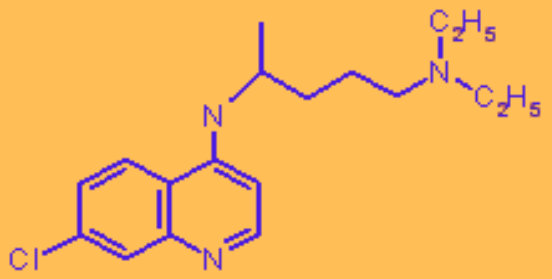
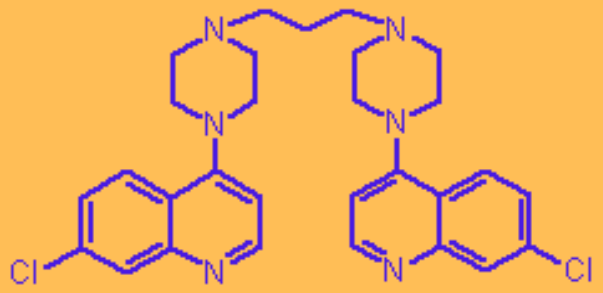
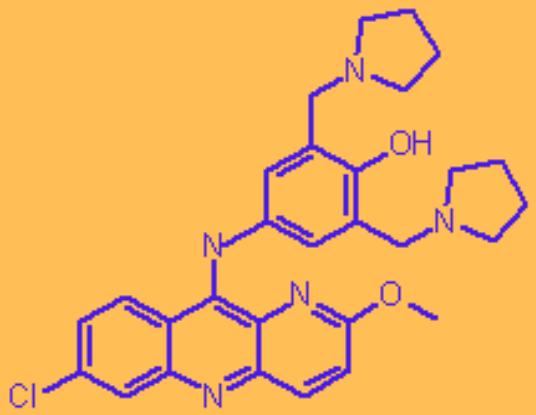
Some Compounds Related to Chloroquine that Are Used against Chloroquine-Resistant Malaria



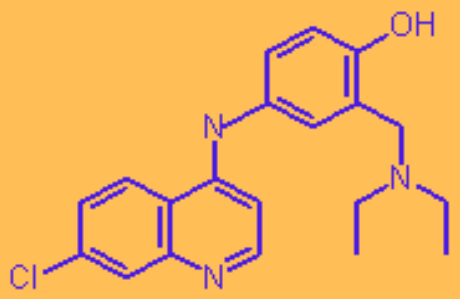
Chloroquine



Piperaquine



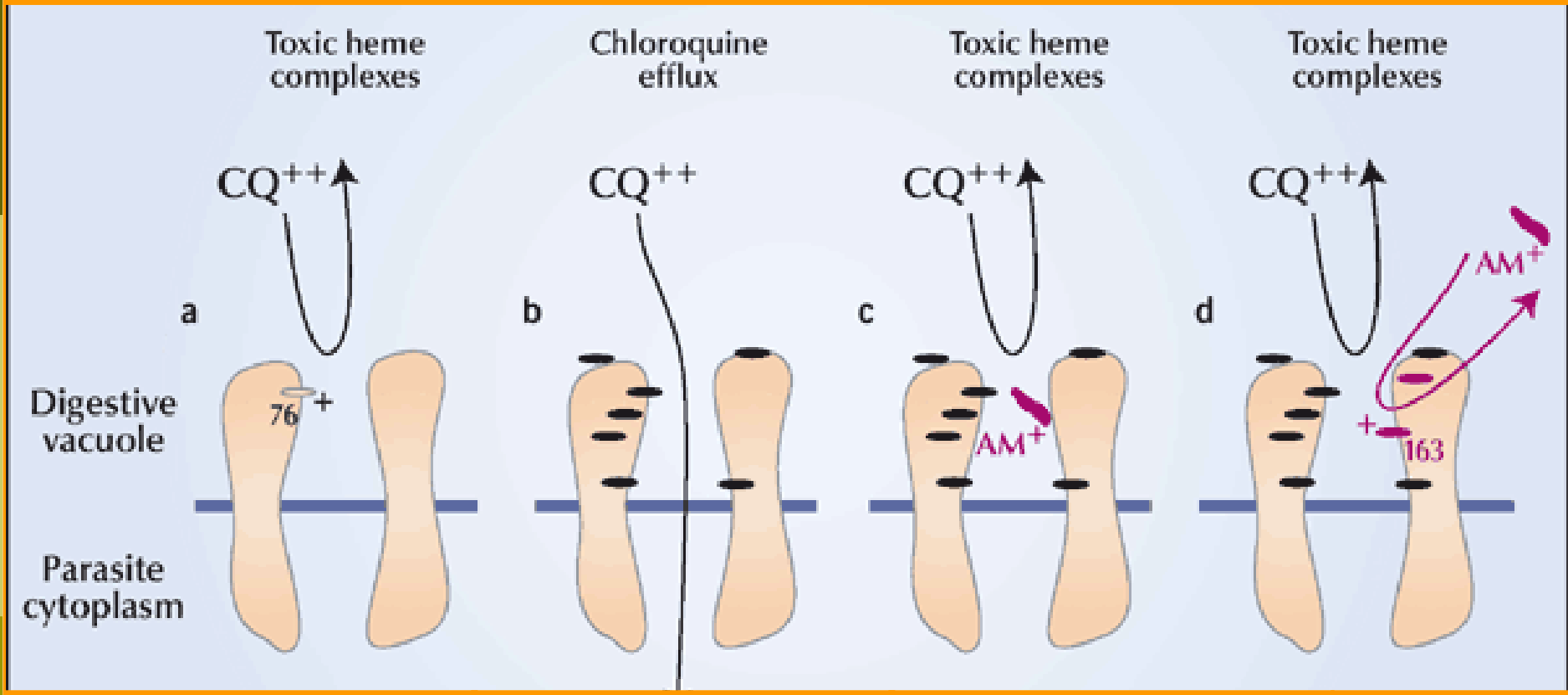
Pyronaridine



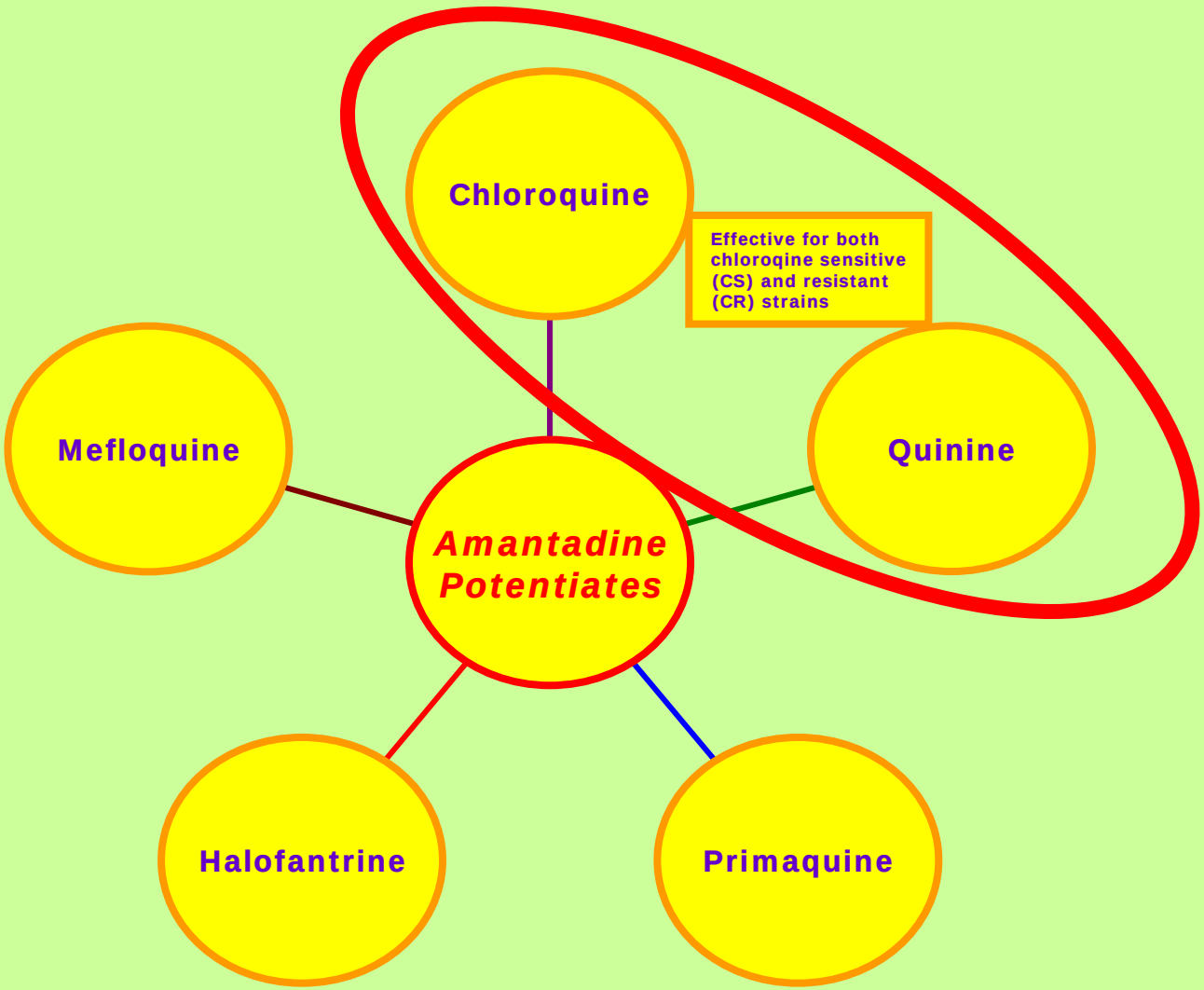
Amodiaquine

PfCRT Mutation and Chloroquine Response
Role of Amantadine for Chloroquine-R Malaria

[Thomas E Wellems1 Nature Medicine 10, 1169 - 1171 (2004)]



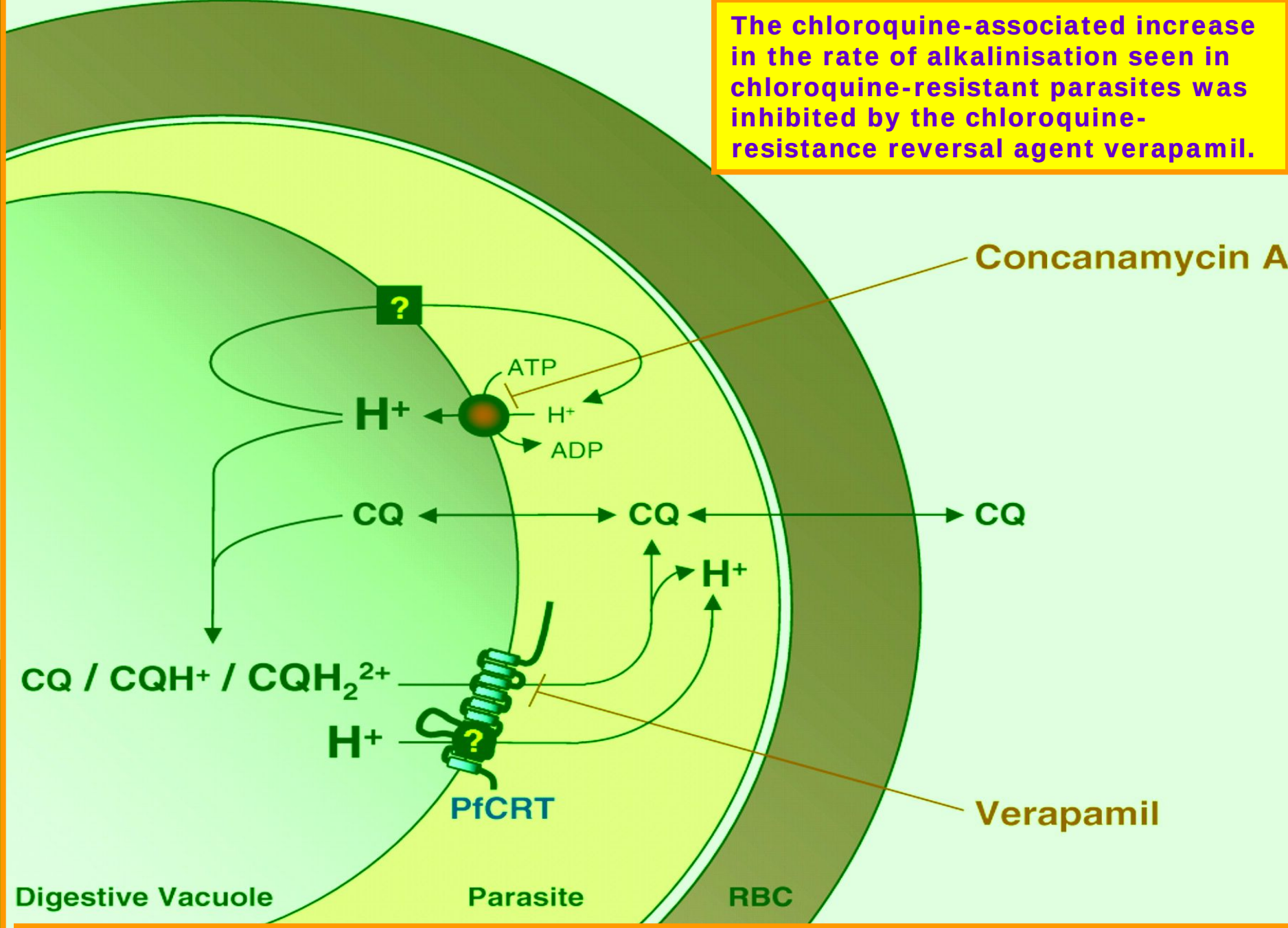
Wild-type parasites carrying PfCRT Lys76	PfCRT mutation confer cloroquine- R	Amantadine reverse chloroquine resistance	I356V Mutant
Positive charge of PfCRT Lys76 prevent efflux of chloroquine from food vacuoles	M74I, N75E, K76T, A220S, Q271E, N326S and R371I PfCRT point mutation remove positive charge of Lys76 ➔ resistance	Positively charged amantadine binds in the PfCRT pore of chloroquine-resistant parasites and prevents chloroquine efflux.	S163R mutation blocks CQ efflux and amantadine binding.



Amantadine potentiated the effect of chloroquine and quinine in both CR and CS strains; it also potentiated the effect of mefloquine, halofantrine and primaquine in the chloroquine-resistant strain but had no effect in the chloroquine-sensitive strain. Amantadine had no effect on the response to pyrimethamine of either strain. Amantadine does not interfere with the activity of these compounds and may possibly enhance it.

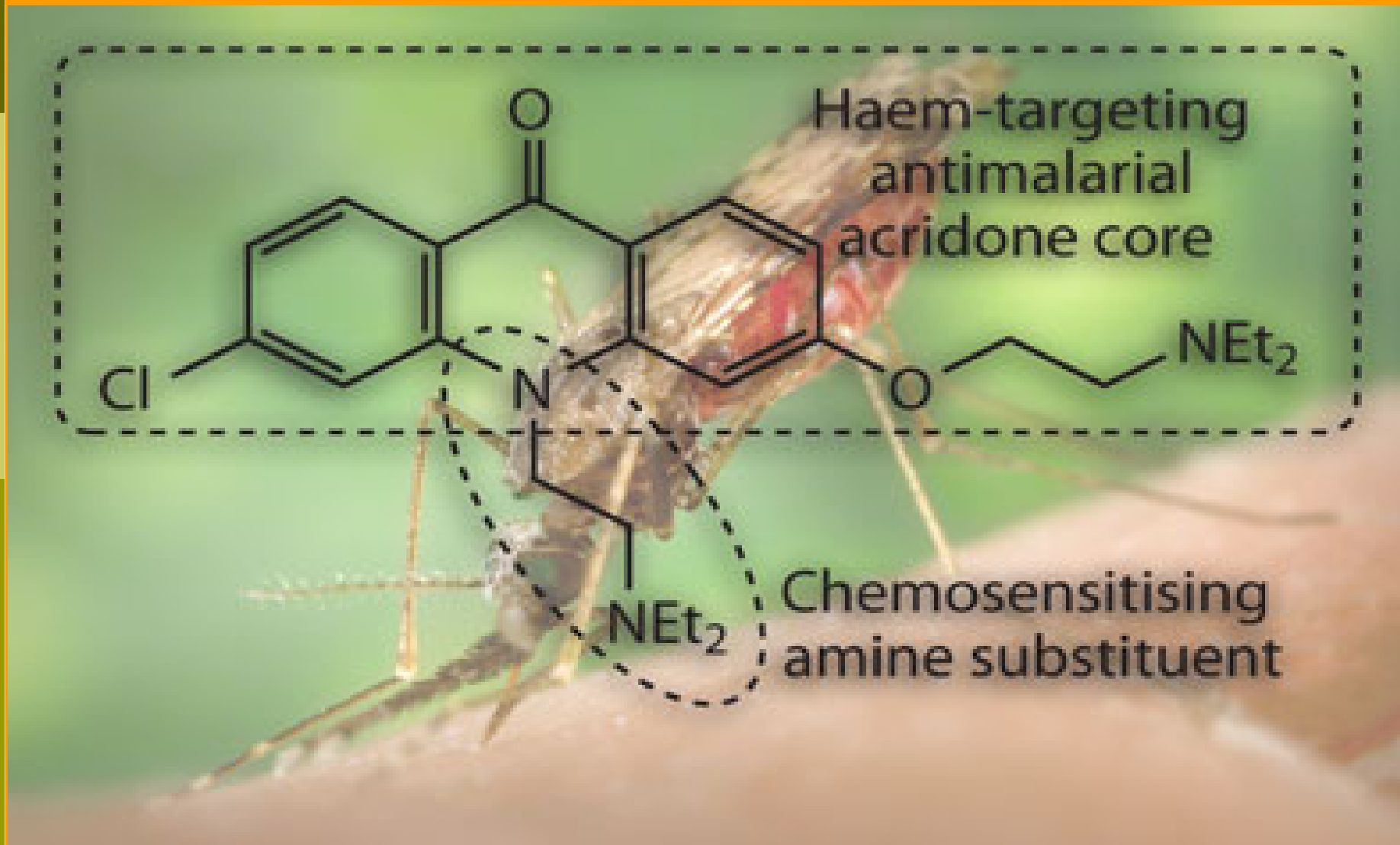
In vitro drug interaction between amantadine and classical antimalarial drugs in Plasmodium falciparum infections Sandra Gail Evans, Ivan Havlik Volume 88, Issue 6, Pages 683-686 (November 1994)

The chloroquine-associated increase in the rate of alkalinisation seen in chloroquine-resistant parasites was inhibited by the chloroquine-resistance reversal agent verapamil.

