Antiparasitic chemotherapy

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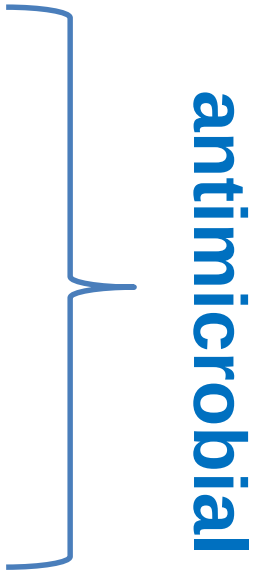
03.04.2019

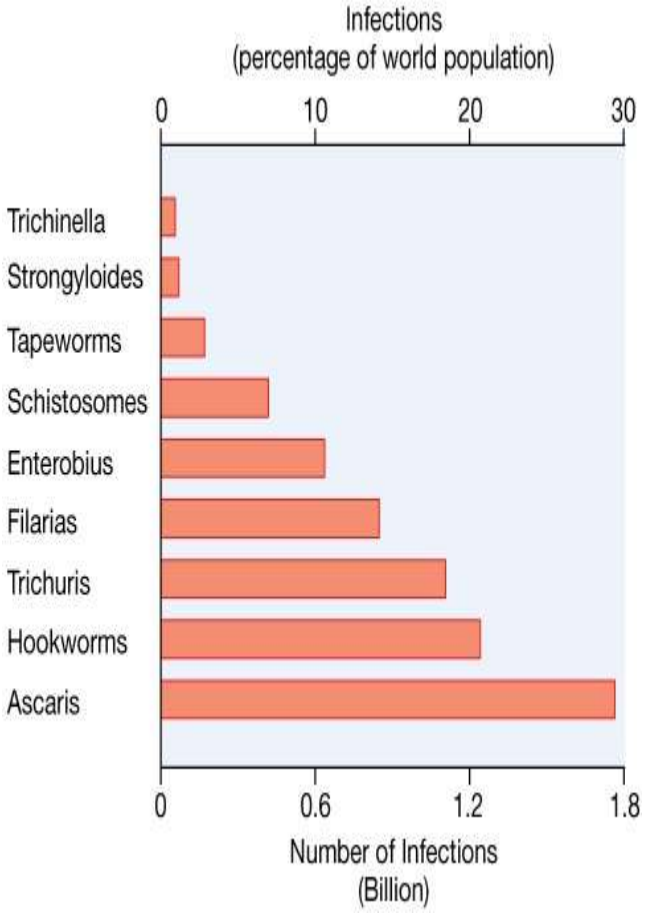
Chemotherapeutic drugs

- antibacterial
- antifungal
- antiviral
- **antiparasitic**
  - antiprotozoal
  - antihelminthic
- cancer chemotherapy
- (immunopharmacology)



Chemotherapy of helminth infections
(background)

- > 2 billion ($2x10^9$) people worldwide
  - roundworms – nematodes
    - ***Ascaris lumbricoides* (roundworm)**
    - *Necator americanus* & *Ancylostoma duodenale* (hookworms)
    - *Trichuris trichiura* (whipworm)
    - *Strongyloides stercoralis*
    - ***Enterobius vermicularis* (pinworm)**
    - *Trichinella spiralis*
    - Filarias (*Onchocerca volvulus*, *Loa Loa*, *Wuchereria bancrofti*, *Brugia malayi*)
    - *Dracunculus medinensis*
  - flatworms
    - flukes – trematodes
      - *Schistosoma* species, *Clonorchis sinensis, Paragonimus westermani*
    - tapeworms – cestodes
      - *Taenia saginata* / *Taenia solium* / *Diphyllobotrium latum* / *Hymenolepis nana* / *Echinococcus granulosus*
- Infection with more than one type simultaneously



Chemotherapy of helminth infections

(common characteristics)

- multicellular organisms
- invasion via skin or GI tract – immature forms
- characteristic tissue distribution
  - gut / liver / lung / eye / brain
- cannot complete their life cycle in the host
  - except: *Strongyloides* and *Echinococcus*
- drugs act **local**ly or **systemic**ally
- **toxicity** is not only **due to** drugs but also to dead or **dying parasites**

Anthelminthic drugs

- benzimidazoles
  - **mebendazole***
  - **albendazole***
- diethylcarbamazine
- **ivermectin**
  - mixture of avermectin B_{1a} + B_{1b}
- pyrantel pamoate
- **praziquantel**
- niclosamide
- ***levamisol****

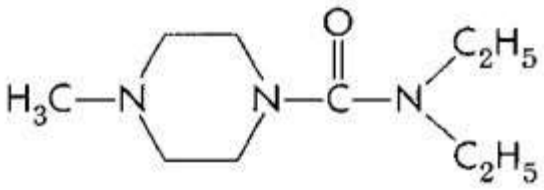
alternatives / rare / new

- benzimidazoles
  - triclabendazole
  - thiabendazole
- bithionol
- metrifonate
- oxamniquine
- piperazine
- doxycycline

