

Malaria

“Bad Air”

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Malaria: Lecture Goals

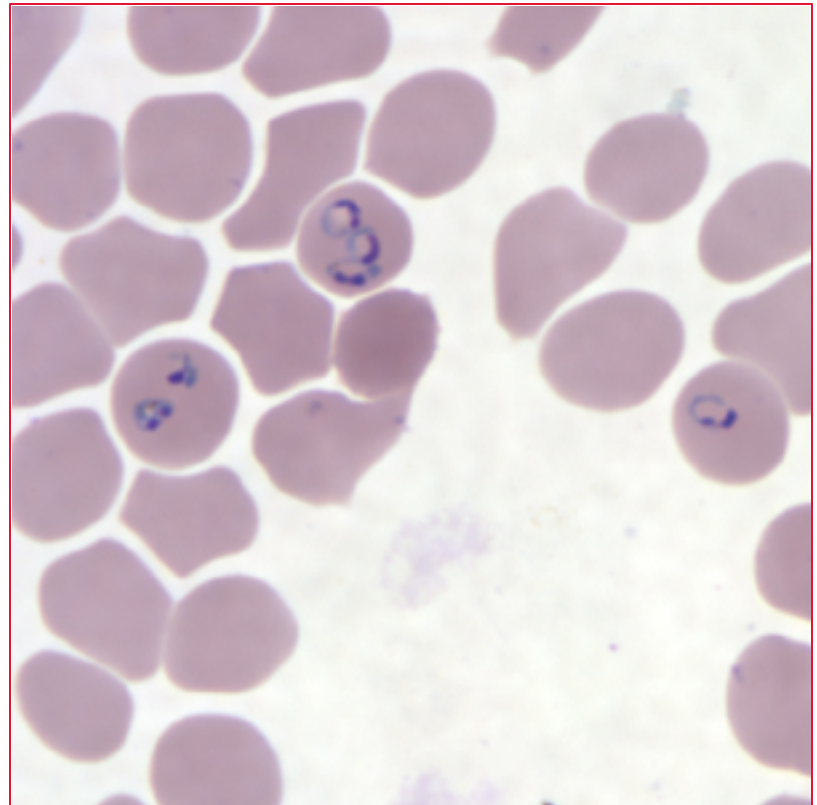
- Understand basic principles of malaria pathogenesis in the context of relevance to clinical disease and epidemiology
- Understand the clinical symptoms of malaria
- Understand the difference between uncomplicated and severe malaria
- Understand how to choose an antimalarial
- Understand where to find up-to-date resources for malaria

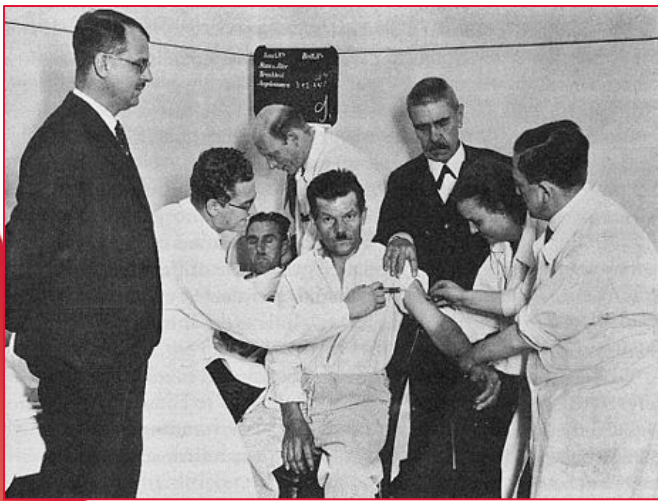
Outline

- Background
 - Organism
 - Epidemiology
 - Pathophysiology
- Clinical
 - Symptoms
 - Differential diagnosis
- Malaria in a complex emergency
 - Who is at risk
 - How to choose a medication

Malaria

- Caused by a protozoal blood parasite
 - *Plasmodium vivax*
 - *Plasmodium ovale*
 - *Plasmodium malaria*
- *Plasmodium falciparum*
- *Plasmodium knowlesi*
 - *Often cause severe malaria