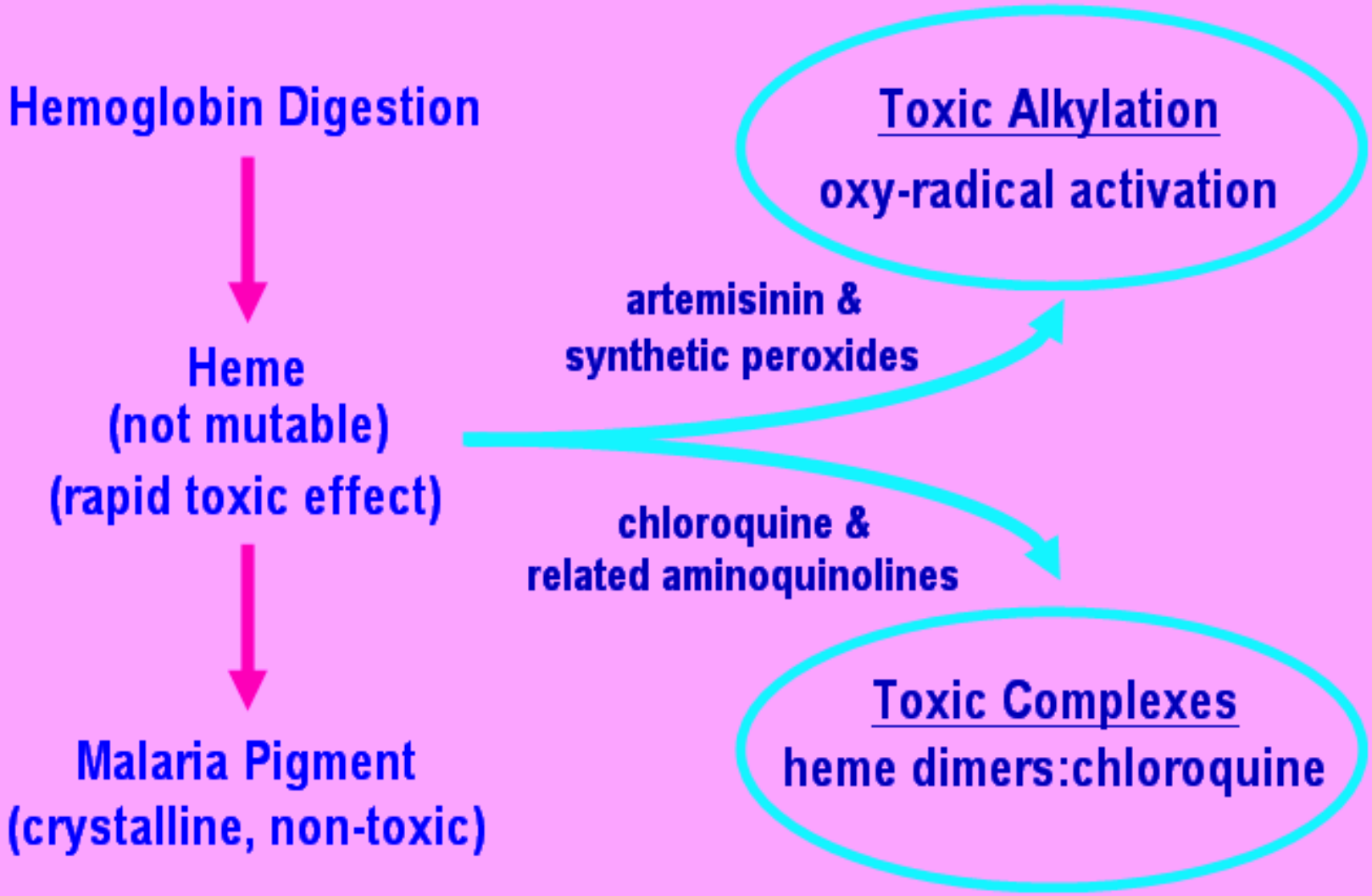


A verapamil-sensitive chloroquine-associated H+ leak from the digestive vacuole in chloroquine-resistant malaria parasites.Lehane AM. Hayward R. Saliba KJ. Kirk K. Journal of Cell Science. 121(Pt 10):1624-32, 2008 May 15.

PfCRT actively pumps drug molecules (e.g. chloroquine) out of the target area, rendering them ineffective. Tricyclic acridone molecules with a short alkyl amine chain attached to the central nitrogen atom could make chloroquine-resistant parasites susceptible to the drug again. This action is attributed to blocking the PfCRT pump protein, meaning that the chloroquine can reach its target. ***(J X Kelly et al, Nature, 2009.)***



Heme Remains an Effective Target for Drugs



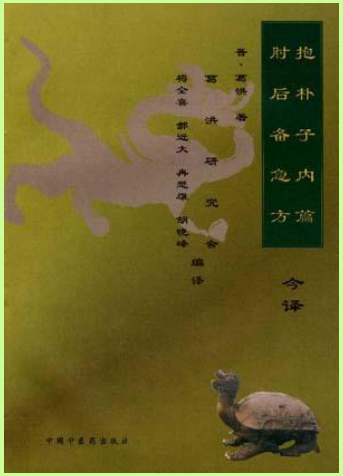
Jefford (2001) *Curr.Med.Chem.* 8:1803-26;
Chou *et al.* (1980) *Biochemistry* 19:1543-9

The Breakthrough of anti-malaria therapy
An ancient drug in China REDISCOVERED

***Artemesia annua* or**
Chinese wormwood
(中草药青篙，学名黄花篙)
➔ artemisinin (青蒿素),

"Fifty-two Prescriptions" of Artemisia annua (annual wormwood), 青蒿 from the Mawangdui Han Dynasty Tombs 200 B.C. unearthed.

瘧 (Nüe) Intermittent Fever



Ge Hong *284–363 肘後備急方*
Emergency Prescriptions to Keep up your Sleeve
Treatment of intermittent fever
'Another recipe: ***qinghao****, one bunch, take two sheng [2 x 0.2 l] of water for soaking it, wring it out (擰乾)* ***take the juice****, ingest it in its entirety'*

屠呦呦 To Youyou
Dihydroartemisinin

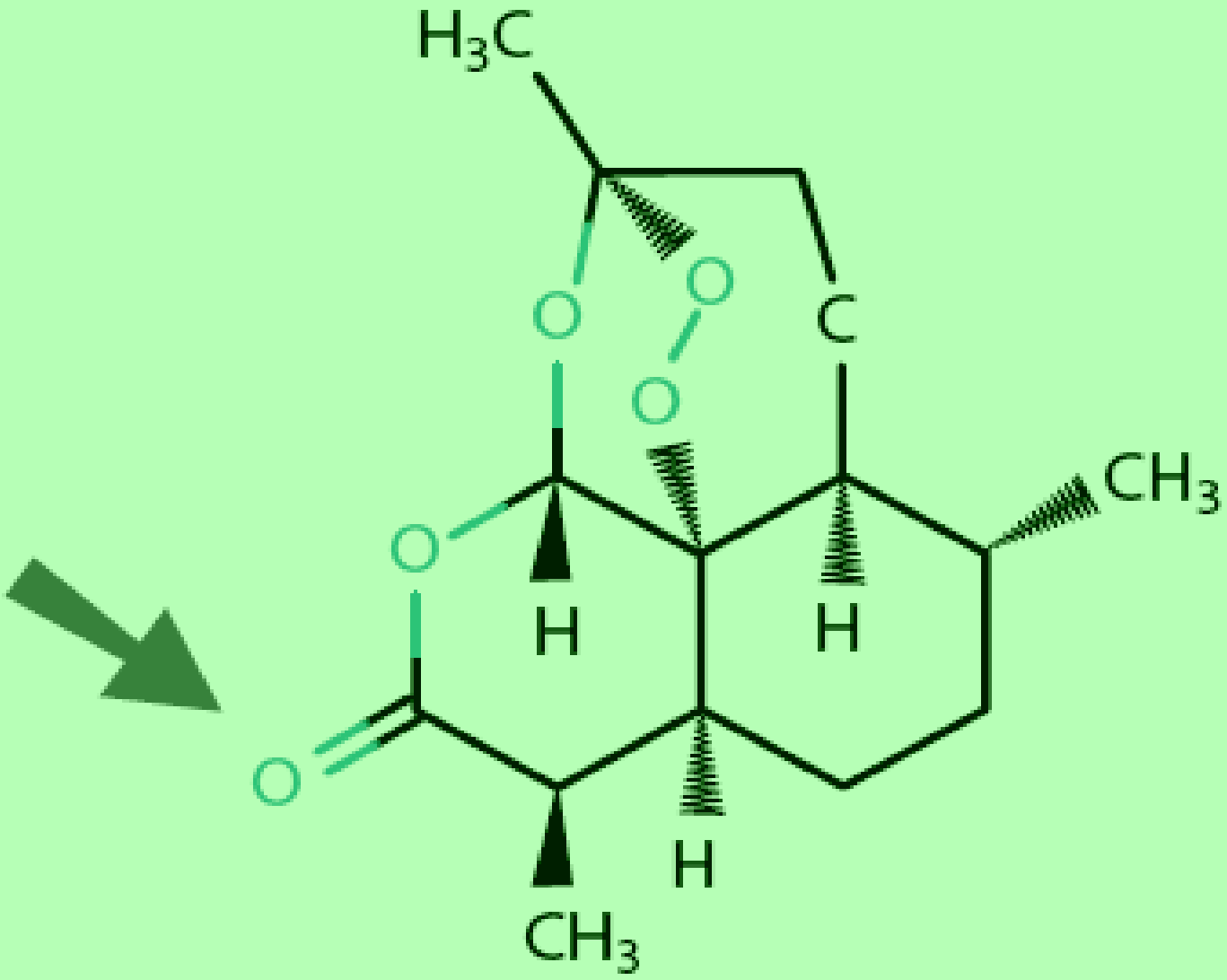
Artemisia annua

Materia medica => 青蒿 Qinghao

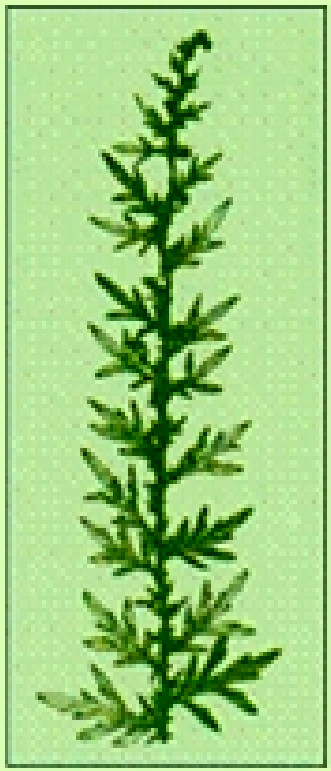
Artemisinin is water insoluble

Artemisinin

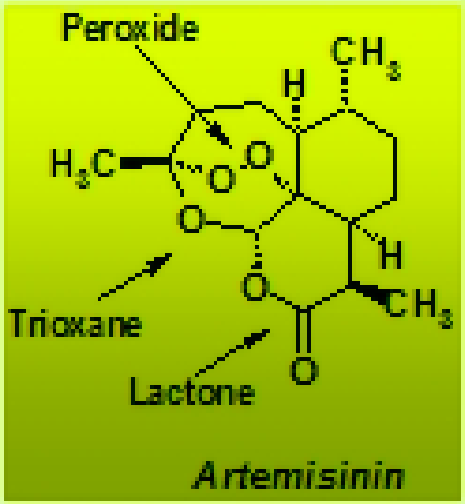
Molecular weight: 282.3

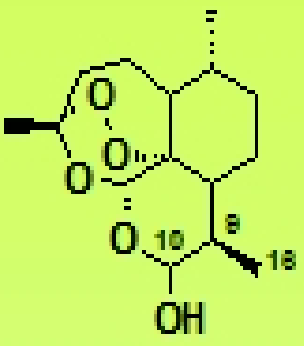


Artemisinin is naturally-occurring endoperoxide sesquiterpene lactone

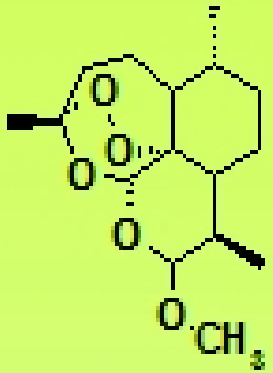


Artemisia annua

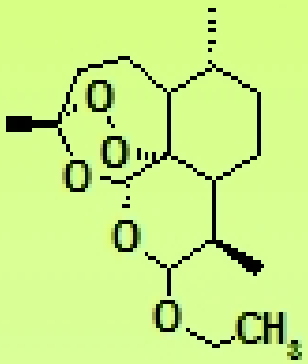




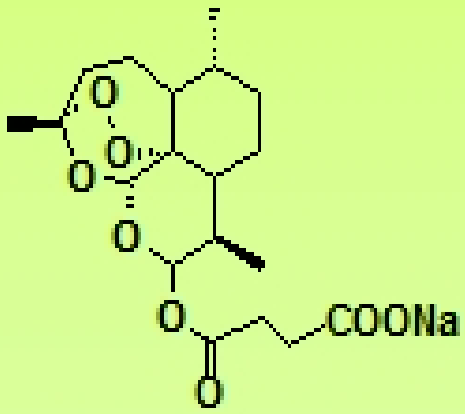
Dihydroartemisinin (DHA) (Artenimol)



Artemether (Artemos)



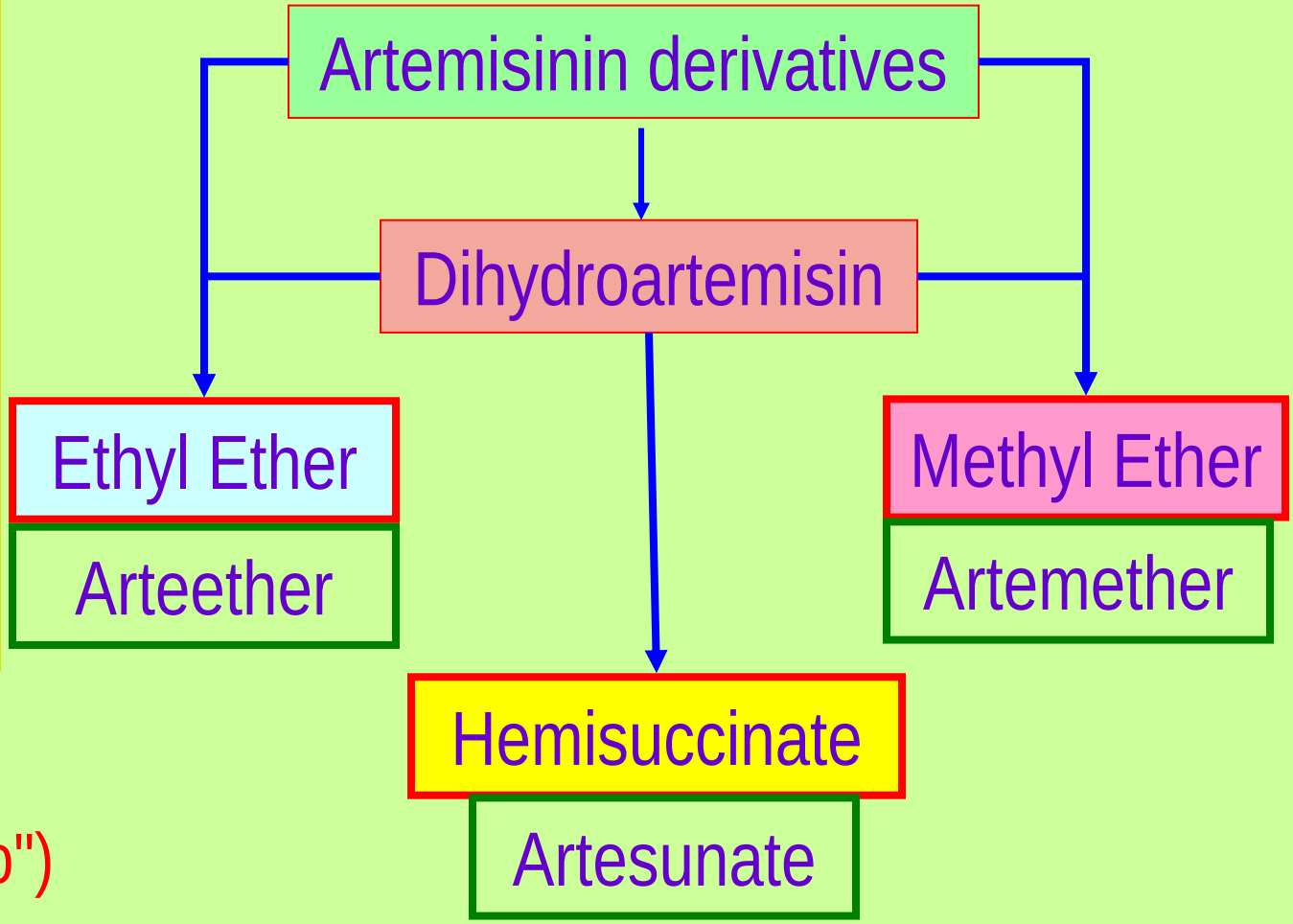
Arteether (Artemotil)



