malarone<sup>a</sup>**



## Antimaláricos III

<b>Fármacos</b>	<b>Estrutura química</b>	<b>Mecanismo de acção</b>
<b>Artemisinina</b> ("qinghausu") Artemether Artesunato	Endoperóxido (lactona sesquiterpénica)	Formação de radicais livres após a clivagem do endoperoxido

Outros: clindamicina, azitromicina

# Cloroquina

## **Farmacocinética**

Boa absorção oral (sal fosfato)

Também i.m.

Met. hepática

Vol. Dist. 100-1000 L/kg

T<sub>1/2</sub> 1-2 meses

Excreção renal

## **Efeitos laterais (normalmente bem tolerada)**

G.I. (náusea, dor abdominal, anorexia)

Urticária (raça negra)

Dermatite

alopecia

Alt. Visão

Hipotensão (grave qd. parentérica)

Alt. ECG

Hemólise grave (G6PD)

Reacções neuropsiquiátricas

Miopatia

Retinopatia

agranulocitose

# Cloroquina

Esquizonticida/gametocida- formas eritrocitárias (trofozoitos, gametócitos)

1ª escolha-Tratamento e profilaxia da malária  
(excepto *P. falciparum* resistente)

# Amodiaquina

~ cloroquina

Melhor sabor

Toxicidade. Agranulocitose, hepatite

Uso na profilaxia da malária

# Primaquina

## **Farmacocinética**

Boa absorção oral

T<sub>1/2</sub> -3-8 h

Metab. Hepática (met. activos)

Excreção renal

## **Efeitos adversos**

G.I.

Hemólise (massiva em def. G6PD)

leucopenia

Cura radical. Erradicação das formas hepáticas  
(*P. Vivax* e *P. ovale*)

# Quinina

## **Farmacocinética**

Boa absorção oral e i.m.

i.V (quinina HCL e gluconato)

Met. Hepática T<sub>1/2</sub> 11 h (> malaria)

Excreção renal (ajuste nos doentes com I.R.)  
(aumenta os níveis de varfarina e digoxina)

## **Efeitos laterais (toxicidade elevada)**

Cinchonismo: zumbidos, cefaleias, náuseas, vômitos, alt. Visão G.I.

Reacções de hipersensibilidade

Hemólise grave (G6PD), hemoglobinúria

Leucopenia

Agranulocitose

Trombocitopenia

Hipoglicemiatromboflebite

Contrações uterinas (3º trimestre)

Hipotensão (grave qd. Parentérica)

Alt. ECG

# Quinina

Esquizonticida/gametocida- formas eritrocitárias (trofozoitos, gametócitos)

**De primeira linha no tratamento da Malaria grave por *P. falciparum* resistente á cloroquina.**

# Mefloquina

## **Farmacocinética**

Boa absorção oral (não há parentérica, irritação local)

Ligação às PP elevada

Extensa distribuição

Eliminação biliar

T<sub>1/2</sub> 20 dias (daí uma dose única por semana)

## **Efeitos adversos**

G.I.

Tonturas

Alterações do sono

Alterações do comportamento

Reacções neuropsiquiátricas (depressão, confusão, psicose, convulsões)

Leucocitose

Trombocitopenia

Arritmias



# Mefloquina

Esquizonticida/gametocida- formas eritrocitárias (trofozoitos, gametócitos)

**Tratamento e profilaxia da Malaria**

**P. falciparum ou outras espécies desde que resistentes á cloroquina)**

**Não é útil em situações graves**

**Pode ser usada em crianças e e em grávidas**

# Artemisinina e seus derivados

## **Farmacocinética**

Boa absorção oral

Metabolito activo- dihidroartemisinina

Semivida curta (1-3 h)

## **Efeitos adversos** (muito bem tolerados)

G.I.

teratogenicidade

Rapidez e eficácia na eliminação das formas eritrocitárias (trofozoitos, gametócitos)