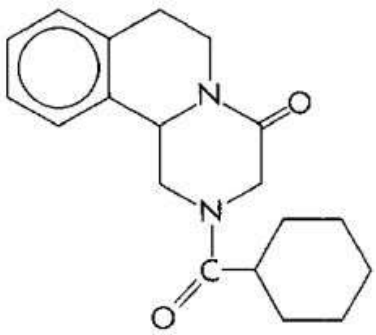
diverse chemical structures, mechanism of action & pharmacologic properties

* approved and available for clinical use in Hungary

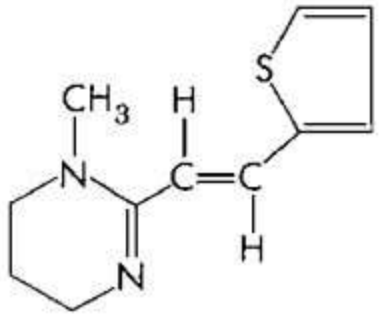
Chemical structures of some anthelmintic drugs



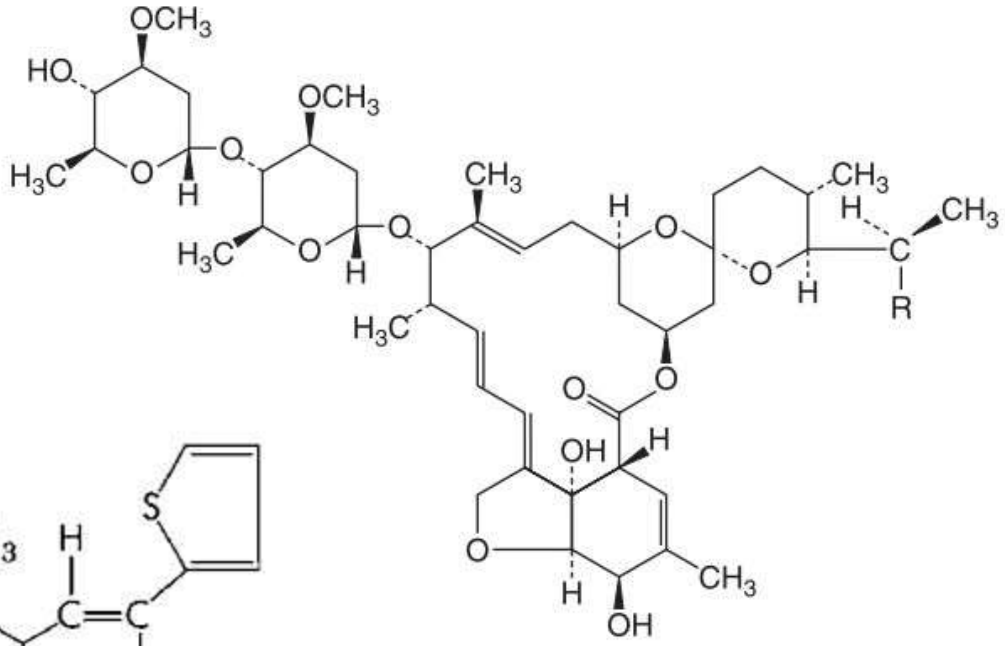
DIETHYLCARBAMAZINE



PRAZIQUANTEL

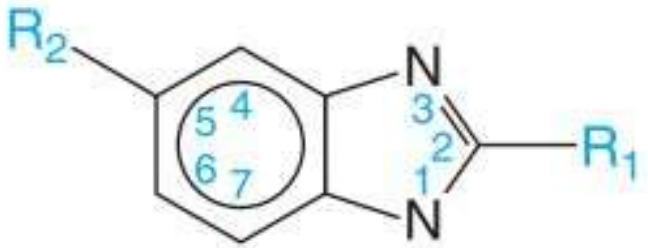


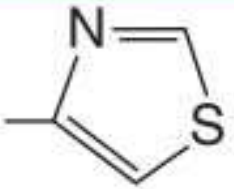
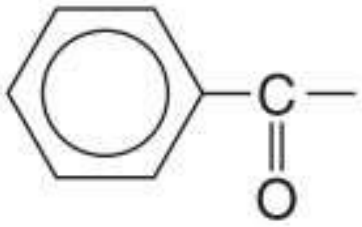
PYRANTEL



IVERMECTIN (R = CH_3 or C_2H_5)