Sodium artesunate

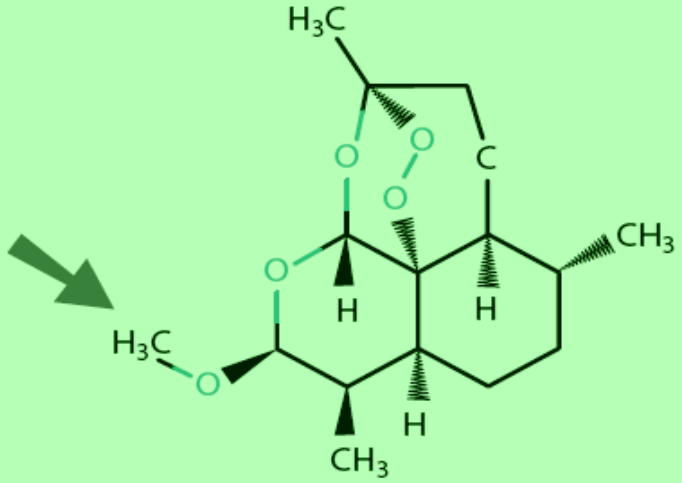
Artemisinins Derivatives

Qinghaosu
("ching-how-soo")



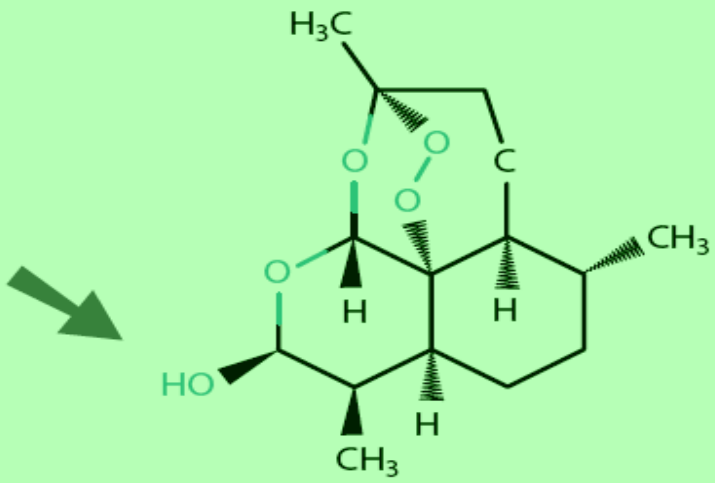
Artemether

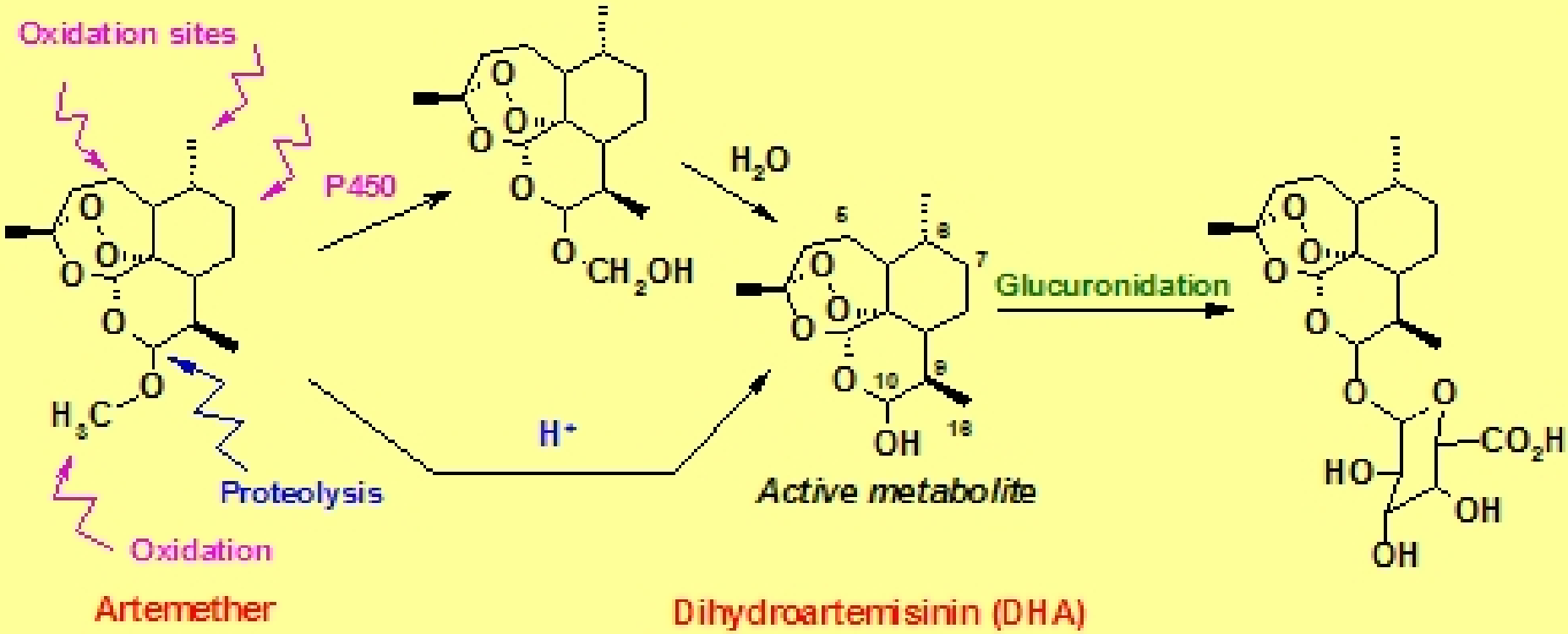
Molecular weight: 298.4

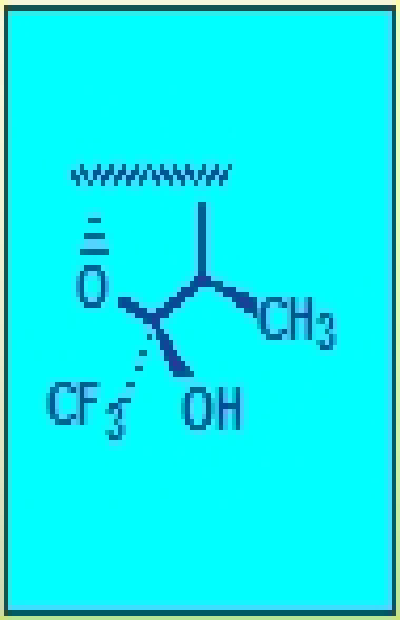


Dihydroartemisinin

Molecular weight: 284.4







Good antimalarial activities, oral administration

good metabolic stability

good compromise lipophilicity/solubility

Good chemical stability

Easily prepared in large scale

1 step , high yield

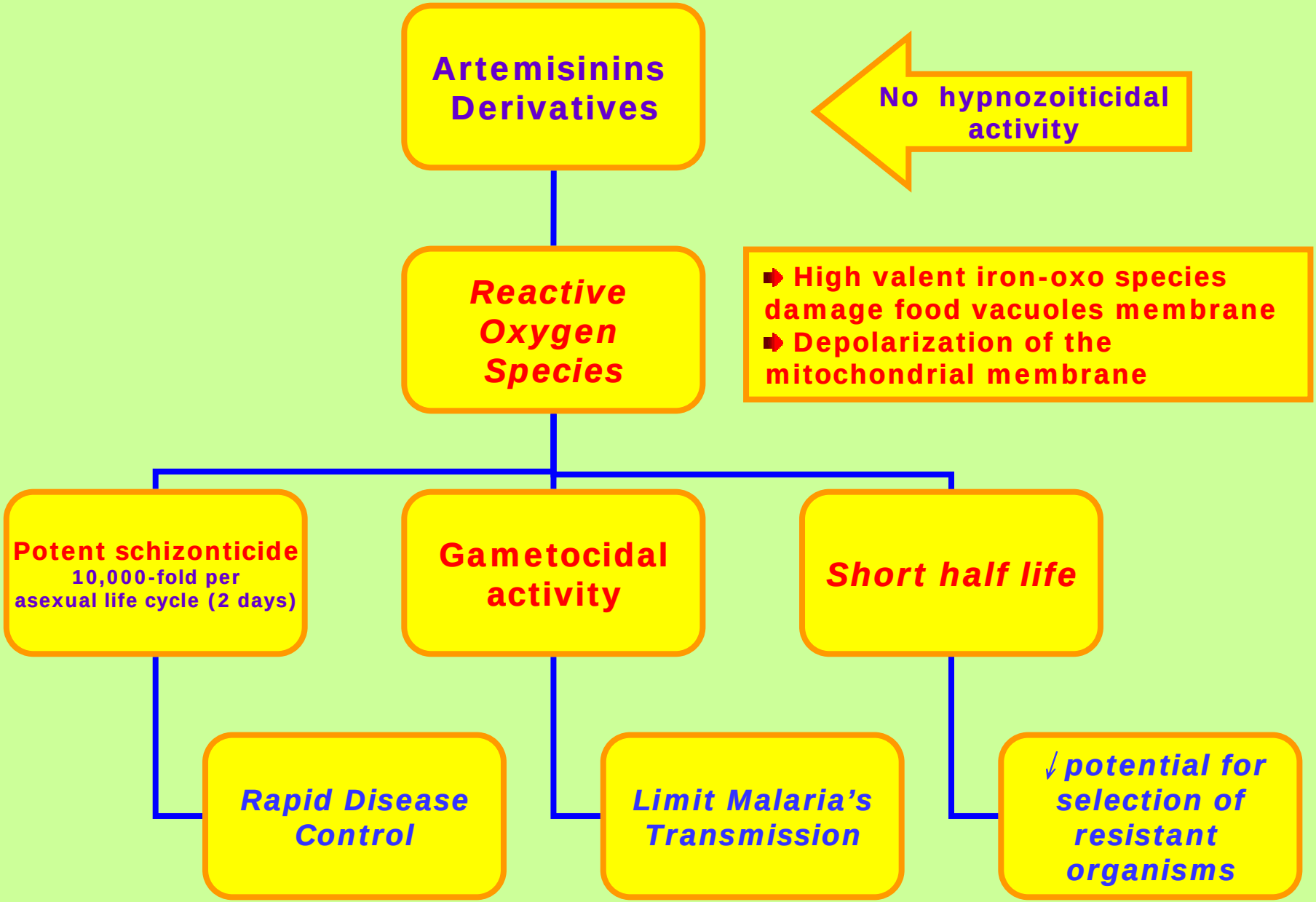
isolation by crystallization

Toxicity

DL_{50} = 820 mg/Kg Therapeutic index : > 190

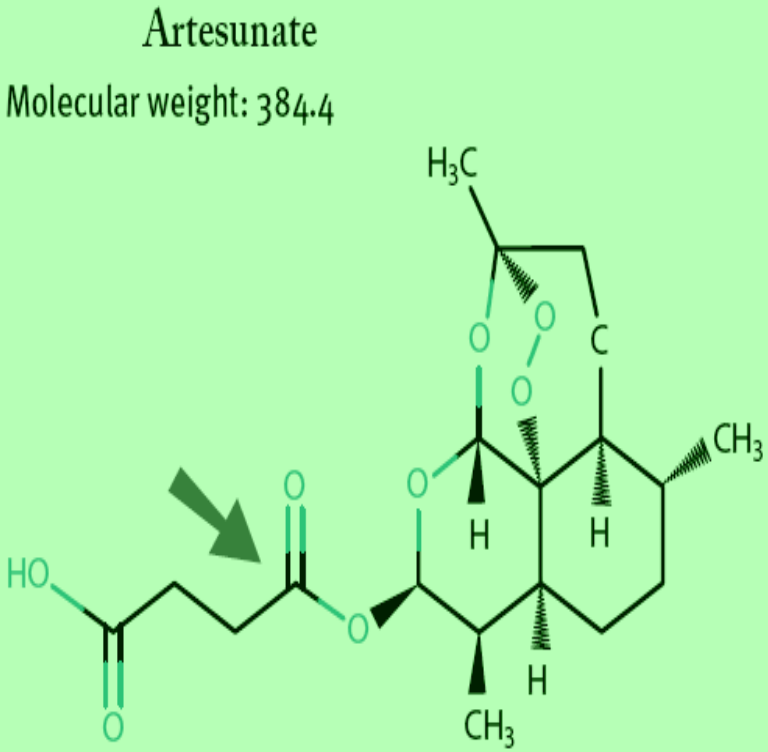
Sub-acute toxicity on rodents and monkeys: no undesirable effects

Dihydroartemisin


Artemisinins Derivatives
No hypnozoiticidal activity
Reactive Oxygen Species
High valent iron-oxo species damage food vacuoles membrane
Depolarization of the mitochondrial membrane
Potent schizonticide
10,000-fold per asexual life cycle (2 days)
Gametocidal activity
Short half life
Rapid Disease Control
Limit Malaria's Transmission
↓ potential for selection of resistant organisms

Artesunate is water-soluble hemisuccinate derivative of dihydroartemisinin
- Available in oral, IVI, IMI and PR form

Artesunate should not be used during the first trimester of pregnancy.



- After parenteral administration, artesunate is rapidly hydrolyzed to the active metabolite dihydroartemisinin. The oral formulation is probably hydrolysed completely before entering the systemic circulation.
- Peak serum levels occur within one hour of an oral dose with elimination half-life of 45 minutes.
- Artesunate has a minimal effect on hepatic cytochrome P450 activity and does not appear to influence the metabolism of mefloquine, a drug likely to be used in combination with artesunate.
- Artersunate does not inhibit the formation of carboxy-primaquine, a metabolite of primaquine.

IV Administration of Artesunate

- Step. 1 : The powder for injection should be reconstituted with **1ml of 5% sodium bicarbonate** and shaken vigorously till the solution becomes clear.
- Step 2 : For I.V. use, add 5 ml (2ml for I.M. use) of normal saline or 5% of glucose and mix again.
- Step 3 : For I.V. use, the required amount of the drug is administered slowly over a period of **2 - 3 minutes**.
- The powder for Injection is difficult to dissolve and care should be taken to **ensure that it is completely dissolved before parenteral administration**. It should always be used immediately after reconstitution. If the solution is cloudy or a precipitate is present, the parenteral preparation should be discarded.
- The speed for intravenous injection is 3-4 ml per minute.

	Hypotension if injected rapidly	Hypotension with rate controlled infusion	ECG QRS widening	ECG QT prolongation
Quinine	+ + +	0	+	+
Quinidine	+ + +	+ +	+	+ + +
Chloroquine	+ + +	0	+	+ / -
Artesunate	0	0	0	0

Cardiovascular effects of intravenously administered antimalarial drugs

[Cardiotoxicity of antimalarial drugs. **White NJ.** ***The Lancet Infectious Diseases. 7(8):549-58, 2007 Aug.***]

	Conduction abnormalities reported	ECG QRS widening	ECG QT prolongation	Cardiovascular toxicity in overdose
Quinine	+	+	+	++
Quinidine	+	+	+++	+++
Chloroquine	+	+	+/–	+++
Amodiaquine	+/–	+/–	+/–	..
Mefloquine	+	0	0	..
Halofantrine	++	+	+++	..
Lumefantrine	0	0	0	..
Piperaquine	0	+	0	..
Primaquine	..	..	..	..
Pyrimethamine	0	0	0	0
(Chlor)proguanil	0	0	0	0
Atovaquone	0	0	0	0
Dihydroartemisinin*	0	0	0	0

