

Anti-Malaria Chemotherapy

- **Causal Prophylaxis**
 - prevent infection (ie, liver stage)
- **Suppressive Prophylaxis**
 - prevent clinical disease (ie, blood stages)
- **Treatment Therapy (or clinical cure)**
 - relieve symptoms
 - eliminate blood stage parasites
- **Curative Therapy (or radical cure)**
 - eliminate parasites w/o regard to symptoms
- **Anti-Relapse Treatment**
 - eliminate hypnozoites

Selected Anti-Malarials

Drug Class	Examples
Fast-acting blood schizontocide	chloroquine (+ other 4-aminoquinolines), quinine, quinidine, mefloquine, halofantrine, antifolates (pyrimethamine, proquanil, sulfadoxine, dapsone), artemisinin derivatives (quinhaosu)
Slow-acting blood schizontocide	doxycycline (other tetracycline antibiotics)
Blood + mild tissue schizontocide	proquanil, pyrimethamine, tetracyclines
Anti-relapsing	primaquine
Gametocidal	primaquine, 4-aminoquinolines (limited?)
Combinations	Fansidar (pyrimethamine + sulfadoxine), Maloprim (pyrimethamine + dapsone), Malarone (atovaquone + proquanil)

Treatment Strategies

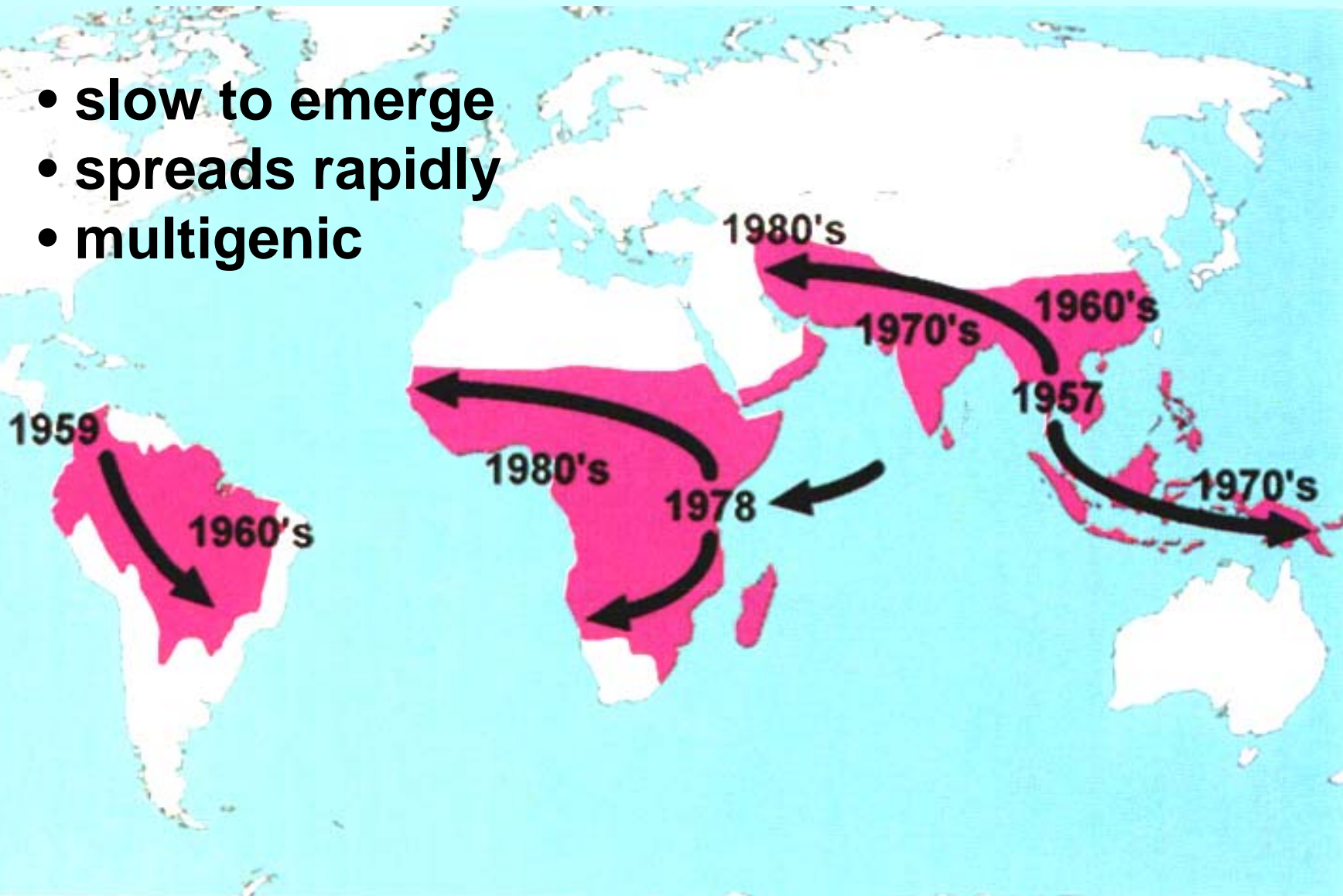
- **chloroquine sensitive (all species)**
 - **CQ + primaquine (vivax/ovale)**
- **chloroquine resistance (or unknown)**
 - **Fansidar, mefloquine, quinine, artemesin derivatives**
- **severe malaria**
 - **i.v. infusion of quinine or quinidine (or CQ, if sensitive)**
 - **i.v. artemisinin derivatives (if available)**