Malaria

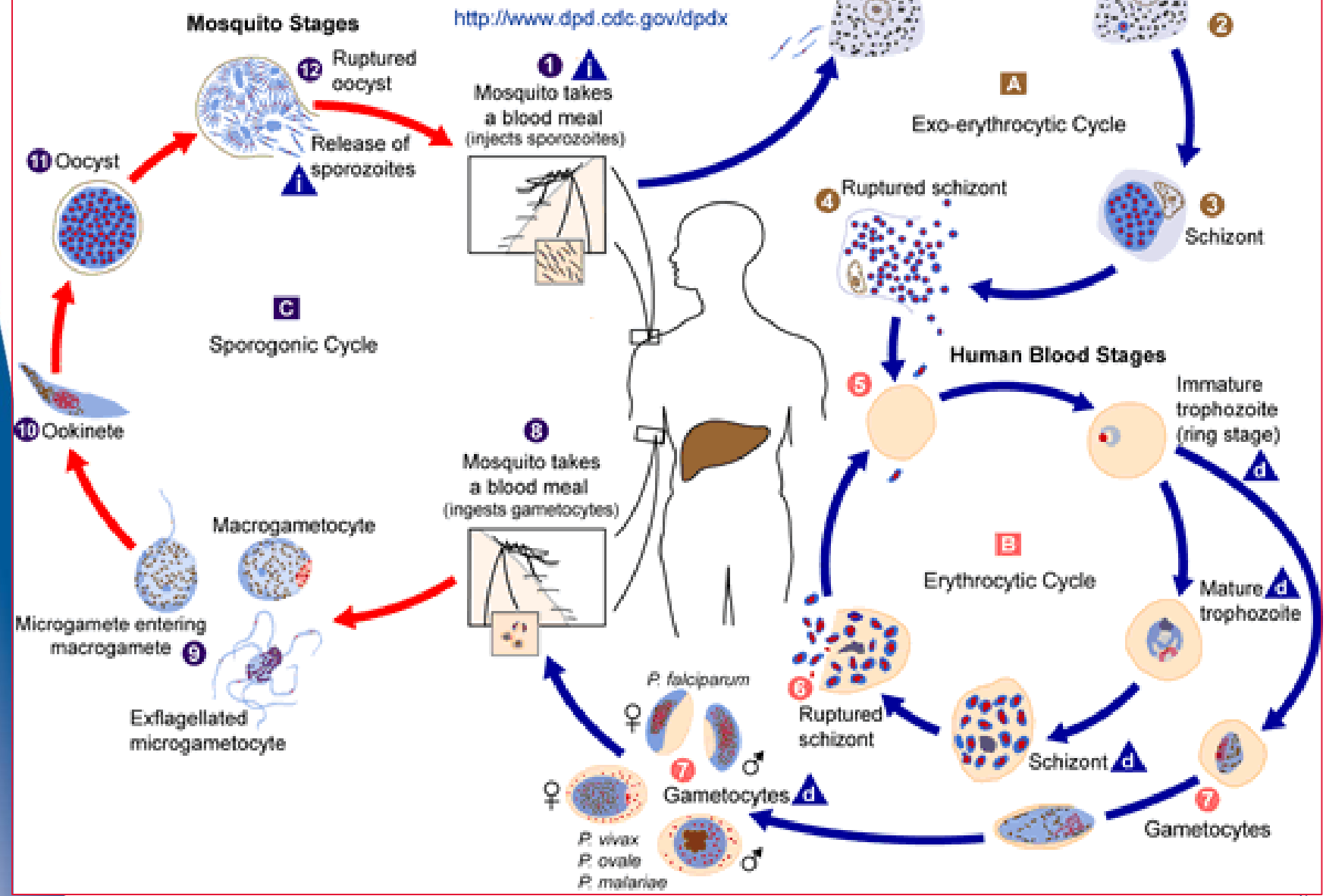


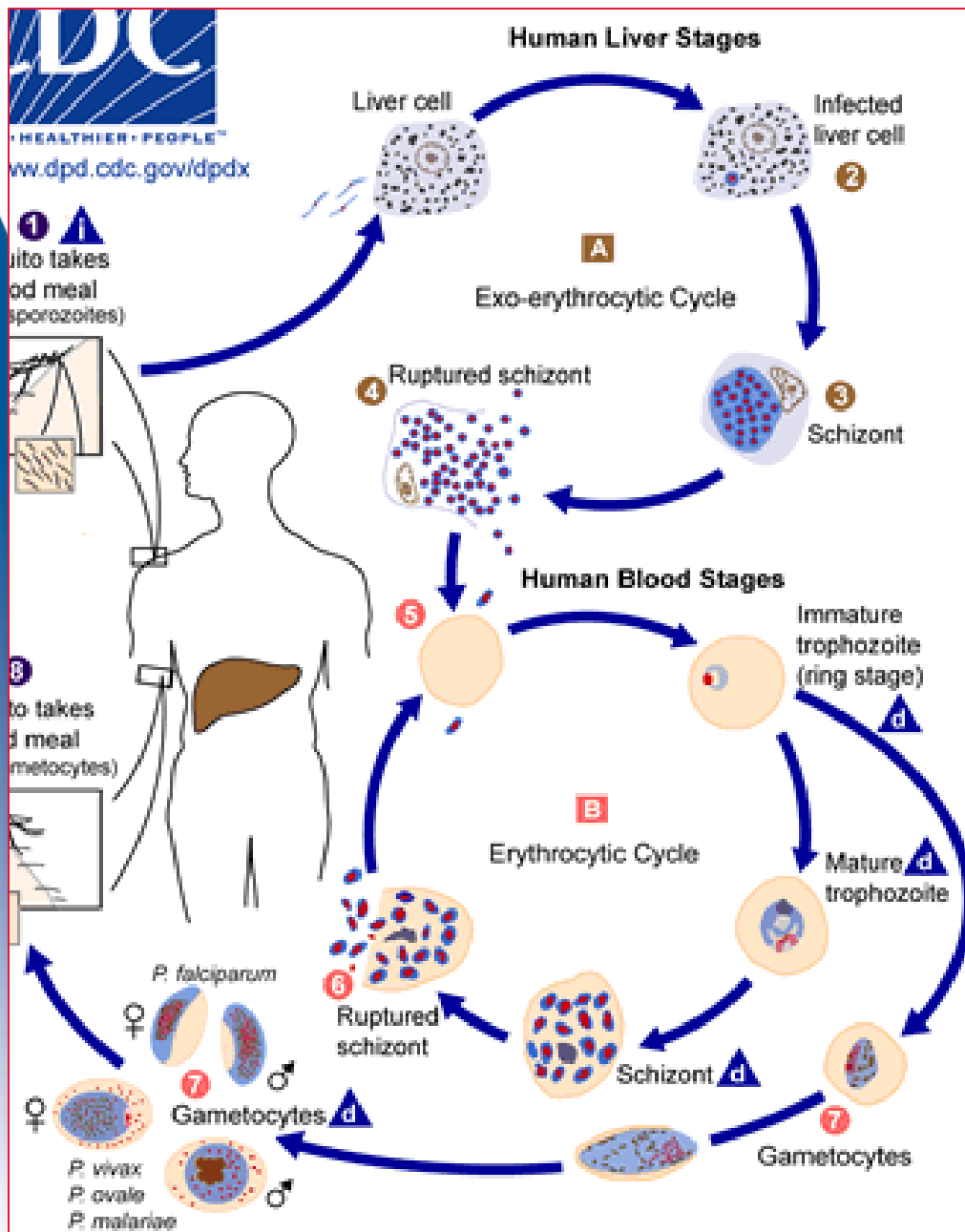
- Transmission: *Anopheles* mosquito
- Wide spectrum symptoms
 - Fever
 - 1927 Nobel Prize: pyrotherapy for syphilis
- Geographical distribution:
 - Tropic / Subtropics
- 350-500 million infections worldwide/year
- 1 million deaths worldwide/year

i = Infective Stage
d = Diagnostic Stage



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<http://www.dpd.cdc.gov/dpdx>