Cardiovascular effects of orally administered antimalarial drugs

Pharmaceutical Preparations of Artemisinin Derivatives for Rectal Administration

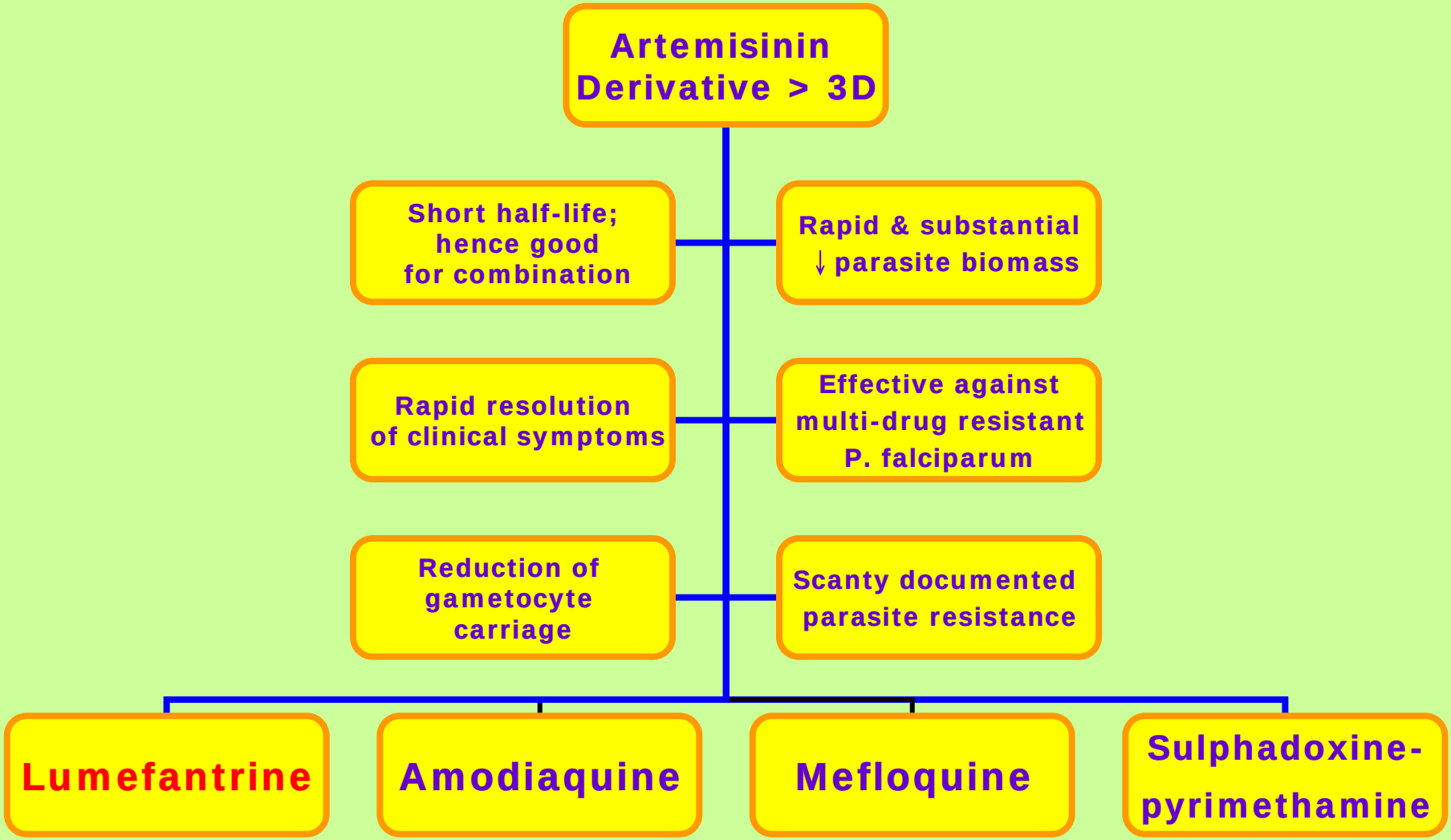
Drug	Current Manufacturer(s)	Trade Name, Dose Strength, and Formulation	Published Studies	Unpublished Studies
Artesunate*	Mepha (Switzerland)	Plasmotrim Rectocaps, 50-mg and 200-mg suppositories	18	3†
	Scanpharm (Denmark)	100-mg, 200-mg, and 400-mg suppositories	0	2†
Artemisinin*	Mediplantex and Vidipha (Vietnam)‡	Polyethylene glycol–base, 500-mg suppositories and fatty-base, 400-mg suppositories	11	0
Artemether	Dafra Pharma (Belgium)	Rectal artemether suppogels	1	0
	Kunming Pharmaceuticals (China)	Artemether in arachis oil (parenteral preparation)§	1	0
Dihydroartemisinin*	Beijing Holley-Cotec (China)	Cotecxin	3	0
	GVS Laboratories (India)	Alaxin	0	0

*A further 2 identified studies of artesunate, 3 of artemisinin, and 1 of dihydroartemisinin were excluded from this review.
†Details of these studies are described in a World Health Organization US Food and Drug Administration application from 2002[7]; 1 additional unpublished study (Joseph Andoh, MD, et al, February 10–March 19, 1998) used the Mepha product.
‡The manufacturer of the suppositories is not specified in many of these studies.
§This formulation has not been marketed for rectal administration.

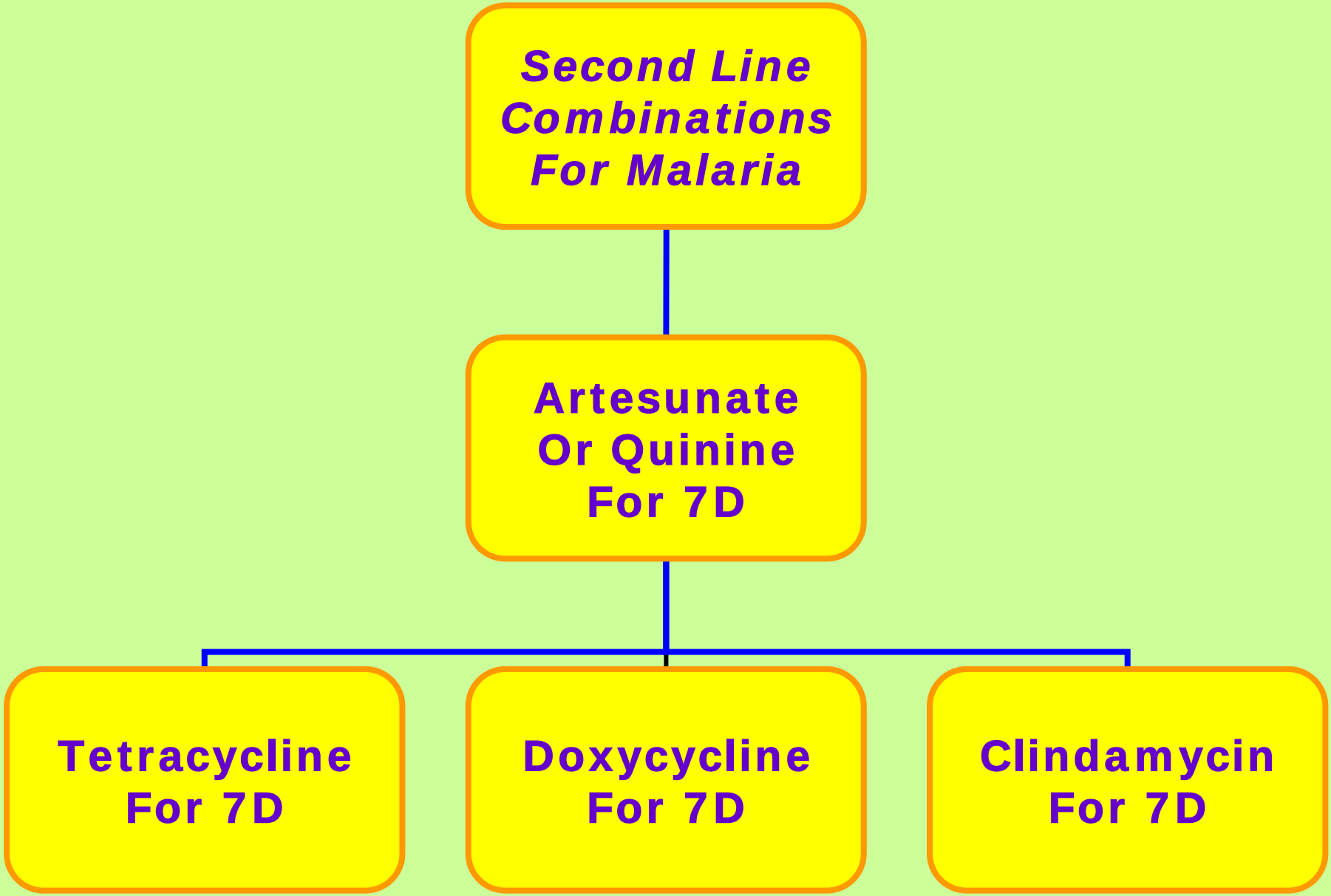
Pharmaceutical Preparations of Artemisinin Derivatives for Rectal Administration
[Karunajeewa: JAMA, Volume 297(21).June 6, 2007.2381–2390]

Artemisinin-based Combination Therapy (ACT) A Major Breakthrough in Anti-malarial Therapy

- Rationale for ACT
  - Resistance to Chloroquine and sulphadoxine-pyrimethamine
  - Protect individual drug from resistance
  - To decrease rate of decline in efficacy
  - To interrupt spread of resistant strains
  - To decrease transmission in a region
  - The combination is often more effective
  - In the rare event of resistance to one of the drugs during the course of the infection, the parasite will be killed by the other drug



Artemisinin-based Combination Therapy (ACT)
A Major Breakthrough in Anti-malarial Therapy



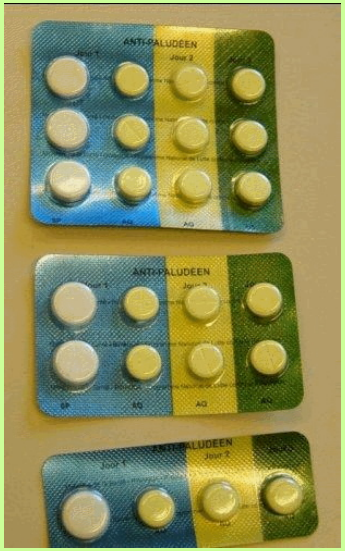
Second line Combinations Therapy

Unit-dose packaged drugs for treating malaria.

Orton L. Barnish G. ***Cochrane Database of Systematic Reviews. (2):CD004614, 2005.***]

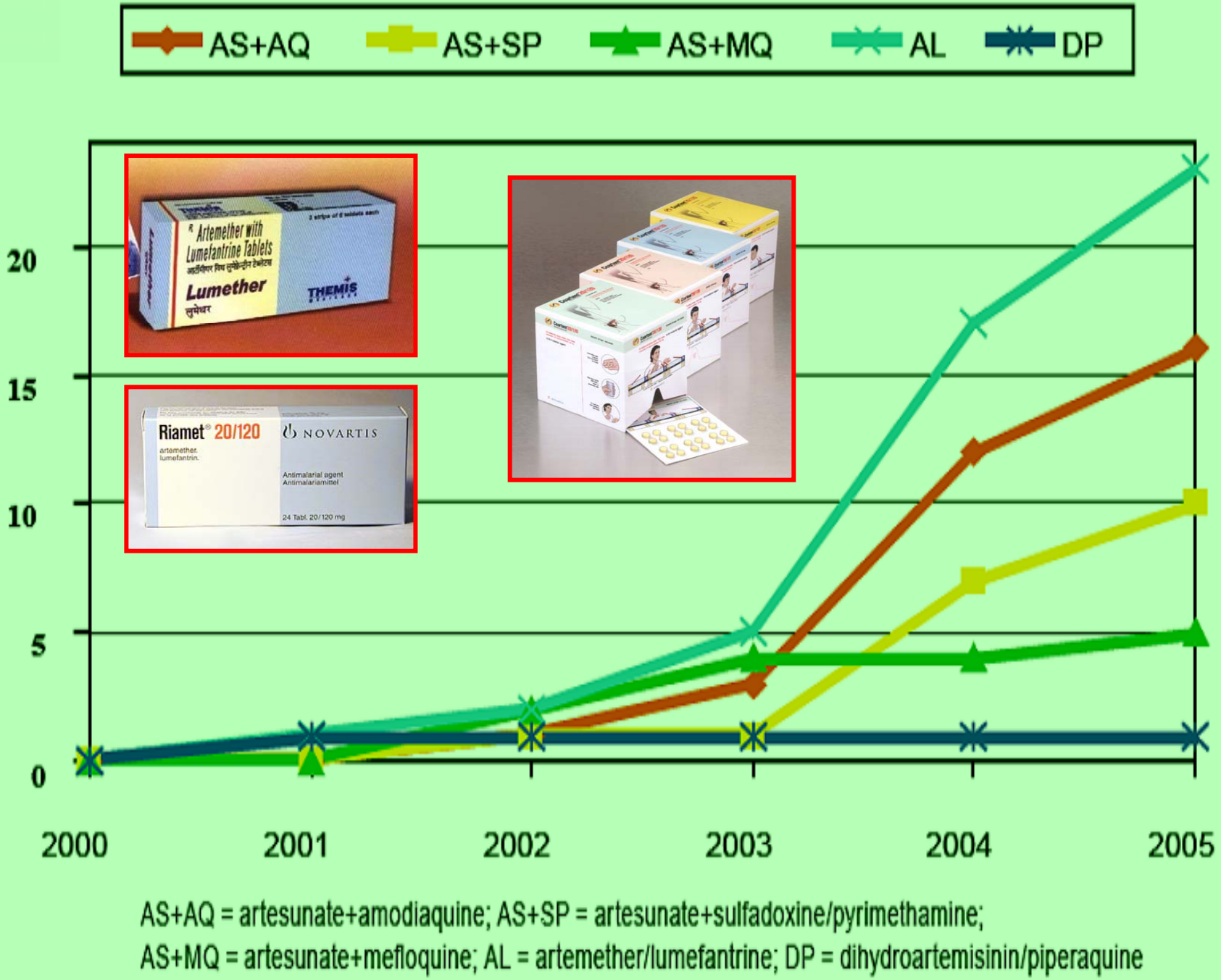
Blister-packed artesunate and mefloquine (from Cambodia)

Blister-packed artemether-lumefantrine (trade name Coartem, Novartis)

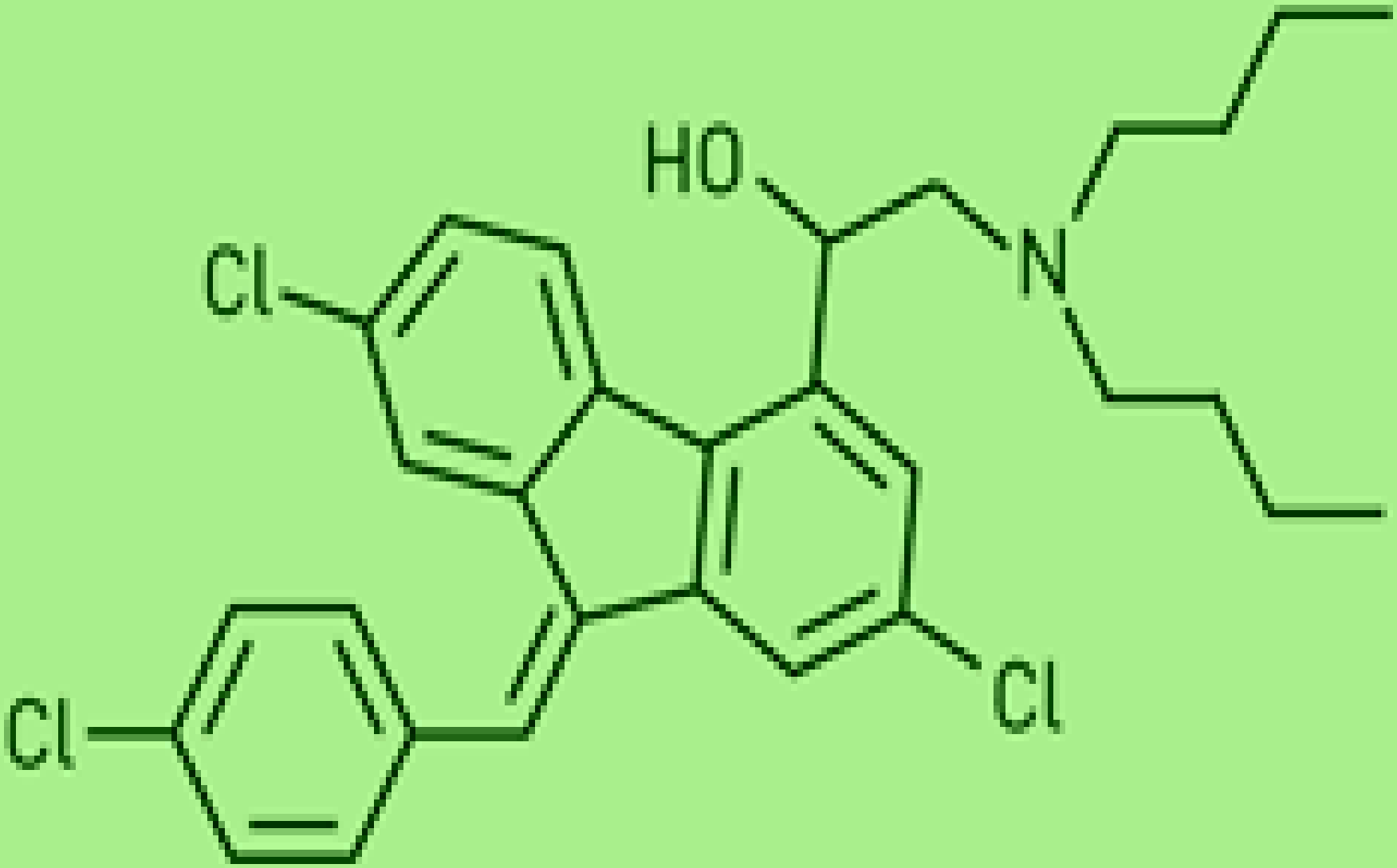


Blister-packed sulfadoxine-pyrimethamine and amodiaquine (from Rwanda)

Sectioned polythene bags of chloroquine (from Ghana)