**Útil para o tratamento da malária-  
papel fundamental no *P. falciparum* multi-resistente.**

**Table 1. Cost, Convenience, and Primary Clinical Application of Antimalarial Therapies.**

<b>Therapy</b>	<b>Cost (\$)*</b>	<b>No. of Doses</b>	<b>Duration of Therapy</b>	<b>Application</b>
Chloroquine	0.11	3	48 hr	Blood-stage schizonticide
Sulfadoxine–pyrimethamine	0.14	1	Single dose	Blood-stage schizonticide
Quinine	0.97	21	7 days	Blood-stage schizonticide
Mefloquine	2.55	1	Single dose	Blood-stage schizonticide
Atovaquone–chloroguanide	48.00†	3	48 hr	Blood-stage schizonticide
Artemether–lumefantrine	9.12‡	6	48 hr	Blood-stage schizonticide, gametocytocide
Artesunate–mefloquine	5.00§	6	48 hr	Blood-stage schizonticide, gametocytocide
Artesunate–sulfadoxine–pyrimethamine	2.40¶	3	48 hr	Blood-stage schizonticide, gametocytocide
Artesunate–amodiaquine	2.00¶	3	48 hr	Blood-stage schizonticide, gametocytocide
Primaquine	1.68	7–14	7 days–8 wk	Tissue-stage schizonticide, gametocytocide

\* Unless otherwise indicated, the cost shown is the cost, in 2003 U.S. dollars, of medication for one adult treatment regimen, purchased in bulk, according to the International Drug Price Indicator Guide (IDPIG) (<http://erc.msh.org/>)

**Table 2. Safety and Tolerability of Available Antimalarial Drugs.\***

<b>Drug</b>	<b>Adverse Effects</b>	<b>Contraindications</b>	<b>Severe Adverse Events</b>
Chloroquine	Gastrointestinal upset, itching, dizziness	Epilepsy	Death from overdose
Sulfadoxine–pyrimethamine	—	Pregnancy, renal disease	Stevens–Johnson syndrome
Quinine	Tinnitus, vertigo, headache, fever, syncope, delirium, nausea	G6PD deficiency, pregnancy, optic neuritis, tinnitus, thrombocytopenic purpura, blackwater fever	Hemolytic anemia, coma, respiratory arrest, renal failure
Mefloquine	Vomiting, headache, insomnia, vivid dreams, anxiety, dizziness	Depression, schizophrenia, anxiety disorder, any psychosis, irregular heartbeat	Psychosis
Atovaquone–chloroguanide	Gastrointestinal upset, headache, stomatitis	Weight of <11 kg in children, pregnancy, breast-feeding, renal impairment	None known
Artemether–lumefantrine	Dizziness, palpitations	Pregnancy, severe malaria	Impaired hearing
Artesunate–mefloquine	Vomiting, anorexia, diarrhea	Depression, schizophrenia, anxiety disorder, any psychosis, irregular heartbeat	None known
Halofantrine	Gastrointestinal upset, prolonged QTc	Conduction abnormalities, pregnancy, breast-feeding, infancy, use of mefloquine	Cardiac arrest
Primaquine	Gastrointestinal upset, elevated levels of methemoglobin	Pregnancy, G6PD deficiency, breast-feeding	Hemolytic anemia

\* Data in the table are from Taylor and White,<sup>25</sup> Centers for Disease Control and Prevention,<sup>26</sup> Phillips-Howard and Wood,<sup>27</sup> and Wernsdorfer.<sup>28</sup> G6PD denotes glucose-6-phosphate dehydrogenase, and QTc QT interval corrected for heart rate.