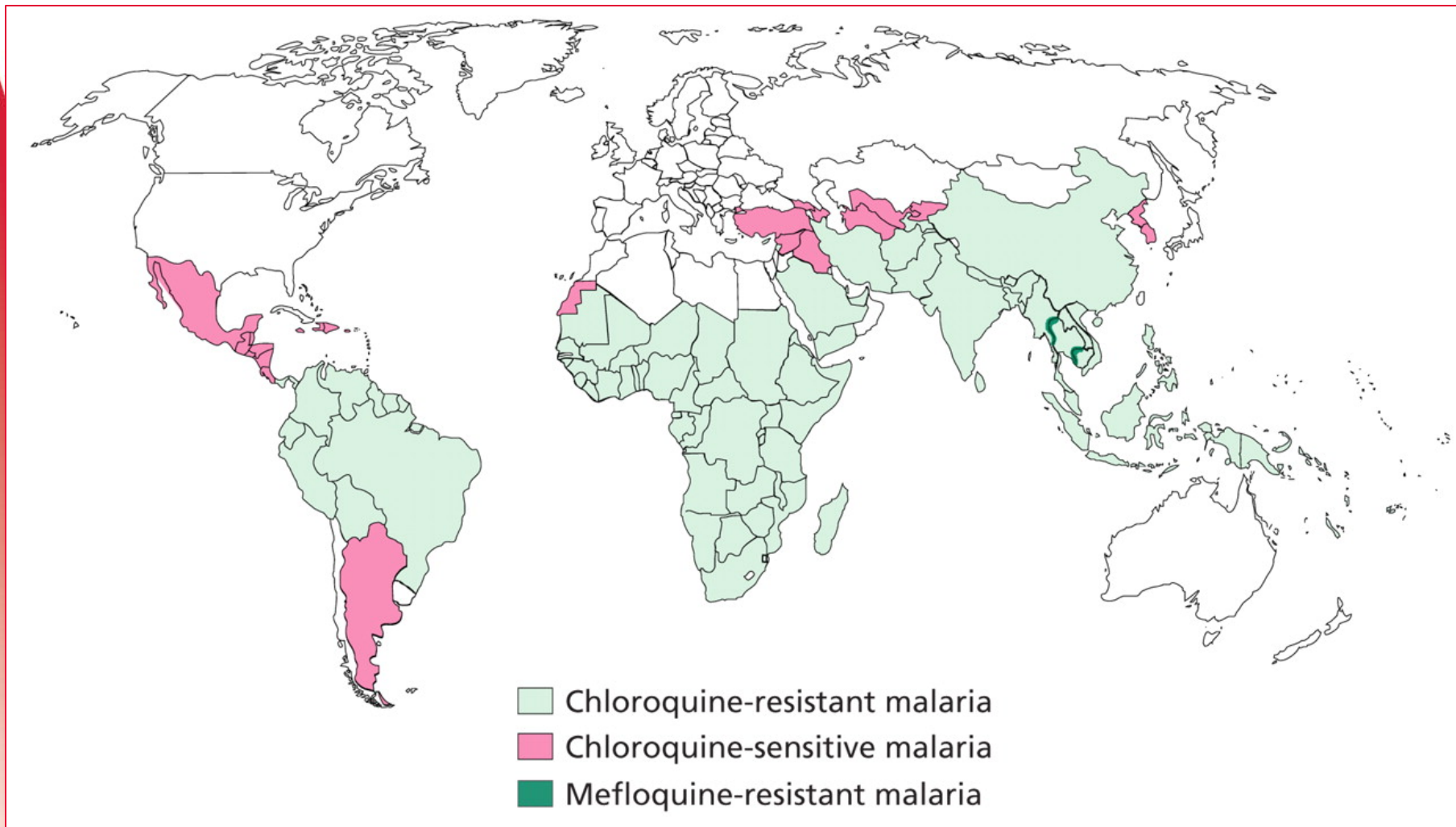


•**Liver stage:** Asymptomatic. With *P. vivax* and *P. ovale*, has dormant form (hypnozoite) that can relapse much later. This form is not killed by most malaria medications.

•**Blood stage:** Symptomatic. Notice the continuous circle. This will continue until medication or immune system eradicates (1-5+ years untreated). Once cycle 3-4 days, except *P. falciparum*.