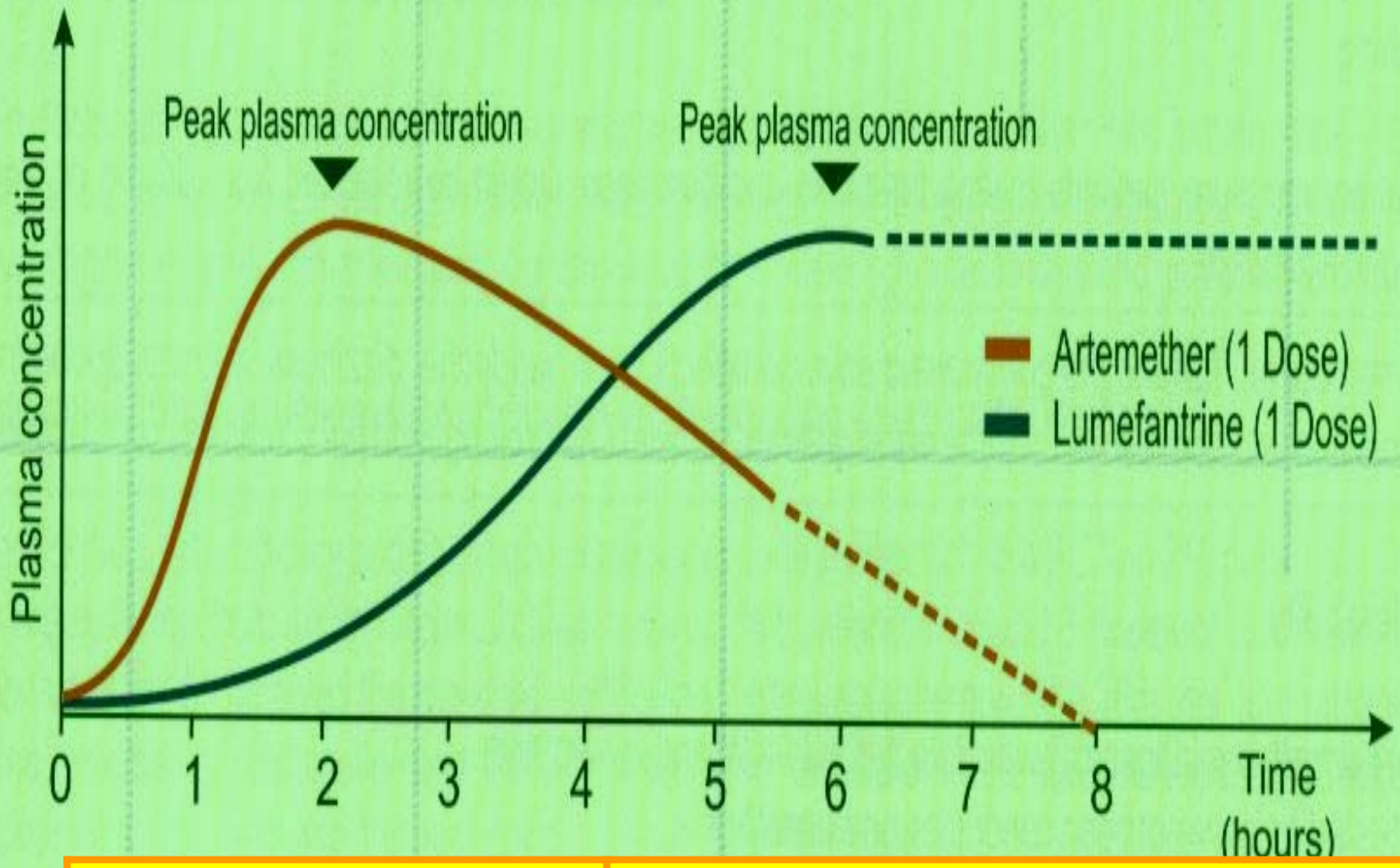
AS+AQ = artesunate+amodiaquine; AS+SP = artesunate+sulfadoxine/pyrimethamine;
AS+MQ = artesunate+mefloquine; AL = artemether/lumefantrine; DP = dihydroartemisinin/piperaquine



Lumefantrine

Lumefantrine

- Schizonticidal; Safe in pregnancy
- AMMS – China discovered it 1970
- Registered for use in 1987
- Half life 3-6 days
- Lumefantrine binds to toxic haemin (FP9) that is produced in the course of haemoglobin digestion the food vacuole of parasite. The binding prevents the polymerisation of haemin to non-toxic malaria pigment.
- The absorption of lumefantrine is dependent on the presence of food in the stomach, which can be difficult as loss of appetite and nausea are frequent during malaria attacks. Intake of about 1.5 g of fat seems sufficient for satisfactory absorption.
- Unlike halofantrine, it has no significant effect on the QT interval.



Artemether acts rapidly, reducing the infecting parasite biomass by approximately 10,000-fold per asexual life cycle (2 days)	Lumefantrine acts over a longer period to eliminate the residual 100-100,000 parasites that remain after artemether is cleared from the body and minimizes the risk of recrudescence.

Peak plasma concentrations of Lumefantrine and Artemether

Areas with multi-drug resistance, Non-immune patients or Stand-by emergency treatment

	Day One		Day Two		Day Three		Total
	12 Noon	8 PM	12 Noon	12 Midnight	12 Noon	12 Midnight	
	0 hour	8 hour	24 hour	36 hour	48 hour	60 hour	
Adults	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	4 tablets	24 tablets
Children 5-<15 kg bodyweight	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	1 tablet	6 tablets
Children 15-<25 kg bodyweight	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	2 tablets	12 tablets
Children 25-<35 kg bodyweight	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	3 tablets	18 tablets

Artemether-Lumefantrine (Coartem, Lumether, Riamet)

Treatment regimen in other cases

	Day One		Day Two		Day Three		Total
	12 Noon	8 PM	12 Noon		12 Noon		
	0 hour	8 hour	24 hour		48 hour		
Adults	4 tablets	4 tablets	4 tablets		4 tablets		16 tablets
Children 5-<15 kg bodyweight	1 tablet	1 tablet	1 tablet		1 tablet		4 tablets
Children 15-<25 kg bodyweight	2 tablets	2 tablets	2 tablets		2 tablets		8 tablets
Children 25-<35 kg bodyweight	3 tablets	3 tablets	3 tablets		3 tablets		12 tablets

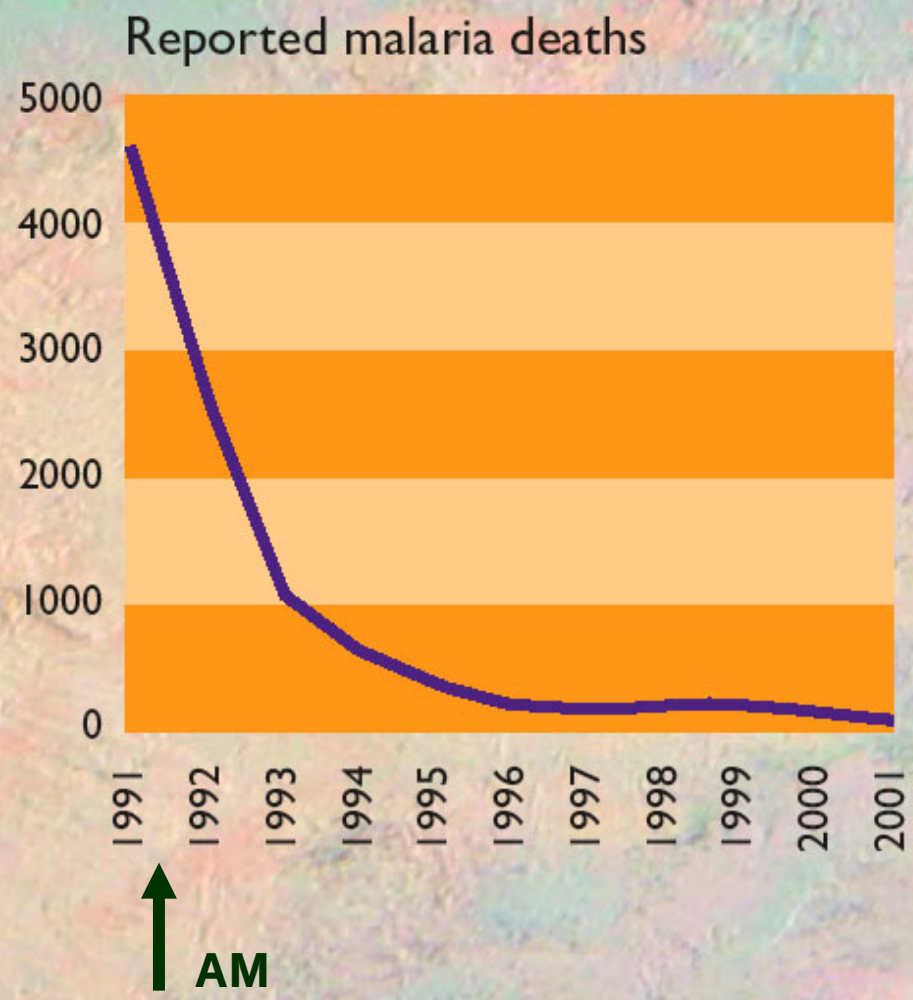
Artemether-Lumefantrine (Coartem, Lumether, Riamet)

What to give in pregnancy ?

- In 1st trimester
  - Quinine + Clindamycin 7 days
- In 2nd and 3rd trimesters
  - Any ACT combination as per rec. or
  - Artesunate + Clindamycin 7 days or
  - Quinine + Clindamycin 7 days
- Lactating women same ACT

Impact on malaria deaths by intensive malaria control program in Viet Nam, 1991-2001

- High level political commitment
- Government production and distribution of bednets and anti-malarials
- Correct treatment policies providing free artemisinin to malaria patients
- Health education in schools, on radio
- Multi-sectoral involvement (traditional leaders, community groups, NGOs, and national industry)



MALARIA
Management Guideline

Summary of recommendations on treatment for uncomplicated falciparum malaria

RECOMMENDATIONS	LEVEL OF EVIDENCE
The treatment of choice for uncomplicated falciparum malaria is a combination of two or more antimalarials with different mechanisms of action.	S, T, O
ACTs are the recommended treatments for uncomplicated falciparum malaria.	S
The following ACTs are currently recommended: – artemether-lumefantrine, artesunate + amodiaquine, artesunate + mefloquine, artesunate + sulfadoxine-pyrimethamine.	S, T, O
The choice of ACT in a country or region will be based on the level of resistance of the partner medicine in the combination: – in areas of multidrug resistance (South-East Asia), artesunate + mefloquine or artemether-lumefantrine – in Africa, artemether-lumefantrine, artesunate + amodiaquine; artesunate + sulfadoxine-pyrimethamine.	 E S
The artemisinin derivative components of the combination must be given for at least 3 days for an optimum effect.	S
Artemether-lumefantrine should be used with a 6-dose regimen.	T, E
Amodiaquine + sulfadoxine-pyrimethamine may be considered as an interim option in situations where ACTs cannot be made available.	E

Summary of recommendations on second-line antimalarial treatment for uncomplicated falciparum malaria

RECOMMENDATIONS	LEVEL OF EVIDENCE
Alternative ACT known to be effective in the region.	0
Artesunate (2 mg/kg bw once a day) + tetracycline (4 mg/kg bw four times a day) or doxycycline (3.5 mg/kg bw once a day) or clindamycin (10 mg/kg bw twice a day). Any of these combinations to be given for 7 days.	0
Quinine (10 mg salt/kg bw three times a day) + tetracycline or doxycycline or clindamycin. Any of these combinations to be given for 7 days.	0

Summary of recommendations on the treatment of uncomplicated falciparum malaria in pregnancy

RECOMMENDATIONS	LEVEL OF EVIDENCE
First trimester: quinine + clindamycin[a] to be given for 7 days. ACT should be used if it is the only effective treatment available.	O, E
Second and third trimesters: ACT known to be effective in the country/region or artesunate + clindamycin to be given for 7 days or quinine + clindamycin to be given for 7 days.	O, E

[a] If clindamycin is unavailable or unaffordable, then the monotherapy should be given.

Summary of recommendations on the treatment of uncomplicated falciparum malaria in lactating women

RECOMMENDATION	LEVEL OF EVIDENCE
Lactating women should receive standard antimalarial treatment (including ACTs) except for tetracyclines and dapsone, which should be withheld during lactation.	E

Summary of recommendations on the treatment of falciparum malaria in non-immune travellers

RECOMMENDATIONS	LEVEL OF EVIDENCE
For travellers returning to non-endemic countries:[a] – atovaquone–proguanil (15/6 mg/kg, usual adult dose, 4 tablets once a day for 3 days); – artemether–lumefantrine (adult dose, 4 tablets twice a day for 3 days); – quinine (10 mg salt/kg bw every 8 h) + doxycycline[b] (3.5 mg/kg bw once a day) or clindamycin (10 mg/kg bw twice a day); all drugs to be given for 7 days	O, E
For severe malaria: – the antimalarial treatment of severe malaria in travellers is the same as shown in section 8; – travellers with severe malaria should be managed in an intensive care unit; – haemofiltration or haemodialysis should be started early in acute renal failure or severe metabolic acidosis; – positive pressure ventilation should be started early if there is any breathing pattern abnormality, intractable seizure or acute respiratory distress syndrome.	O, E

[a] Halofantrine is not recommended as first-line treatment for uncomplicated malaria because of cardiotoxicity.

[b] Doxycycline should not be used in children under 8 years of age.

Summary of recommendations on the treatment of severe malaria

RECOMMENDATIONS	LEVEL OF EVIDENCE
Severe malaria is a medical emergency. After rapid clinical assessment and confirmation of the diagnosis, full doses of parenteral antimalarial treatment should be started without delay with whichever effective antimalarial is first available.	**E**
Artesunate 2.4 mg/kg bw i.v. or i.m. given on admission (time = 0), then at 12 h and 24 h, then once a day is the recommended choice in low transmission areas or outside malaria endemic areas	**S**
For children in high transmission areas, the following antimalarial medicines are recommended as there is insufficient evidence to recommend any of these antimalarial medicines over another for severe malaria: – artesunate 2.4 mg/kg bw i.v. or i.m. given on admission (time = 0), then at 12 h and 24 h, then once a day; – artemether 3.2 mg/kg bw i.m. given on admission then 1.6 mg/kg bw per day; – quinine 20 mg salt/kg bw on admission (i.v. infusion or divided i.m. injection), then 10 mg/kg bw every 8 h; infusion rate should not exceed 5 mg salt/kg bw per hour.	**S, T, O, E**

Summary of recommendations on the treatment of hyperparasitaemia in falciparum malaria

RECOMMENDATIONS	LEVEL OF EVIDENCE
Hyperparasitaemic patients with no other signs of severe disease should be treated with oral artemisinin derivatives under the following conditions: – patients must be monitored closely for the first 48 h after the start of treatment, – if the patient does not retain oral medication, parenteral treatment should be given without delay.	O, E
Non-immune patients with parasitaemia of > 20% should receive parenteral antimalarial treatment.	E

Immediate clinical management of severe manifestations and complications of falciparum malaria

Manifestation/complication	Immediate management[a]
Coma (cerebral malaria)	Maintain airway, place patient on his or her side, exclude other treatable causes of coma (e.g. hypoglycaemia, bacterial meningitis); avoid harmful ancillary treatment such as corticosteroids, heparin and adrenaline; intubate if necessary.
Hyperpyrexia	Administer tepid sponging, fanning, cooling blanket and antipyretic drugs.
Convulsions	Maintain airways; treat promptly with intravenous or rectal diazepam or intramuscular paraldehyde.
Hypoglycaemia (blood glucose concentration of <2.2 mmol/l; <40 mg/100ml)	Check blood glucose, correct hypoglycaemia and maintain with glucose-containing infusion.
Severe anaemia (haemoglobin < 5 g/100ml or packed cell volume < 15%)	Transfuse with screened fresh whole blood
Acute pulmonary oedema[b]	Prop patient up at an angle of 45°, give oxygen, give a diuretic, stop intravenous fluids, intubate and add positive end-expiratory pressure/continuous positive airway pressure in life-threatening hypoxaemia.
Acute renal failure	Exclude pre-renal causes, check fluid balance and urinary sodium; if in established renal failure add haemofiltration or haemodialysis, or if unavailable, peritoneal dialysis. The benefits of diuretics/dopamine in acute renal failure are not proven.
Spontaneous bleeding and coagulopathy	Transfuse with screened fresh whole blood (cryoprecipitate, fresh frozen plasma and platelets if available); give vitamin K injection.
Metabolic acidosis	Exclude or treat hypoglycaemia, hypovolaemia and septicaemia. If severe add haemofiltration or haemodialysis.
Shock	Suspect septicaemia, take blood for cultures; give parenteral antimicrobials, correct haemodynamic disturbances.
Hyperparasitaemia	See section 8.14.

[a] It is assumed that appropriate antimalarial treatment will have been started in all cases.

[b] Prevent by avoiding excess hydration.

Summary of recommendations on the treatment of uncomplicated vivax malaria

RECOMMENDATIONS	LEVEL OF EVIDENCE
Chloroquine 25 mg base/kg bw divided over 3 days, combined with primaquine 0.25 mg base/kg bw, taken with food once daily for 14 days is the treatment of choice for chloroquine-sensitive infections. In Oceania and South-East Asia the dose of primaquine should be 0.5 mg/kg bw.	O, E
Amodiaquine (30 mg base/kg bw divided over 3 days as 10 mg/kg bw single daily doses) combined with primaquine should be given for chloroquine-resistant vivax malaria.	O, E
In moderate G6PD deficiency, primaquine 0.75 mg base/kg bw should be given once a week for 8 weeks. In severe G6PD deficiency, primaquine should not be given.	O, E
Where ACT has been adopted as the first-line treatment for *P. falciparum* malaria, it may also be used for *P. vivax* malaria in combination with primaquine for radical cure. Artesunate + sulfadoxine-pyrimethamine is the exception as it will not be effective against *P. vivax* in many places.	O, E

MALARIA
Management Guideline

Management of Acute Attack

- Anti-malarial chemotherapy should be administered as soon as the diagnosis is made
- Monitor blood for parasites and repeat testing is needed if the diagnosis is strongly suspected
- Maintain fluid and electrolytes balance; avoid overhydration
- Renal failure regime for blackwater fever; treat hypoglycaemia and/or shock if present
- Pulmonary oedema may develop, treated by prop up, oxygen,loop diuretic, venodilator; if hypoxic may need positivepressure ventilation
- Avoid sedatives and corticosteroids
- Watch for relapse (usually within 2 months) and signs of peritoneal irritation (splenic rupture)

Anti-malarial Chemotherapy for Uncomplicated P. vivax, P. malariae and P. ovale

- ***Chloroquine*** 600 mg base po stat and 300 mg base 6 hours later then 300 mg base daily for 2 more days **plus** ***Primaquine*** 15 mg base (0.25 mg/kg) po daily taken with food for 14 days in P. vivax and P. ovale infection to eradicate hypnozoites in the liver
- NOTE 1 Chloroquine-resistant P. vivax reported from Oceania and South America, ***Mefloquine*** 750 mg po, then 500 mg 12 hours later
- NOTE 2 Primaquine-resistant P. vivax reported in South-east Asia and Western Pacific. An increased of the dose to 22.5 – 30 mg daily (or 0.5 mg/kg) is effective
- NOTE 3 Primaquine is contraindicated in pregnancy. In G6PD deficiency, primaquine is safe in dosage of 30 mg once a week for 8 weeks. Monitor Hb level.