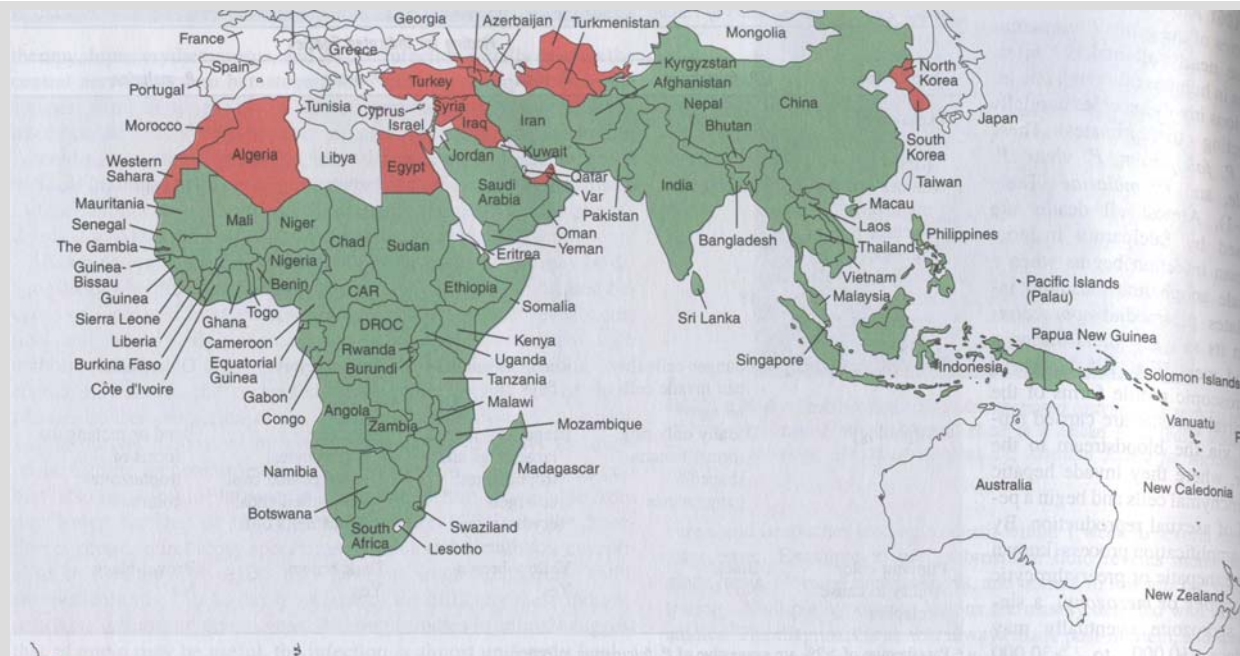
the resolution of fever.<sup>29</sup> Diim de et al.<sup>30</sup> showed that RESISTANCE

**Table 53–3.** Treatment of malaria.

Clinical Setting	Drug Therapy <sup>1</sup>	Alternative Drugs
Chloroquine-sensitive <i>P falciparum</i> and <i>P malariae</i> infections	Chloroquine phosphate, 1 g then 500 mg in 6 hours, followed by 500 mg daily for 2 days  or—  Chloroquine phosphate, 1 g at 0 and 24 hours, then 0.5 g at 48 hours	
<i>P vivax</i> and <i>P ovale</i> infections	Chloroquine (as above), then (if G6PD normal) primaquine, 26.3 mg daily for 14 days	
Uncomplicated infections with chloroquine-resistant <i>P falciparum</i>	Quinine sulfate, 650 mg 3 times daily for 3–7 days  plus one of the following—  Doxycycline, 100 mg twice daily for 7 days  or—  Clindamycin, 600 mg twice daily for 7 days  or—  Fansidar, three tablets once	Mefloquine, 15 mg/kg once or 750 mg, then 500 mg in 6–8 hours  or—  Malarone, 4 tablets (total of 1 g atovaquone, 400 mg proguanil) daily for 3 days  or—  Artesunate or artemether single daily doses of 4 mg/kg on day 0, 2 mg/kg on days 2 and 3, 1 mg/kg on days 4–7  or—  Halofantrine, 500 mg every 6 hours for 3 doses; repeat in 1 week
Severe or complicated infections with <i>P falciparum</i> <sup>3</sup>	Quinidine gluconate, <sup>2,3</sup> 10 mg/kg IV over 1–2 hours, then 0.02 mg/kg IV/min  or—  15 mg/kg IV over 4 hours, then 7.5 mg/kg IV over 4 hours every 8 hours.	Artesunate, <sup>3</sup> 2.4 mg/kg IV or IM, then 1.2 mg/kg every 12 hours for 1 day, then every day  or—  Artemether, <sup>3</sup> 3.2 mg/kg IM, then 1.6 mg/kg/d IM