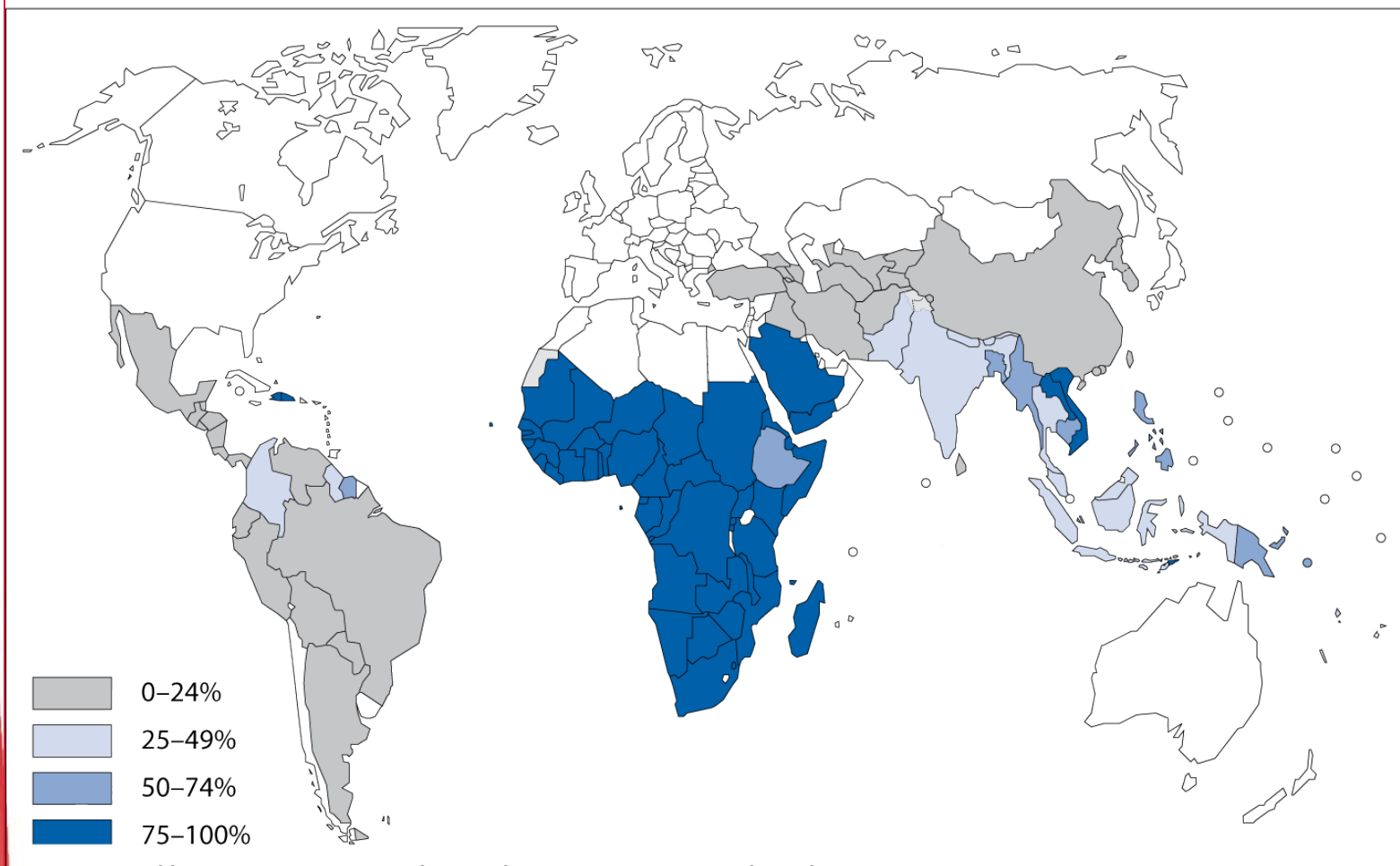


Malaria: Endemicity and Resistance



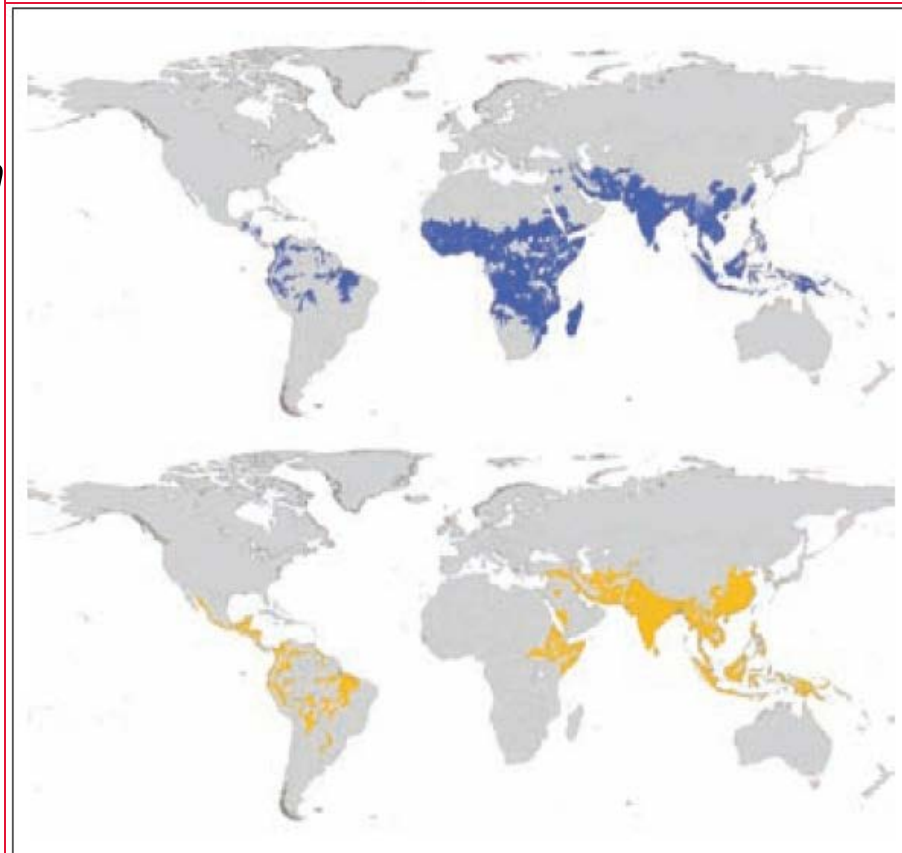
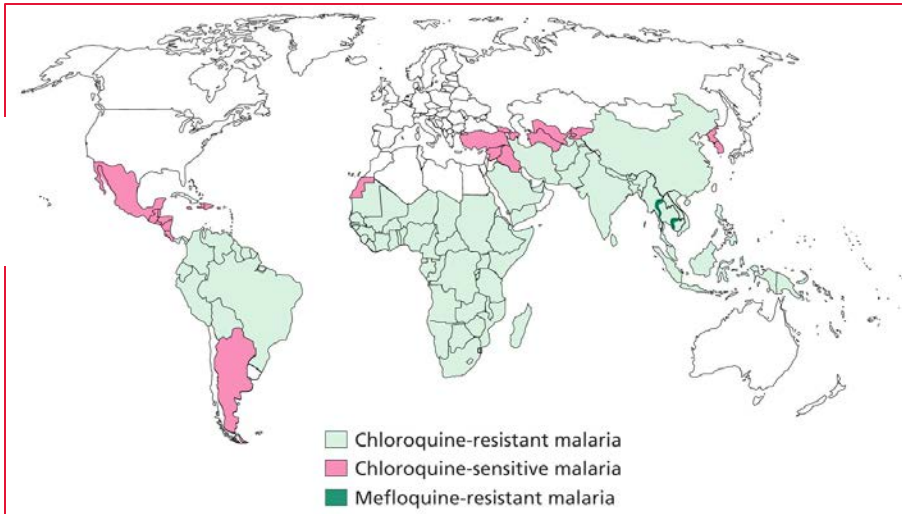
% Malaria *P. falciparum*

Estimated percentage of malaria cases due to *P. falciparum*, 2006



http://www.who.int/gho/map_gallery/en/

Chloroquine Resistance



P. falciparum areas

P. vivax areas

- Chloroquine resistance and *P. falciparum* overlap, with exceptions:
 - Central America West of Panama Canal
 - Haiti/Dominican Republic
 - Middle East
 - **Make easy: Rx *P. falciparum* with ACT**
- Mixed infection possible
 - **Asia 20-30%**
 - Africa usually *P. falciparum*
 - Americas usually *P. vivax*

P. falciparum: Dangerous

- Infects various RBC stages
- Makes RBCs “sticky”
- Result:
 - Severe hemolysis
 - Obstruction of microcirculation
 - Obstruction of capillaries
- Holo/hyperendemic
- Good News? Does not have hypnozoite
 - Hypnozoite: dormant liver form that causes relapse with *P. ovale*, *P. vivax*
 - Does not relapse, but can recrudesce





Malaria in a Complex Emergency: Symptoms

- UNCOMPLICATED
- **Fever**
 - **Not always cyclic!**
- Chills, sweats
- Headache
- Myalgia
- Diarrhea, nausea, emesis
- Anemia (pallor of palms)
- Thrombocytopenia
- Hepatosplenomegaly
- SEVERE
- > 5% parasitemia
- Severe anemia
- Hemoglobinuria
- Bleeding diathesis
- Shock/Hypotension
- Renal failure
- Hypoglycemia
- Acidosis
- **Neurologic abnormalities**
 - **Biggest killer**

“George Clooney Answers Your Questions About Malaria”



“The symptoms are fever, the chills, and exciting adventures in the toilet..weak..really just very bad flu conditions with a little food poisoning thrown in to make you the perfect party guest.”