Uncomplicated P. falciparum malaria

- **Definition:** symptomatic malaria without signs of severity or evidence of vital organ dysfunction
- **Treatment**:
  - a. ***Artesunate*** 200 mg (4 mg/kg) po daily for 3 days **plus** ***Mefloquine*** 1000 mg base po on day 2, then 500 mg po on day 3
  - b. ***Quinine*** 600 mg salt (10 mg/kg) po 8 hourly for 7 days **plus** ***Doxycycline*** 100 mg po bid for 7 days

Severe P. falciparum malaria

- **Definition**: presence of **one or more** of the following clinical or laboratory features, after excluding other obvious cause of their symptoms:
- **Clinical**: Prostration, Impaired consciousness, Respiratory distress (acidotic breathing), Multiple convulsions, Circulatory collapse,Pulmonary oedema (radiological), Abnormal bleeding, Jaundice,Haemoglobinuria
- **Laboratory**: Severe anaemia, Hypoglycaemia, Acidosis, Renal impairment, Hyperlactataemia, Hyperparasitaemia (>5%)

Treatment of Severe P. falciparum malaria

- a. ***Artesunate*** 2.4 mg/kg i.v. or i.m. given on admission (time = 0), then at 12 h and 24 h, then once a day until oral medication could be taken, treat for a total of 7 days **plus** ***Doxycycline*** 100 mg po bid for 7 days once oral medication could be taken **or** *Mefloquine* as in above section B2a
- b. ***Quinine dihydrochloride*** 20 mg/kg loading dose in 5% dextrose infused over 4 hours, maintenance dose 10 mg/kg infused over 2 – 4 hours every 8 hours. Change to oral dose when feasible to complete a 7-day course **plus** ***Doxycycline*** as in above section C2a
- Note 1 Consider *Primaquine* 45 mg single dose to eradicate gametocytes in blood at the end of treatment of falciparum malaria
- Note 2 Do not use loading dose if patient has received quinine,quinidine, or mefloquine in preceding 24 hours.

Exchange transfusion

- CDC recommends that exchange transfusion be strongly considered for persons with a parasite density of more than 10% or if complications such as cerebral malaria, non-volume overload pulmonary edema, or renal complications exist.
- Its beneficial effect by removing infected red cells, improving the rheological properties of blood, and reducing toxic factors such as parasite derived toxins, harmful metabolites, and cytokines.

'A Really Nasty Business'

Fake pharmaceuticals look like the real thing—but they can be lethal

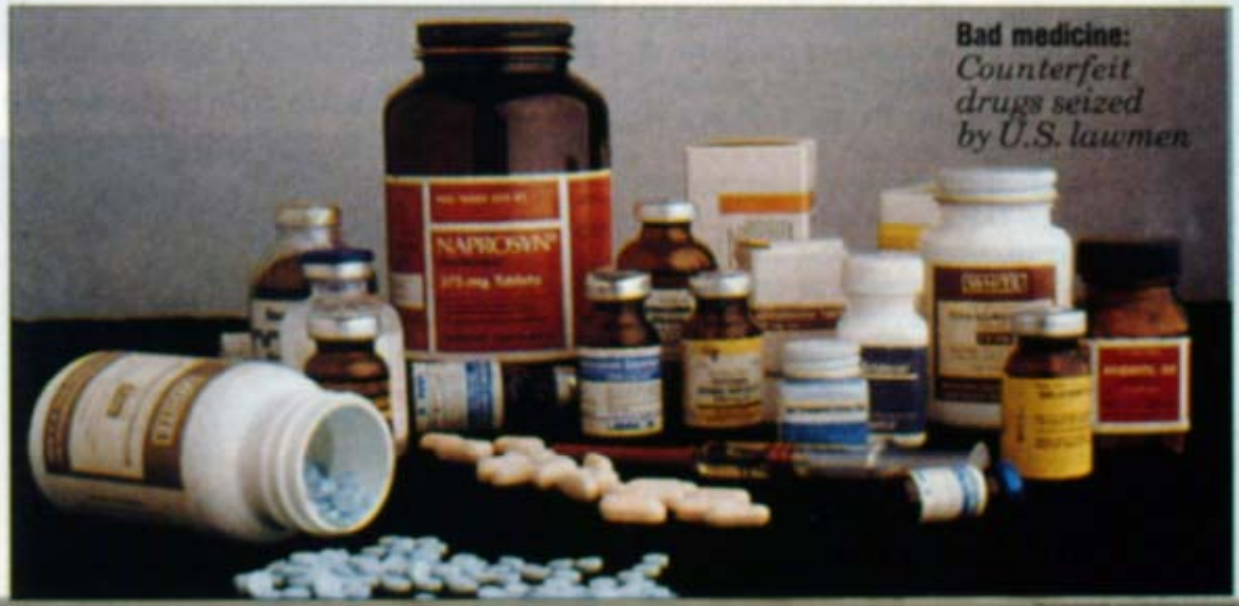
BY TOM MASLAND AND RUTH MARSHALL

36% counterfeit antimalarials

In Nigeria last month, authorities learned [illegible] children had died of kidney failure after ingesting an industrial solvent; hospitals mixed [illegible] in the belief it was a pharmaceutical chemical made in the Netherlands. In Mexico, officials confiscated 15,000 counterfeit burn remedies containing [illegible] coffee or [illegible] In Burma [illegible] perished after taking worthless copies of a drug meant to combat malarial fever. In Europe, hospitals and pharmacies handed out millions of pirate doses of a cardiac medicine, some at only half the purported strength. (There were no known casualties.) In the United States, the emergence of a $100 million black market in anabolic steroids has spurred drug counterfeiting despite a congressional crackdown in 1988.

Over the last decade, the profits to be made in the $150 billion pharmaceutical market have inspired a new form of forgery: drugs that are not what they seem. The names are familiar. They include Zantac, the world's best-selling ulcer drug; Selokeen, a hospital-administered cardiac beta-blocker; Adriamicin, for leukemia victims; Fansidar, used against malaria. The nation that does not recognize international drug patents—India, for example, or Thailand. From there a finished drug or its basic chemical components may be shipped anywhere through a series of cut-rate brokers and middlemen. "The trail of fakes found in Britain may be [illegible] Argentina, Spain, Italy," said Paul Carratu, whose London investigative firm currently has 60 counterfeiting cases. "The brokers have never checked the [illegible] they don't want to know." The problem is one the multinational drug companies are reluctant to acknowledge. It's "like asking someone how his wife is in bed," says an attorney for a big U.S. drug firm. The companies spend millions fighting the counterfeiters. But nearly all the big manufacturers deny that it's even an issue. "We would not dream of saying we have a counterfeiting problem; otherwise nobody would buy our product," says Jeffrey Foote, an attorney who recently retired from Britain's Wellcome Foundation, a leading drug manufacturer.

Drug piracy has hit the poorest nations like a plague. "If [the counterfeiters] would confine themselves to fake diarrhea pills or



Bad medicine: *Counterfeit drugs seized by U.S. lawmen*

Dusk to Dawn Feeders

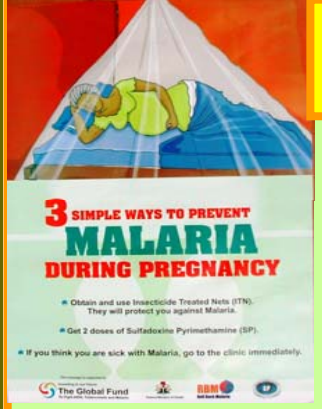
Prevention is Better than cure

Insecticides
Coil and spray

Insecticide
impregnated
Bednets

Screened
windows
& doors

Protective
clothings



- Intermittent Preventive Tx in preg: $0.35

- Malaria treatment:
  - CQ, SP, AQ, Lap-Dap: $0.10 – 0.50
  - Artemisinin-combinations: $2.00 or more

Preventing & controlling malaria during pregnancy

Providing prompt access to curative treatment

- $2.50 -- 5.00

Promoting the use of insecticide-Rx mosquito nets

Three Effective Malaria Interventions can reduce <u>all-cause</u> child mortality by 20%-25%

Insecticide-treated tarpaulins (天蓬及遮陽蓬)used for malaria prevention in a refugee camp in Sierra Leone.

Card for Travelers Who Expect to Be in Areas Endemic for Malaria

- **Malaria Information for Traveler**
  - You will be visiting countries with malaria and may be exposed to malaria, which can progress rapidly and kill.
- **Ways to Reduce Risk**
  - Stay in accommodations with screens in windows and doors.
  - Go indoors from dusk to dawn.
  - Use an effective insect repellant, such as one that contains diethyltoluamide (DEET).
  - Treat your clothing with insecticide, such as permethrin.
  - Sleep under an insecticide-treated bed net.
  - Take medication that suppresses malaria as recommended by a travel medicine specialist.
  - If you tolerate malaria medication well, continue taking it even if others tell you there is no need.
- **Symptoms of Malaria**
  - Symptoms may start as early as 7 to 8 days after exposure but may be delayed for weeks or months (rarely >1 year) after exposure.
  - Symptoms include fever, which may be intermittent; body ache; weakness; headache; vomiting; abdominal pain; cough.
- **Seek Medical Attention**
  - If you have any of the symptoms, seek medical evaluation as soon as possible, even if fever is not constant.
  - Inform the clinicians that evaluate your fever that you may have been exposed to malaria.
  - Check blood tests, including malaria smears, every 12 to 24 hours until at least 3 sets of smear results are negative for malaria.

ABCDE of Malaria For Travellers

- A – be AWARE of the risk
- B – avoid mosquito BITES
  - Skin cover (wear long sleeves and long pants in tropical areas.)
  - Use a DEET based repellent
  - Knockdown sprays
  - Screens, air conditioning and nets
- C – take your CHEMOPROPHYLAXIS (medication to help prevent malaria)
- D – DIAGNOSE quickly
- E – if more than 24hrs from medical attention take a course of EMERGENCY stand-by treatment

Drugs and dosage for chemoprophylaxis				
Drugs	**Dosage**		**Pros and Cons**	**Adverse Effects**
	Adults	**Children**		
Atovaquone plus Proguanil (Malarone?)	**Adult tablet** of 250 mg atovaquone and 100 mg proguanil - 1 tab. daily	**Pediatric tablet** of 62.5 mg atovaquone and 25 mg proguanil: 5-8 kg: 1/2 tablet daily >8-10 kg: 3/4 tablet daily >10-20 kg: 1 tablet daily >20-30 kg: 2 tablets daily >30-40 kg: 3 tablets daily **>40 kg: 1 adult tablet daily**	Daily dosing; only have to continue for 7 days after exposure; not in pregnancy and lactation	Nausea, vomiting, abdominal pain, diarrhea, increased liver enzyme levels; rarely seizures, rash, mouth ulcers
Chloroquine (Tablet with 150mg base)	300 mg base once weekly	5mg/kg base weekly; maximum 300 mg	Long-term safety known; chloroquine resistance reported from most parts of the world; not for persons with epilepsy, psoriasis	Pruritis, nausea, headache, skin eruptions, nail and mucous membrane discoloration, partial hair loss, photophobia, nerve deafness, myopathy, blood dyscrasias, psychosis and seizures
Proguanil	200 mg daily	**< 2 yrs:** 50 mg/day; **2-6 yrs:**100 mg/d **7-9 yrs:** 150 mg/day; **>9 yrs:** 200 mg/d	Used in combination	
Doxycycline (100mg)	100mg once daily	1.5mg base/kg once daily (max. 100 mg) <25kg or <8 yr: Not given 25-35kg or 8-10 yr: 50mg 36-50kg or 11-13 yr: 75mg >50kg or >14 yr: 100mg	Daily dosing required; not in pregnancy and lactation	Abdominal discomfort, vaginal candidiasis, photosensitivity, worsening of renal function tests in renal diseases, allergic reactions, blood dyscrasias, esophageal ulceration
Mefloquine (Tablet with 250mg base, 274mg salt)	250 mg base once weekly	<15 kgs: 5mg of salt/kg; 15-19 kg: ?tab/wk; 20-30 kg: ?tab/wk; 31-45 kg: ?tab/wk; >45 kg: 1 tab/wk	Weekly dosing; occasional reports of severe intolerance; not in first trimester of pregnancy, breast feeding, high altitudes or deep sea diving, patients with epilepsy, psychosis, heart blocks, receiving β blockers	Dizziness, headache, sleep disorders, nightmares, nausea, vomiting, diarrhea, seizures, abnormal coordination, confusion, hallucinations, forgetfulness, emotional problems including anxiety, aggression, agitation, depression, mood changes, panic attacks, psychotic or paranoid reactions, restlessness, ?suicidal ideation and suicide

Areas with chloroquine sensitive *P. falciparum*	
Chloroquine	Start one week before exposure, continue during exposure and for 4 weeks thereafter
Areas with chloroquine resistant *P. falciparum* (low degree, not wide spread)	
Chloroquine Plus	Start one week before, continue during exposure and for 4 weeks thereafter
Proguanil	Start 1-2 days before, continue during exposure and for 4 weeks thereafter
Areas with chloroquine resistant *P. falciparum* (High degree, widespread)	
Chloroquine Plus Proguanil	As above
OR Mefloquine	Start 2-3 weeks before, continue during exposure and for 4 weeks thereafter
OR Doxycycline	Start 2 days before, continue during exposure and for 4 weeks thereafter
OR Atovaquone Plus Proguanil	Start 2 days before, continue during exposure and for 7 days thereafter

Compatibility of Anti-Malaria Drugs

	Pregnancy	Breast Feeding	Epilepsy	Psoriasis	Altitude	Scuba Diving
Chloroquine	OK	OK	NO	NO	OK	OK
Paludrine	OK	OK	OK	OK	OK	OK
Mefloquine	OK*	NO	NO	OK	NO	NO
Doxycycline	NO	NO	OK	OK	OK	OK
Malarone	NO	NO	OK	OK	OK	OK

* These drugs are not suitable during the first trimester of pregnancy.

Length of Prophylaxis

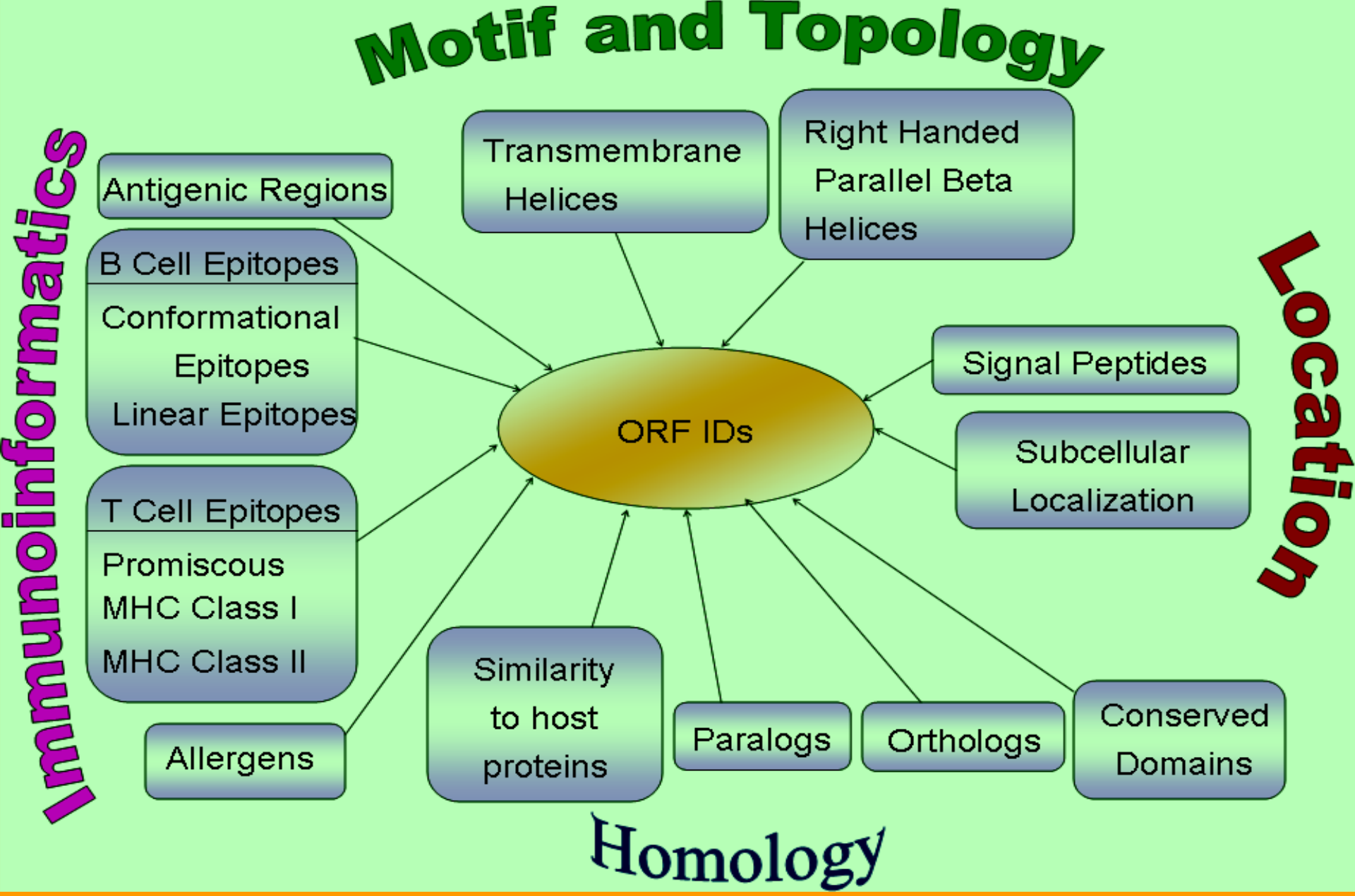
Chloroquine, Proguanil & Maloprim	Start **one week** before travel, throughout your stay in an endemic area and continue for **four weeks** after return.
Mefloquine (Lariam)	Start **two and a half weeks** before travel, throughout your stay in an endemic area and continue for **four weeks** after return.
Doxycycline	Start **two days** before travel, throughout your stay in an endemic area and continue for **four weeks** after return.
Malarone	Start **two days** before travel, throughout your stay in an endemic area and continue for **one week** after return.