Chemoprophylaxis

- recommended for transient visits to endemic areas
- choice of drug depends on risk of malaria and degree of resistance in that area
- many non-toxic drugs of limited use because of resistance
 - eg., chloroquine, pyrimethamine, proguanil
- presumptive (or 'standby') treatment
 - carry Fansidar, mefloquine, quinine

Spread of Chloroquine Resistance

- slow to emerge
- spreads rapidly
- multigenic



Drug Resistance

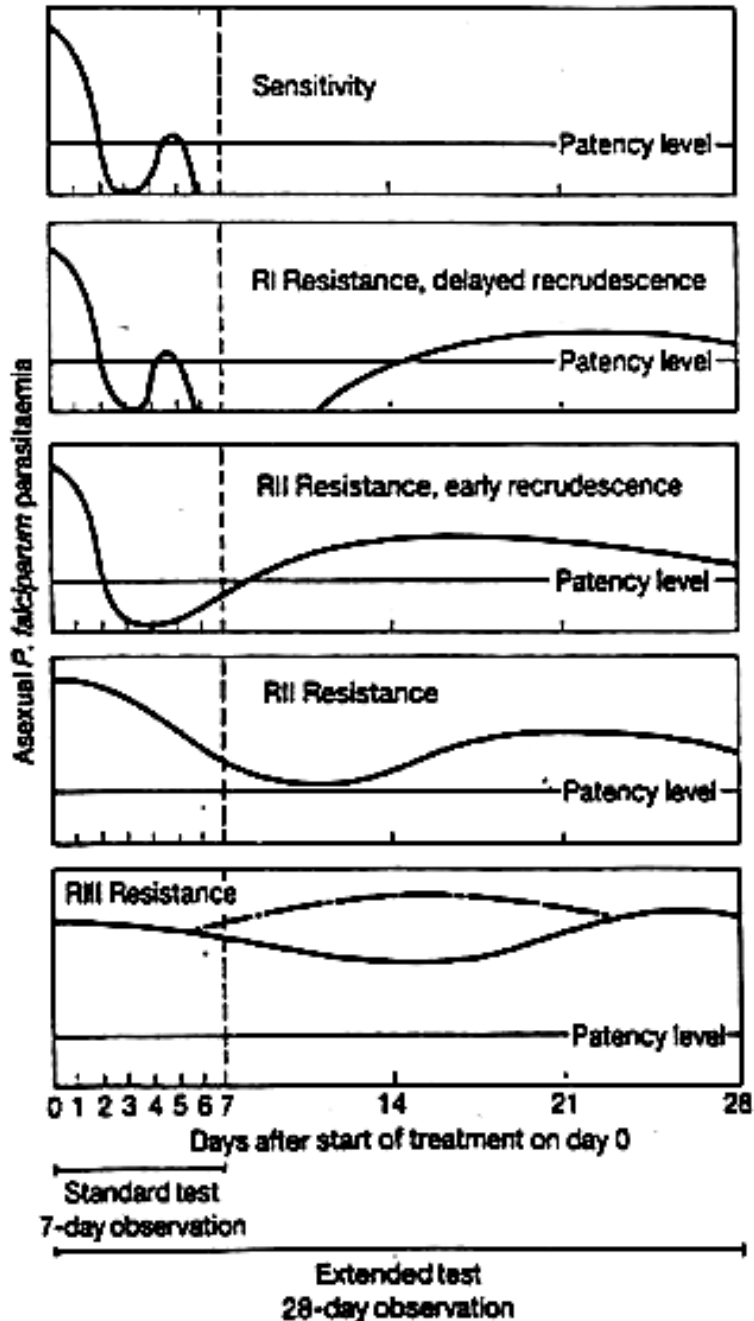
Mechanisms

- mutations in target gene
- ↑ production of target
- ↓ drug accumulation
(includes ↑ efflux)
- drug inactivation

Spread

- self treatment
- poor compliance
- mass administration
- long drug half-life

Drug Resistance



- defined by treatment failures
- rule out other factors:
 - non-compliance
 - bad quality
 - wrong dose
 - vomiting
- 28-day or other tests (RI, RII, RIII levels of resistance)

Modified Protocol

- introduced by WHO in 1996
- more practical in areas of intense transmission
 - difficult to distinguish re-infection from recrudescence
 - parasitemia in the absence of clinical symptoms is common
- based on clinical outcome:
 - adequate clinical response (ACR)
 - late treatment failure (LTF)
 - early treatment failure (ETF)

ACR

nothing at day 14

LTF

reappearance
during days 4-14

ETF

persistence
during days 1-3

Distribution of Malaria

A world map with a grid overlay, showing the distribution of malaria. The map is dark with white outlines for continents and a white grid. The regions of South America, sub-Saharan Africa, and parts of Southeast Asia and the Pacific are highlighted in a light yellow color, indicating endemic areas. The rest of the world is in dark grey.

- **tropical and subtropical climates**
- **formerly widespread in temperate zones (ague)**
- **40% of worlds population live in endemic regions**