Malaria in a Complex Emergency: Who is at Risk for severe disease?

- Highest risk populations:
 - Non-immune
 - Immunocompromised, malnourished
 - Infants, young children, pregnant
 - Infected with *P. falciparum*
- In endemic areas, older children and adults develop partial immunity
 - Can have “asymptomatic” infection
 - Can have subacute or chronic symptoms



Malaria in a Complex Emergency

- Displaced people within malaria endemic areas creates risk for a severe epidemic, particularly if the displaced persons are from less endemic areas (highlands to lowlands)
- Laboratory diagnosis may be impractical
- May become necessary to:
 - Treat some people based on clinical history
 - Do mass fever treatment

Malaria: Practical Aspects of Diagnosis

- Presumptive treatment has been commonplace for decades
 - Problematic, but hard to change
- Even in holoendemic countries, WHO estimates $<1/3^{\text{rd}}$ of febrile episodes due to malaria
- In Africa, $<20\%$ of suspected cases receive a confirmatory diagnostic test

Malaria in a Complex Emergency

- Important, when possible, to at least establish a fever epidemic is due to malaria
 - Do some diagnostics
 - Combination of smears and rapid diagnostic tests
 - To establish malaria as cause
 - To monitor epidemic curve
 - Evaluate for other diseases
 - Monitor clinical response

Malaria: Differential Diagnosis

- Malaria can involve many organs
- Coinfection well described
- Differential diagnosis is broad
 - *Salmonella typhi* and non-typhi
 - *Staphylococcus aureus* with focus (bone, joint, muscle, lung, heart)
 - Dengue, yellow fever, japanese encephalitis
 - Pneumonia
 - Viral and bacterial meningitis/encephalitis
 - Leshmaniasis
 - Schistosomiasis
 - Tuberculosis
 - Liver abscess/cholangitis
 - Oncologic process

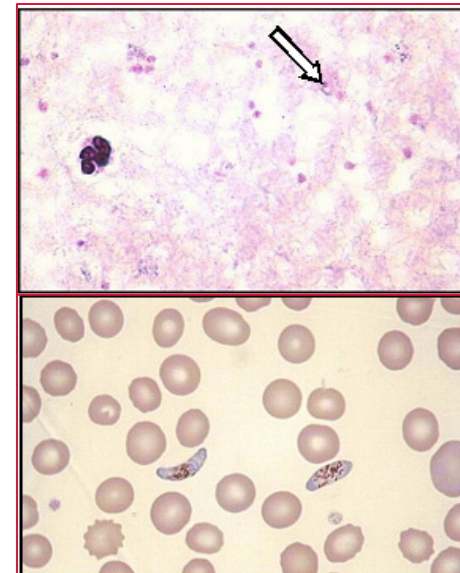
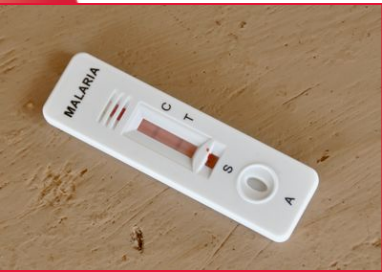
Malaria: Diagnostics


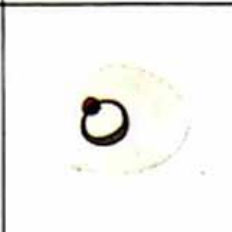
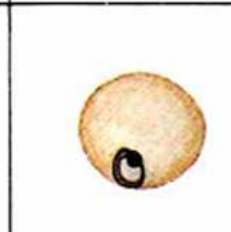




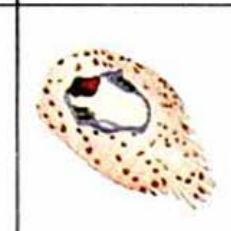



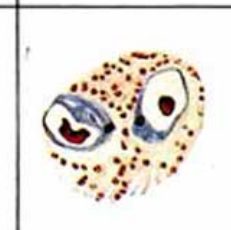



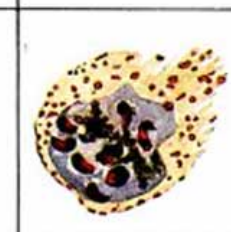







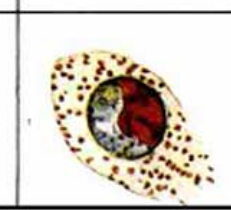
- Rapid diagnostic test (RDT)

- Lateral flow test, relies on antibody-antigen interactions
- Some RDTs specific for *P. falciparum*
- WHO quality assurance programs underway
 - Clinician/Public acceptance large problem
- USA: only to confirm species

- Microscopy

- Thick: diagnosis
- Thin
 - Identification and parasitemia
 - % parasitized RBCs