IMPORTANT!

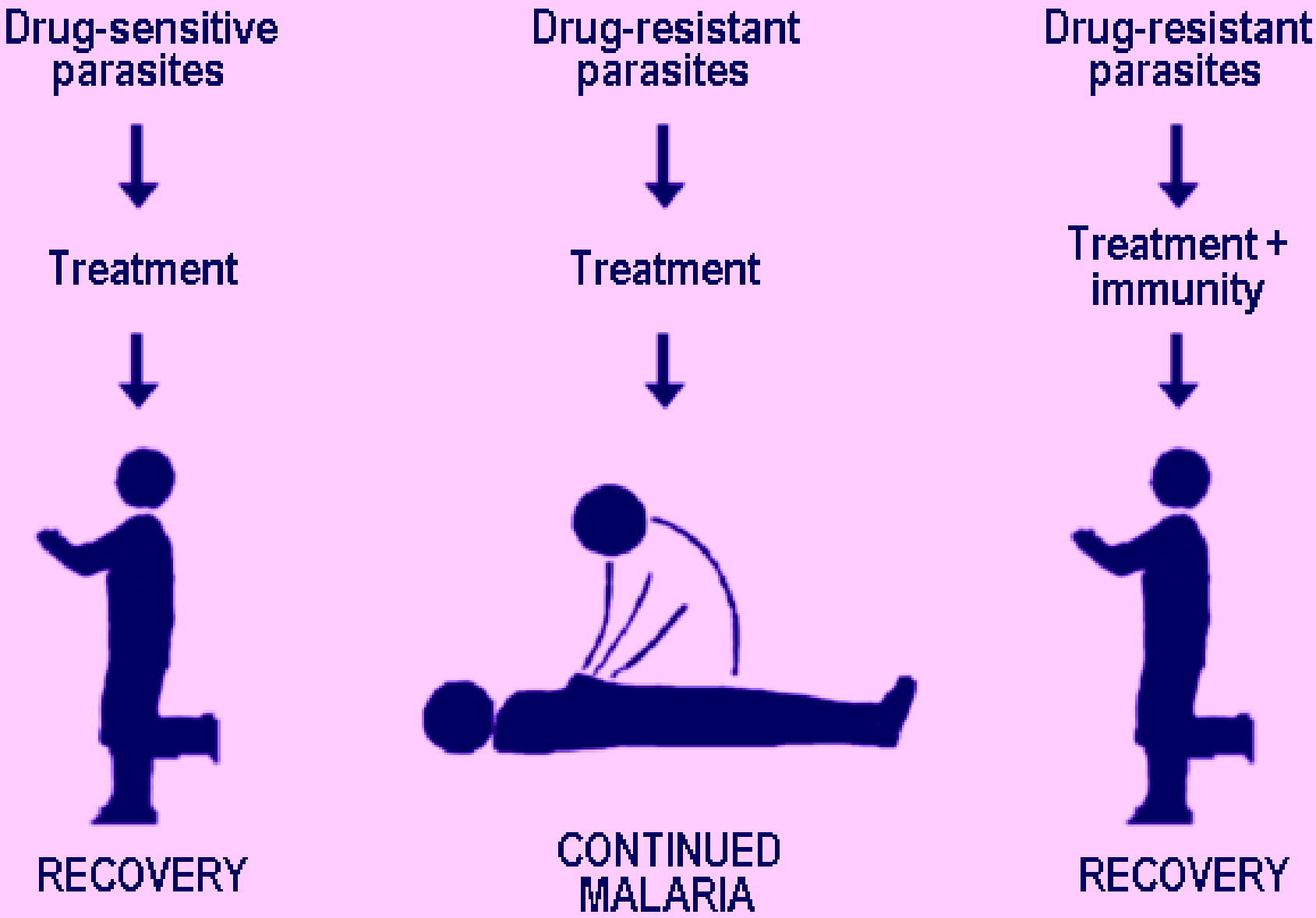
Take the tablets absolutely regularly, preferably with or after a meal.

Reasons why travelers fail to take chemoprophylaxis

- Incorrect belief that acquired immunity is maintained after leaving a malarious area
- Incorrect belief that some areas are free of malaria
- Don't know that resistance to chloroquine has developed
- Fears of drug side-effects

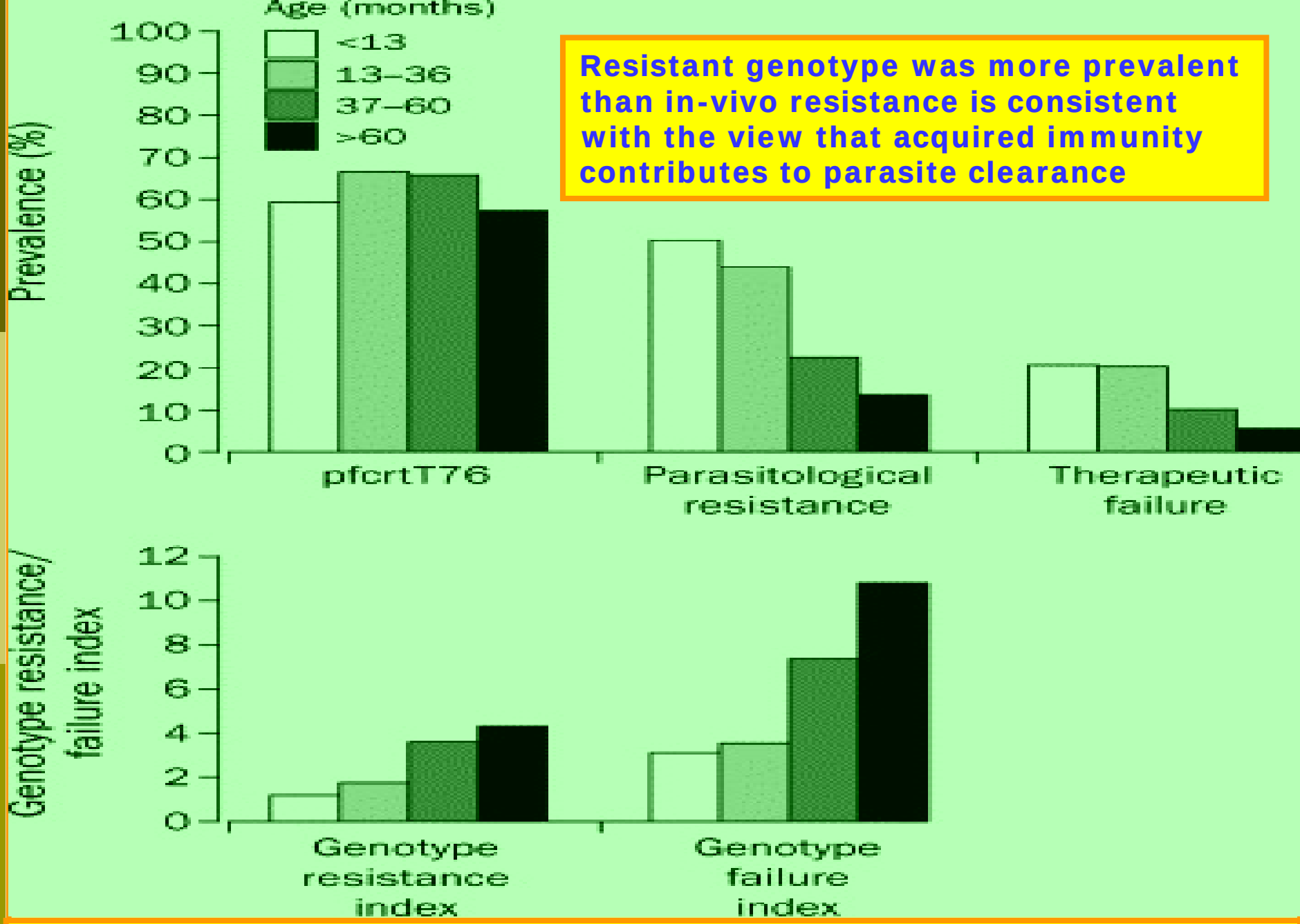


Malaria Vaccine



Immunity and Chloroquine Treatment Outcome

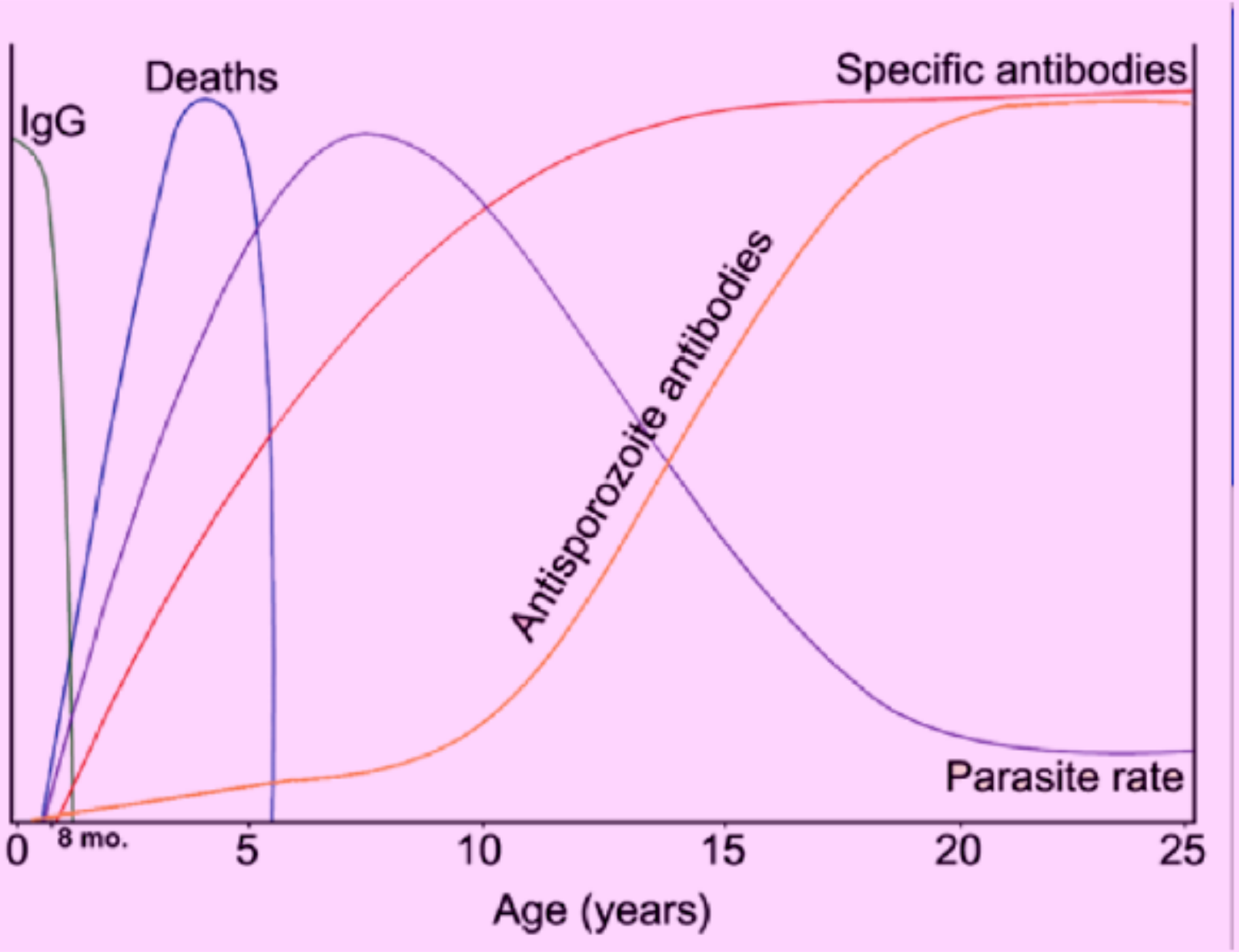
Chloroquine-resistant malaria 2001: Wellems T E; Plowe C V The Journal of infectious diseases 2001;184(6):770-6.



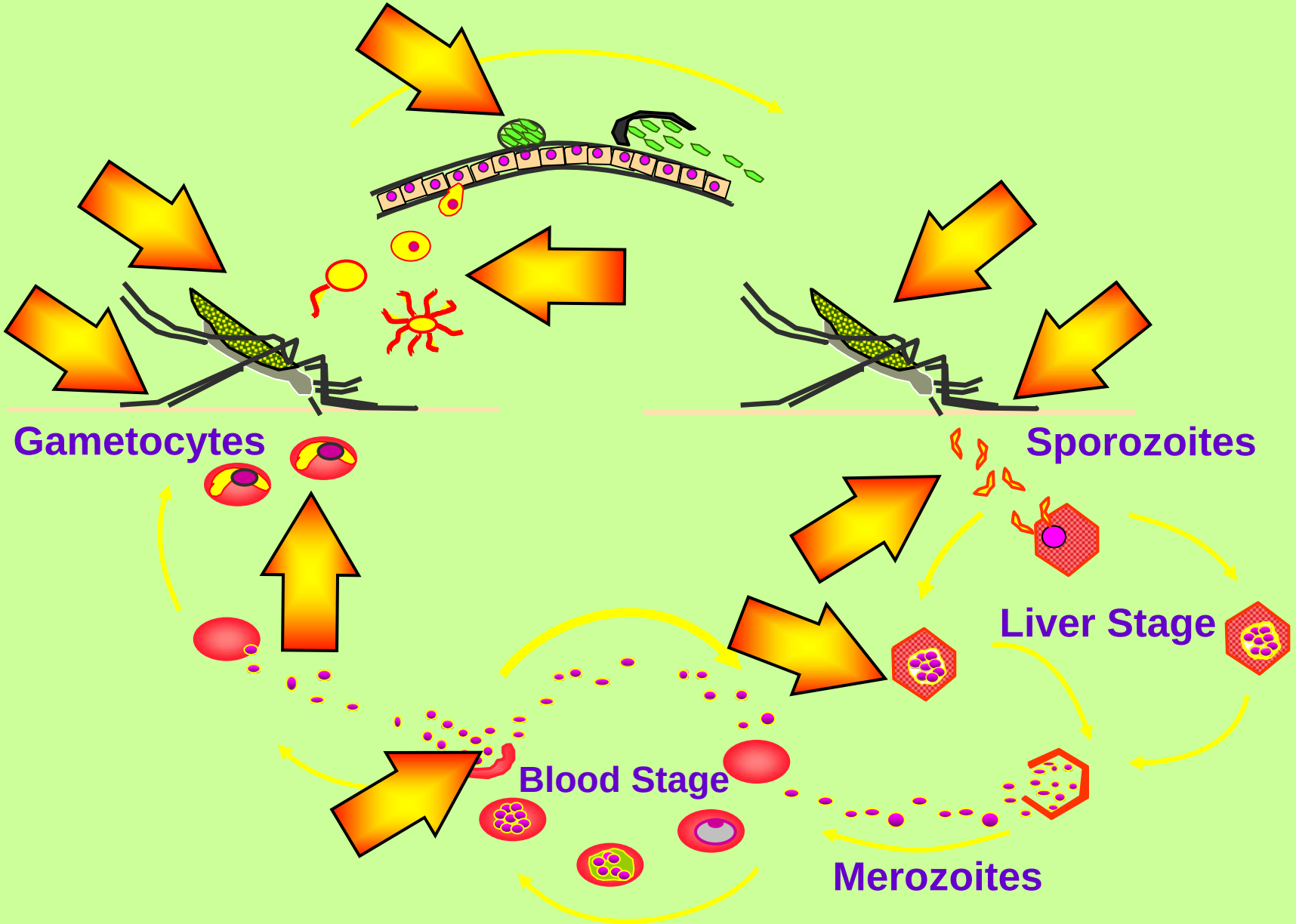
Resistant genotype was more prevalent than in-vivo resistance is consistent with the view that acquired immunity contributes to parasite clearance

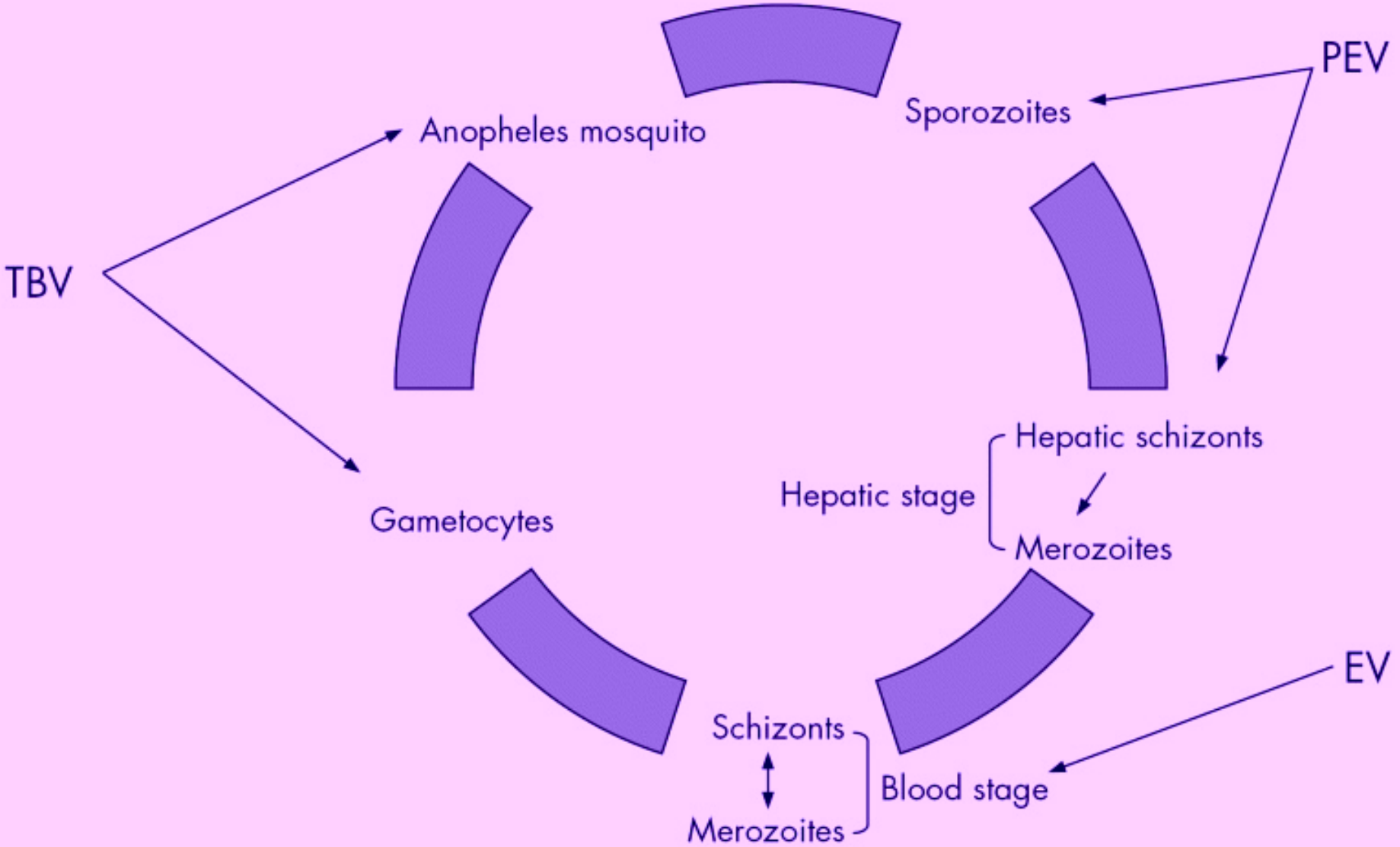
Application of a molecular marker for surveillance of chloroquine-resistant falciparum malaria The Lancet, Volume 358, Issue 9285, Pages 890 - 891, 15 September 2001

Susceptibility to malaria, antibody production, and lethality.