Distribution of Malarial Parasites

P. vivax

most widespread, found in most endemic areas including some temperate zones

P. falciparum

primarily tropics and subtropics

P. malariae

similar range as *P. falciparum*, but less common and patchy distribution

P. ovale

occurs primarily in tropical west Africa

Malaria Epidemiology

Stable or Endemic Malaria

- ~constant incidence over several years
 - includes seasonal transmission
- immunity and disease tolerance correlates with level of endemicity (especially adults)

Endemicity

Levels:

- holo-
- hyper-
- meso-
- hypo-

Unstable or Epidemic Malaria

- periodic sharp increase in malaria
- little immunity
- high morbidity and mortality

Roper et al (1996) AJTMH 54:325

Date Tested	% Incidence (smear/PCR)*	
Sep 93	13% (2/8)	} 33% reported symptoms
Jan 94	19% (4/11)	
Apr 94	24% (8/11)	} no symptomatic cases
Jun 94	19% (0/14)	

*Number of individuals testing positive by blood smear and PCR. PCR assay detects ~2.5 parasites/ μ l (4-10X more sensitive than thick smears).

- eastern Sudan (mesoendemic, seasonal)
 - rainy season June-Sept.
 - peak symptomatic malaria Oct.-Nov.
- followed cohort of 79 individuals using thick films and PCR (*P. falciparum*)

Mosquito Transmission

- susceptibility of anopheline species
- feeding habits
- density
- longevity
- climatic factors
 - temperature, humidity, rainfall, wind, etc



Anopheles

"Everything about malaria is so moulded by local conditions that it becomes a thousand epidemiological puzzles."

Hackett (1937)

Malaria Control

Reduce Human-Mosquito Contact

- **impregnated bed nets**
- **repellants, protective clothing**
- **screens, house spraying**

Reduce Vector

- **environmental modification**
- **larvacides/insecticides**
- **biological control**

Reduce Parasite Reservoir

- **diagnosis and treatment**
- **chemoprophylaxis**