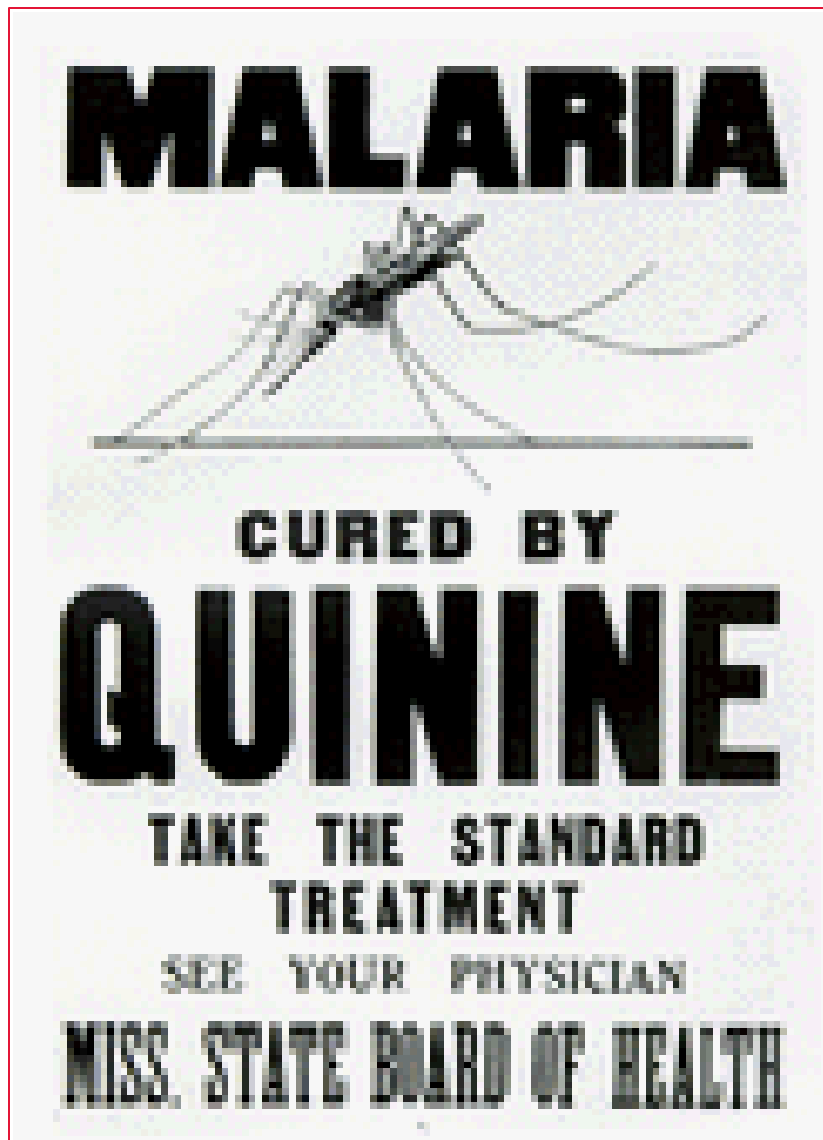


		<i>P. falciparum</i>	<i>P. vivax</i>	<i>P. malariae</i>	<i>P. ovale</i>
Trophozoites	Young				
	Old				
Schizonts	Immature				
	Mature				
Gametocytes	Male				
	Female				

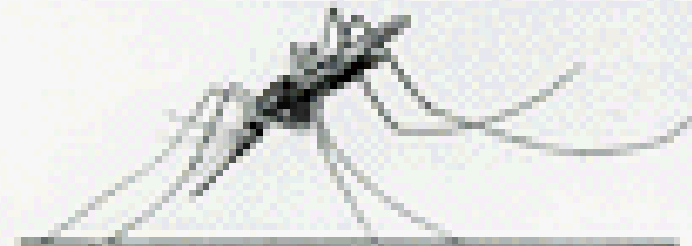
Clues to *P. falciparum*:

- Trophozoites most commonly seen, and are small, delicate rings, often multiple per RBC; infect all ages of RBC. Gametocytes “banana” shaped.

Malaria: Treatment



MALARIA



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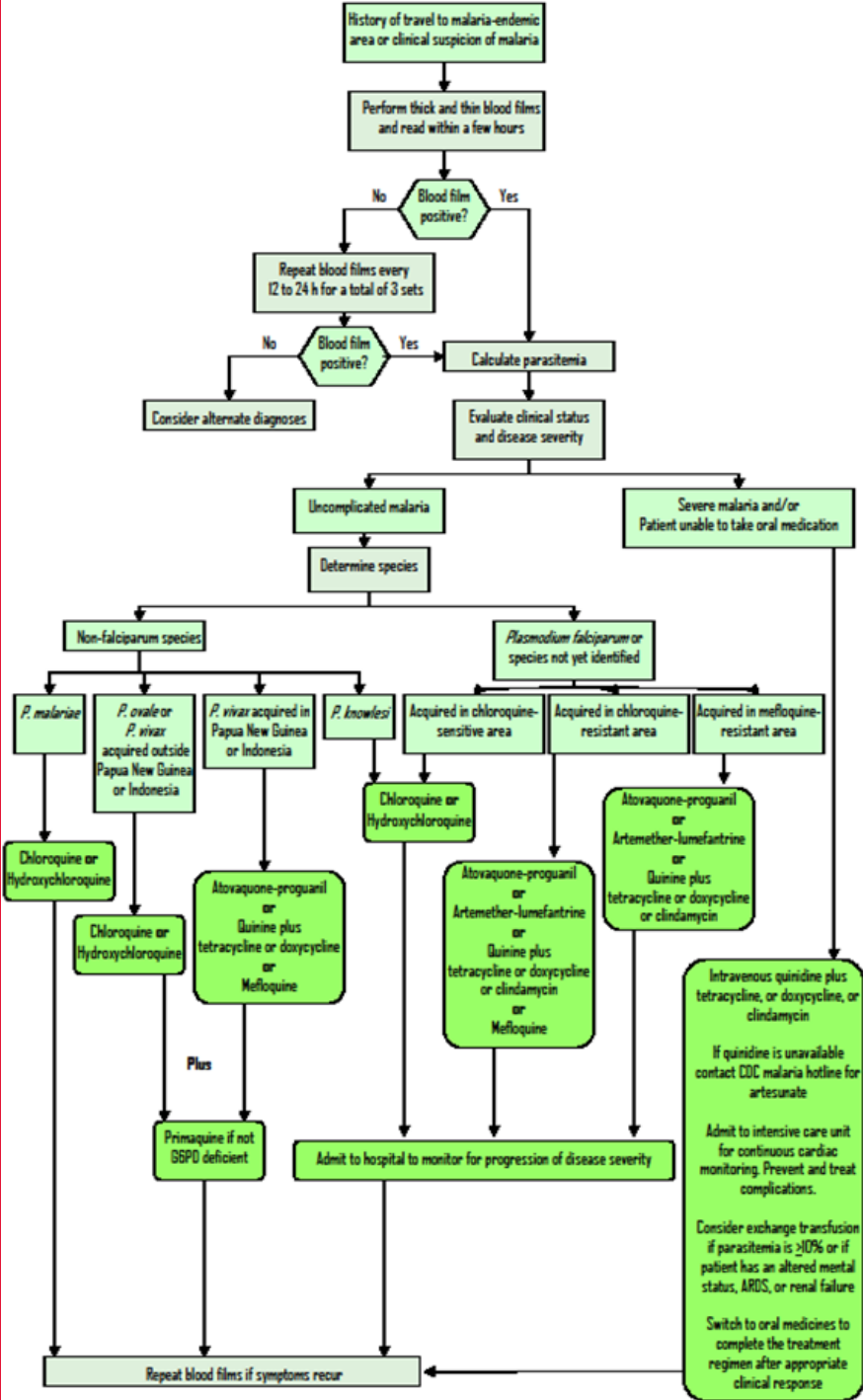
QUININE