Malaria: Plasmodium Life Cycle

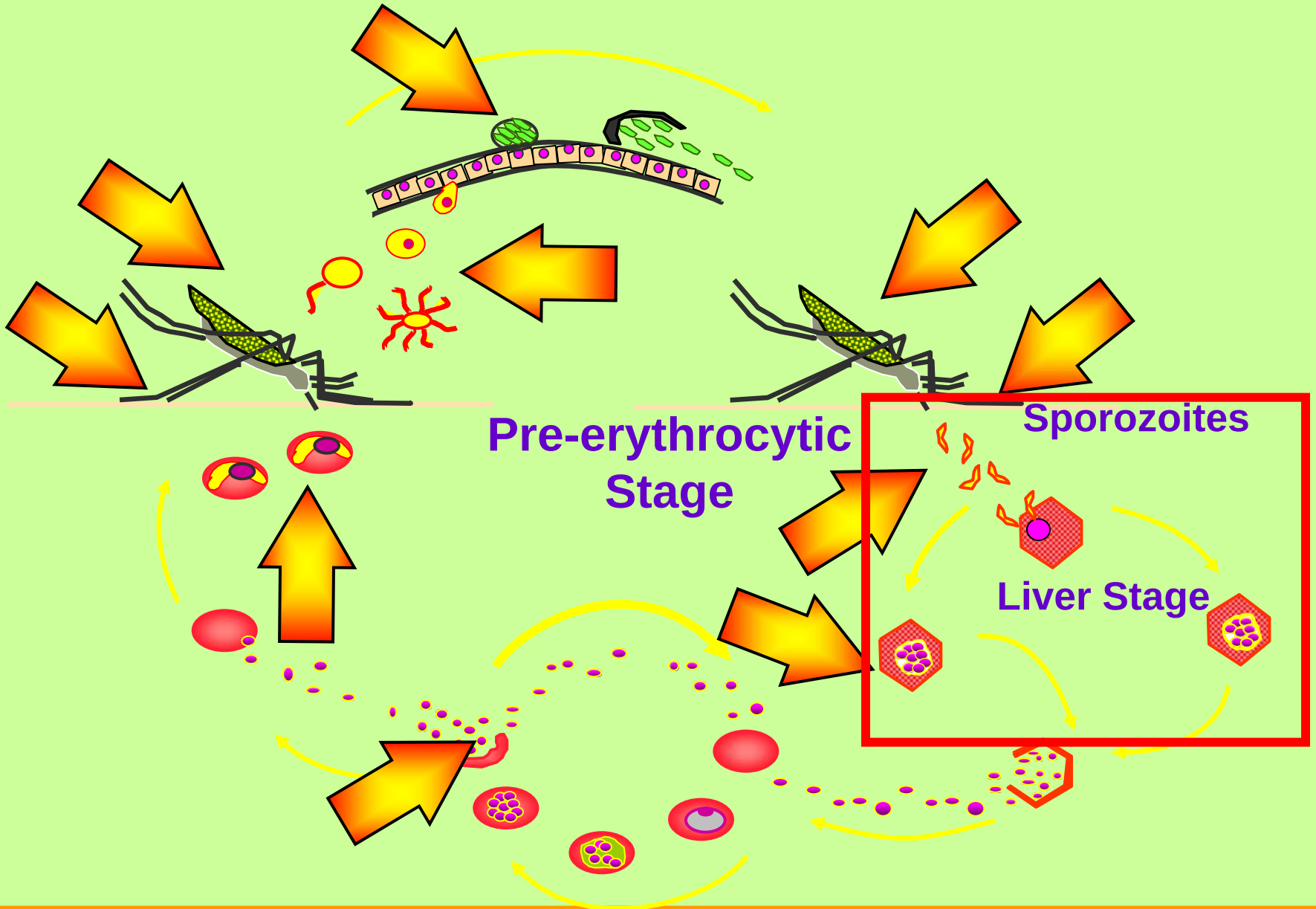




Plasmodium life cycle and theoretical activity points of the different malaria vaccines.

[Aide: Arch Dis Child, Volume 92(6).June 2007.476-479]

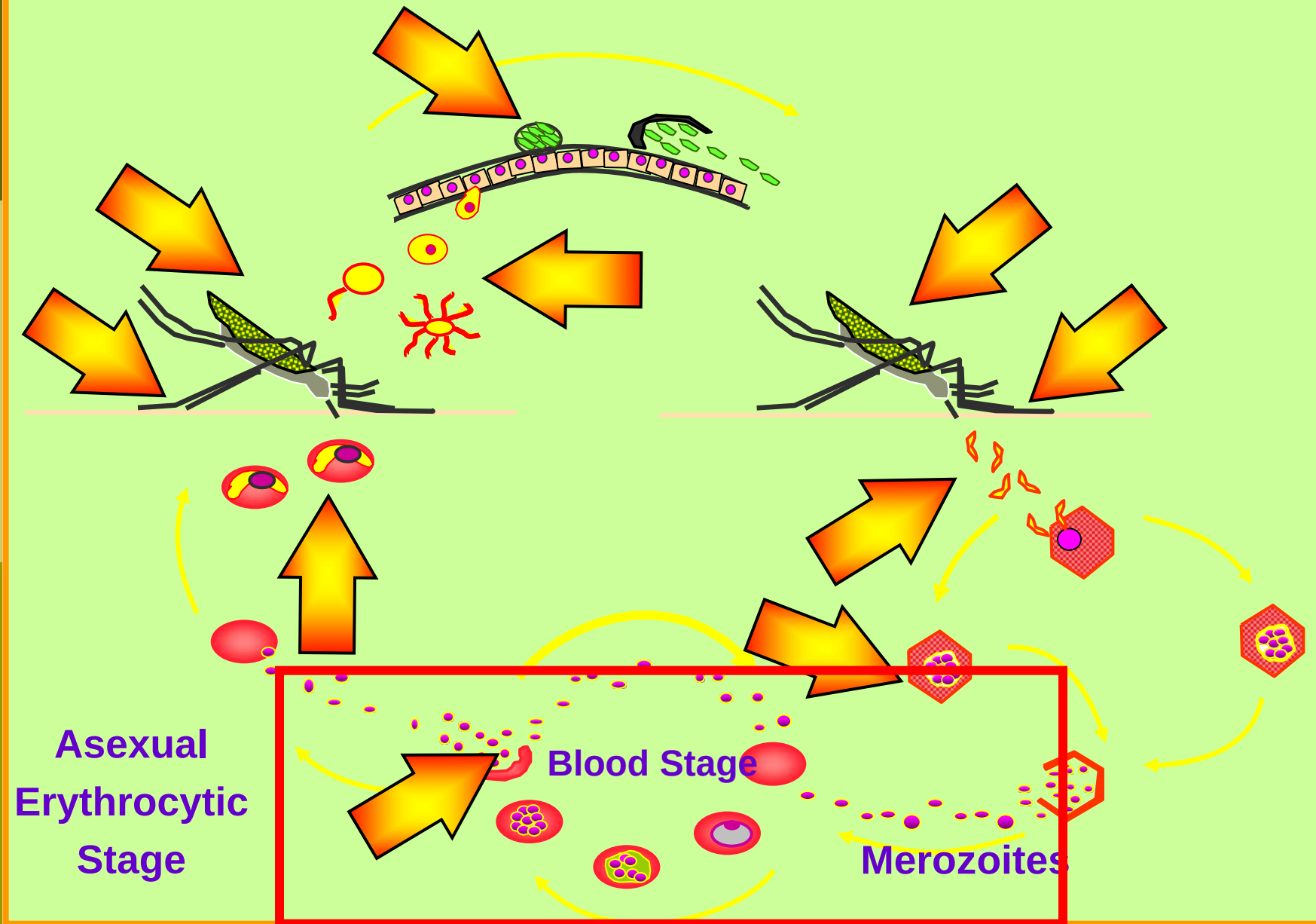
Malaria: Plasmodium Life Cycle



Pre-erythrocytic Stage Vaccines

- How they work:
  - Generates antibody response against sporozoites and prevents them from invading the liver
  - Prevents intra-hepatic multiplication by killing parasite-infected hepatocytes
- Intended Use:
  - Ideal for travelers - protects against malaria infection

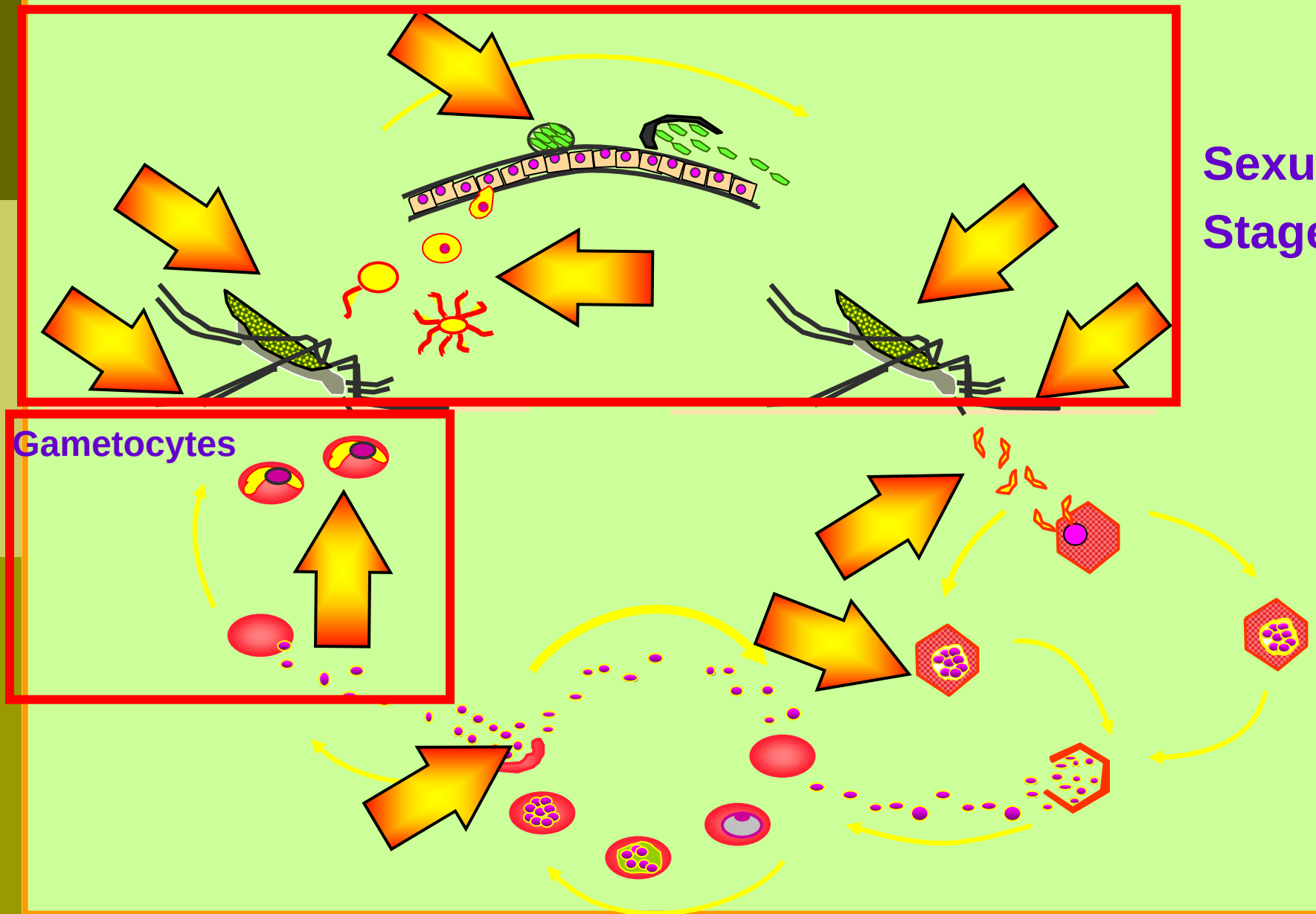
Malaria: Plasmodium Life Cycle



Asexual Erythrocytic Stage Vaccines

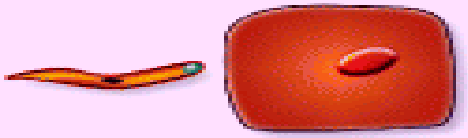
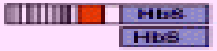
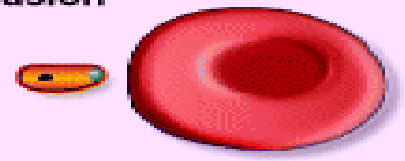
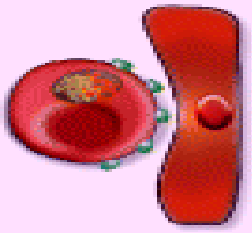
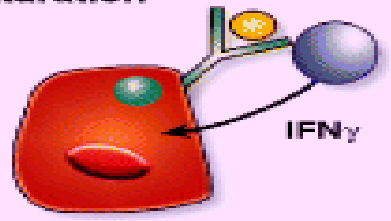
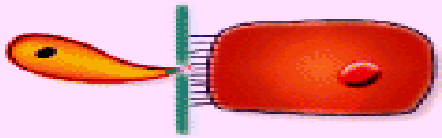
- How they work:
  - Elicit antibodies that will inactivate merozoites and/or target malarial antigens expressed on RBC surface
  - Inhibit development of parasite in RBCs
- Intended Use:
  - Morbidity reduction in endemic countries

Malaria: Plasmodium Life Cycle



Sexual Stage Vaccines

- How they work:
  - Induces antibodies against sexual stage antigens
  - Prevents development of infectious sporozoites in salivary glands of mosquitoes
  - Prevent or decrease transmission of parasite to new hosts
- Intended Use:
  - Decreased malaria transmission

Plasmodium life cycle stage	Targets	Vaccine	Clinical Phase
Sporozoite invasion  Anti-parasite: Inhibitory antibodies reduce inoculation dose	CSP 	RTS/S 	Phase III
	TRAP 		Phase II
	AMA-1 		Phase I
Merozoite invasion  Anti-parasite: Inhibitory antibodies prevent high parasitemia	MSP1 	FMPI 	Phase IIb
	MSP3 		Phase I
	AMA-1 		Phase I
Cytoadhesion  Anti-disease: Inhibitory antibodies block sequestration	var2CSA 		Research
	PfEMP1s 		Preclinical
Liver stage maturation  Anti-parasite: IFNγ-secreting T-cells destroy infected hepatocytes		GAP 	Research
Ookinete penetration  Altruistic vaccine: Inhibitory antibodies reduce transmission rate	Pfs25 		Research
	Pfs28 		

Challenges for Malaria Vaccine

- Four antigenetically distinct malaria species
  - Each has ~6,000 genes
  - First gene only identified in 1983
- Immunity in malaria is complex and immunological responses and correlates of protection are incompletely understood.
- Identifying and assessing vaccine candidates takes time and is expensive
- There is no clear ‘best approach’ for designing a malaria vaccine


La Malaria (1850-1851), oil on canvas by French artist Antoine Auguste Ernest Hébert (1817-1908).
Useful websites on malaria.
Centers for Disease Control and Prevention
http://www.cdc.gov/malaria/
World Health Organization
http://www.who.int/topics/malaria/en/
The Malaria Foundation
http://www.malaria.org
Travel doctor
http://www.traveldoctor.co.uk/tables.htm