## **Aumento dos casos de Malária nos últimos anos**

- Aumento de resistências dos plasmódios á quimioterapia
- Aumento de resistências do Mosquito Anopheles /vector) aos insecticidas
- Alterações ecológicas e Climatéricas
- Aumento de viagens internacionais para locais com Malaria endémica



**Table 53–2.** Drugs for the prevention of malaria in travelers.<sup>1</sup>

Drug	Use <sup>2</sup>	Adult Dosage <sup>3</sup>
Chloroquine	Areas without resistant <i>P falciparum</i>	500 mg weekly
Mefloquine	Areas with chloroquine-resistant <i>P falciparum</i>	250 mg weekly
Doxycycline	Areas with multidrug-resistant <i>P falciparum</i>	100 mg daily
Malarone	Areas with chloroquine-resistant <i>P falciparum</i>	1 tablet (250 mg atovaquone/100 mg proguanil) daily
Primaquine <sup>4</sup>	Terminal prophylaxis of <i>P vivax</i> and <i>P ovale</i> infections	26.3 mg (15 mg base) daily for 14 days after travel



<http://www.who.int/ith/countrylist>

## **BRAZIL**

**Capital:** Brasilia

**Altitude:** 1000 m

**Malaria:** Malaria risk—*P. vivax* (77%), *P. falciparum* (23%)—is present in most forested areas below 900 m within the nine states of the “Legal Amazonia” region (Acre, Amapá, Amazonas, Maranhão (western part), Mato Grosso (northern part), Pará (except Belém City), Rondônia, Roraima and Tocantins. Transmission intensity varies from municipality to municipality, but is higher in jungle areas of mining, lumbering and agricultural settlements less than 5 years old, than in the urban areas, including in large cities such as Pôrto Velho, Boa Vista, Macapá, Manaus, Santarém and Marabá, where the transmission occurs on the periphery of these cities. In the states outside “Legal Amazonia”, malaria transmission risk is negligible or non-existent. Multidrug-resistant *P. falciparum* reported.

Recommended prophylaxis in risk areas: **mefloquine**.

<http://www.who.int/ith/countrylist>

## **DOMINICAN REPUBLIC**

**Capital:** Santo Domingo

**Altitude:** 380 m

No vaccination requirements for any international traveller.

**Malaria:** Low malaria risk—exclusively due to *P. falciparum*—exists throughout the year, especially in rural areas of the western provinces such as Castañuelas, Hondo Valle and Pepillo Salcedo. There is no evidence of *P. falciparum* resistance to any antimalarial drug.

Recommended prophylaxis in risk areas: **chloroquine**.

<http://www.who.int/ith/countrylist>

## **GUINEA-BISSAU**

**Capital:** Bissau

**Altitude:** 0 m

**Malaria:** Malaria risk—predominantly due to *P. falciparum*—exists throughout the year in the whole country. Resistance to chloroquine reported.

Recommended prophylaxis: **mefloquine**

<http://www.who.int/ith/countrylist>

## **MOZAMBIQUE**

**Capital:** Maputo

**Altitude:** 50 m

**Malaria:** Malaria risk—predominantly due to *P. falciparum*—exists throughout the year in the whole country. *P. falciparum* resistant to chloroquine and sulfadoxine–pyrimethamine reported.

Recommended prophylaxis: **mefloquine**.

<http://www.who.int/ith/countrylist>

## **INDIA**

**Capital:** New Delhi

**Altitude:** 210 m

**Malaria:** Malaria risk exists throughout the year in the whole country below 2000 m, with 40% to 50% of cases due to *P. falciparum*. There is no transmission in parts of the states of Himachal Pradesh, Jammu and Kashmir, and Sikkim. *P. falciparum* resistance to chloroquine and sulfadoxine–pyrimethamine reported.

Recommended prophylaxis in risk areas: **chloroquine plus proguanil**. In Assam: **mefloquine**