**TAKE THE STANDARD
TREATMENT**

SEE YOUR PHYSICIAN

MISS. STATE BOARD OF HEALTH

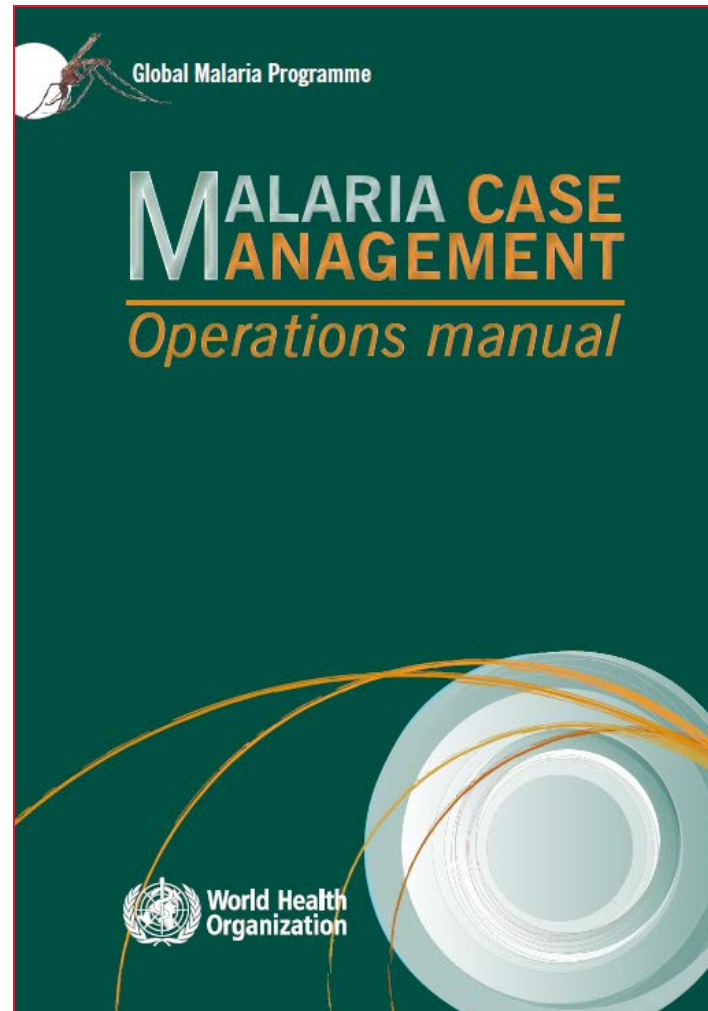
CDC Algorithm for Traveler Returned to US



* Not the same as WHO

Note: CDC now recommending treating severe malaria with artesunate; treat with atovaquone-proguanil until it arrives (5-12 hours). To enroll a patient with severe malaria in this treatment protocol, contact the CDC Malaria Hotline: 770-488-7788 (M-F, 8am-4:30pm, eastern time) or after hours, call 770-488-7100 and request to speak with a CDC Malaria Branch clinician.
http://www.cdc.gov/malaria/diagnosis_treatment/treatment.html

Malaria: Treatment



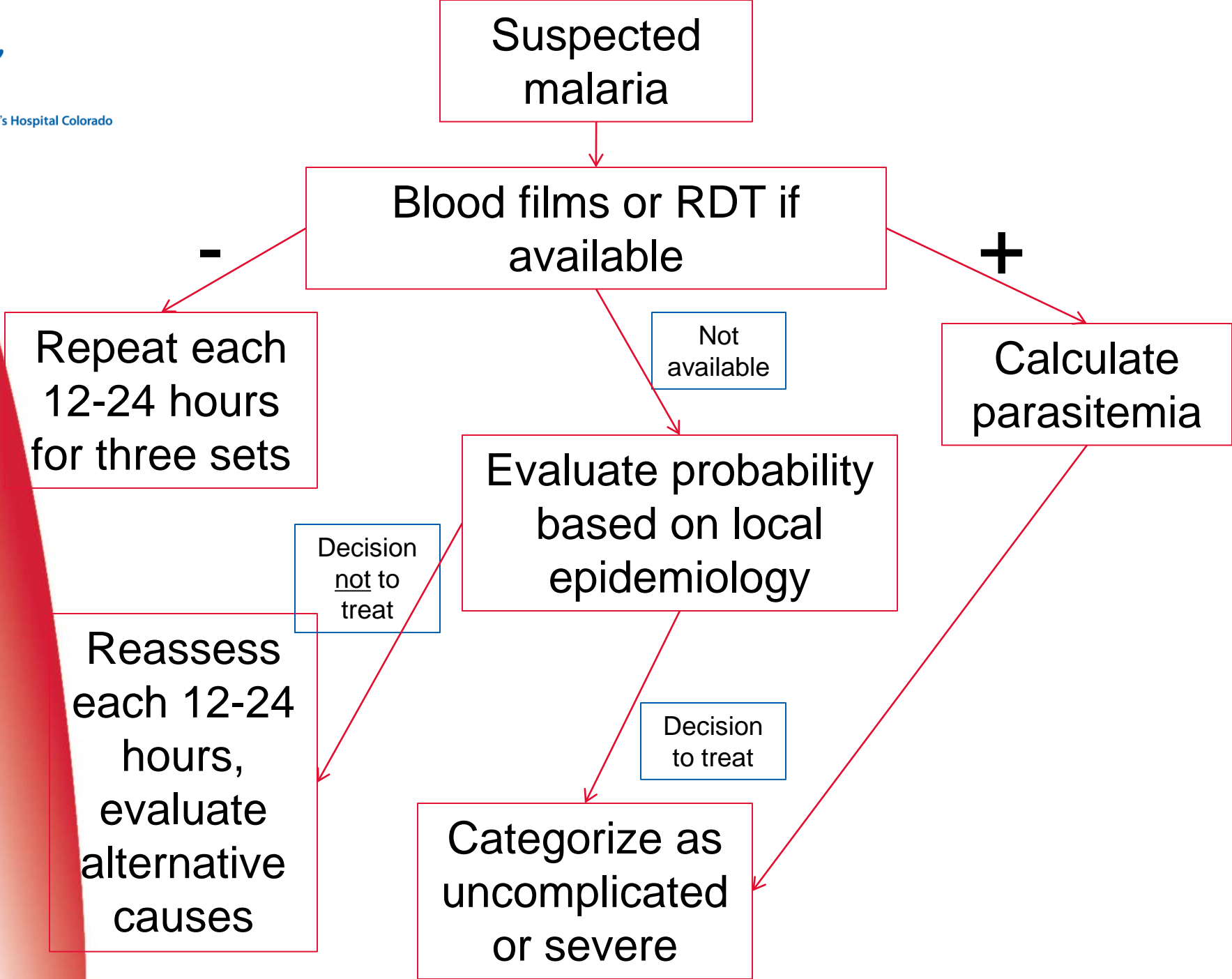
WHO guidelines and update can be found at:

<http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html>

Malaria: Therapy Options

Default ACT
in the
Interagency
Emergency
Health Kit

- ACT (Artemisinin based combination therapies)
 - **Artemethur + lemefantrine (coartem®)**
 - Artesunate + amodiaquine (coarsucam/ASAQ Winthrop®)
 - Artesunate + mefloquine (AS+MQ)
 - Artesunate + sulfadoxine-pyrimethamine (AS+SP)
 - Not for *P. vivax*
- Artesunate + doxycycline or clindamycin
- Dihydroartemisinin plus piperaquine (DHA+PPQ)
- Quinine + doxycycline or clindamycin
- Atovaquone + proguanil (malarone®)
- Mefloquine (larium®)
- Chloroquine (widespread resistance)
- Primaquine (kills liver phase for *P. vivax/ovale*)
- IV and IM: Artesunate, artemethur, quinine
- Rectal: Artesunate



Uncomplicated malaria: treatment

P. falciparum possible by epidemiology or smear?

-

+

Use local resistance patterns to choose medication:

- **Chloroquine**
- **ACT**
- Hydroxychloroquine
- Atovoquone-proguanil
- Mefloquine
- Quinine + doxycycline
- * Re-dose if emesis within 30 min

Use local resistance patterns to choose medication:

- **ACT**
- artesunate plus tetracycline /doxycycline/clindamycin
- Quinine plus tetracycline /doxycycline/clindamycin
- Atovoquone-proguanil
- Mefloquine
- Quinine + doxycycline
- * Re-dose if emesis within 30 min

If *P. vivax/ovale* and patient not G6PD deficient, treat with primaquine

Consider admission to monitor disease progression

Severe Malaria: WHO Criteria

One or more of the following:

- *Clinical features:*
- Impaired consciousness, prostration
- Failure to feed
- Seizures
- Respiratory distress
- Circulatory collapse
- Clinical jaundice plus evidence of other vital organ dysfunction
- Gross hemoglobinuria
- Abnormal spontaneous bleeding
- Pulmonary edema (radiological)
- *Laboratory findings:*
- Hypoglycemia (blood glucose < 2.2 mmol/l or < 40 mg/dl)
- Metabolic acidosis (plasma bicarbonate < 15 mmol/l)
- Severe normocytic anaemia (Hb < 5 g/dl, packed cell volume < 15%)
- Hemoglobinuria
- Hyperparasitaemia (> 2%/100 000/ μ l in low intensity transmission areas or > 5% or 250 000/ μ l in areas of high stable malaria transmission intensity)
- Hyperlactatemia (lactate > 5 mmol/l)
- Renal impairment (serum creatinine > 265 μ mol/l).

Severe malaria: Treatment the same regardless of species!
Therapy + supportive care:

Intravenous medications available?

no

yes

Give oral or rectal until patient can be transferred to referral center:

- rectal artesunate
- quinine IM
- artesunate IM
- artemether IM

Ongoing supportive care, including:

- evaluation for blood transfusion
- treatment for coinfection
- treatment of seizures

Treat IV x 24 hours minimum
Artesunate IV or IM
Artemether
Quinine

If illness is with *P. ovale/vivax*, follow with primaquine if not G6PD deficient

Follow with full course of oral antimalarial:

- ACT
- artesunate plus clindamycin or doxycycline
- quinine plus clindamycin or doxycycline

Malaria: Prevention

- Bed Nets!!!!!!
 - 1000 nets save 5 lives
 - Insecticide impregnated best
 - Cochrane Review, 2009
- Indoor/personal insecticides
- Vaccine: on the horizon?
 - Some candidates reaching clinical trials, with short-lived efficacy

Take Home Points

- Malaria endemicity and seasonality depends on mosquito habits, seasonality, and *Plasmodium spp.*
- Resistance to medications is species and location dependant
 - If *P. falciparum*, assume chloroquine resistant
 - Exception: Island of Hispaniola
- Clinical:
 - Who is at highest risk
 - How to differentiate severe vs. uncomplicated malaria
 - Differential diagnosis
- How to choose an anti-malarial treatment:
 - ACTs are preferred therapies, all species
 - ACT if oral, artesunate if IV
 - Severe malaria treated same regardless of species
- Where to find up-to-date resources on Malaria

Malaria: Resources

- Interactive map on malaria activity:
 - <http://cdc-malaria.ncsa.uiuc.edu/>
- How to do a malaria smear:
 - C:\Documents and Settings\dr003093\Desktop\MMWR diagnosis of malaria.mht
- How to interpret a malaria smear:
 - http://dpd.cdc.gov/dpdx/html/Frames/M-R/Malaria/body_Malariadiagfind2.htm
 - <http://www.dpd.cdc.gov/dpdx/HTML/DiagnosticProcedures.htm>
- How to treat Malaria
 - WHO guidelines:
<http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html>