Structure of the Benzimidazoles



R_1	R_2	Derivative
	H—	Thiabendazole
$-NHCO_2CH_3$		Mebendazole
$-NHCO_2CH_3$	$CH_3CH_2CH_2S-$	Albendazole

drug name	mechanism of action
benzimidazoles	**inhibit microtubule polymerization** by binding to β-tubulin / higher affinity for parasite β-tubulin
diethylcarbamazine	**unclear** (may impair intracellular processing and transport of certain macromolecules to the helminth plasma membrane)
ivermectin	hyperpolarization and tonic muscle paralysis by **increasing ligand (glutamate, GABA) gated Cl^- permeability** of the nerve or muscle cell membrane
pyrantel pamoate	**depolarizing neuromuscular blockade** → spastic paralysis of the worm
praziquantel	**increase cell membrane permeability to Ca^{2+}** → paralysis of tapeworms/flukes / tegumental damage → immune response
niclosamide	inhibition of mitochondrial **ATP synthesis**
levamisole	**unclear** (nACh agonist, appears to act by paralysing susceptible worms which are subsequently eliminated from the intestines)

Primary drugs against nematodes

- broad spectrum
  - **mebendazole**
  - albendazole
  - pyrantel pamoate
    - **ascariasis**, hookworm, **pinworm**
- narrow spectrum
  - ivermectin
    - *Onchocerca volvulus* (onchocerciasis – river blindness)
    - *Strongyloides stercoralis*
  - diethylcarbamazine
    - *W. bancrofti*; *B. malayi* (lymphatic filariasis); *Loa loa*

Primary drugs against trematodes (flukes)

- praziquantel

Primary drugs against cestodes (tapeworms)

- praziquantel
- niclosamide
- albendazole
  - cysticercosis (*Taenia solium* (pork tapeworm) larval stage)
  - *Echinococcus granulosus* (hydatid disease, dog tapeworm)

Oral absorption of antihelminthic drugs

drug name	oral absorption
mebendazole	poor (oral F=0.22 – rapid first pass)
albendazole	variable (enhanced by fatty food)
pyrantel pamoate	poor
ivermectin	good – rapid
diethylcarbamazine	good – rapid
praziquantel	good
niclosamide	minimal

Mebendazole

- oral – poor absorption, rapid first pass
  - fatty meal may increase
- inactive metabolites
- **broad spectrum**
  - ascariasis / trichuriasis / hookworm / pinworm
  - alternative for *T. saginata*
- minimal adverse effects with short term therapy
  - treatment duration 1-3 days
- unsafe in pregnancy
- caution in children < 2 y.o.

Albendazole

- oral – absorption improved by fatty meal
  - intraluminal – empty stomach
  - tissue parasite – fatty meal
- albendazole sulfoxide – active metabolite
- **broad spectrum**
  - ascariasis / trichuriasis / hookworm / pinworm
  - cysticercosis (pork tapeworm (*Taenia solium)* larval stage)
    - glucocorticoid coadministration
  - hydatid disease (*E. granulosus*)
    - e.g. as adjunctive in the perioperative period
- adverse effects
  - well tolerated: GI upset / cytopenias / liver enzyme ↑
  - unsafe in pregnancy and young children
  - **monitor blood counts / liver enzymes**
    - when used for prolonged periods (neurocysticercosis / hydatid dis)

Diethylcarbamazine

- rapid oral absorption
- urinary excretion
  - $t_{1/2}$ depends on urinary pH (shorter when acidic)
- narrow spectrum - **filarias**
  - *W. bancrofti, B. malayi, Loa loa*
- adult parasites killed slowly
  - longer course (2-3 weeks)
- initially lower dose
  - allergic reactions to dying microfilariae
- mild adverse effects
  - anorexia, nausea, headache
  - problem: host response to destruction of microfilariae

Ivermectin

- rapid oral absorption
- wide distribution (but not BBB!)
- fecal excretion
- narrow spectrum
  - **onchocerciasis** (microfilaricidal) – single dose
    - monthly / yearly repeated doses (even for 10 years)
  - **strongyloidiasis** – two daily doses
- adverse effects
  - **Mazzotti reaction** – dying microfilariae (fever, somnolence, rash, pruritus)
  - rare reversible eye lesions (e.g. corneal opacities)
- **avoid other GABAergic drugs**

Pyrantel pamoate

- poor absorption
  - mainly against luminal
  - single dose therapy
- **broad spectrum**
  - **pinworm, ascariasis**, hookworms
- rare and mild adverse reactions
  - GI: nausea, vomiting, diarrhea
  - headache
  - caution in liver dysfunction
    - transient liver enzyme ↑ observed

Praziquantel

- rapid oral absorption
- CSF levels 14-20% of plasma
- liver metabolism
  - inactive metabolites
- wide spectrum - **flukes and tapeworms**
  - schistosomiasis (two doses)
  - taeniasis, diphyllobothriasis
  - alternative in cysticercosis
  - *H. nana*
- common mild and transient adverse effects
  - abdominal discomfort / drowsiness
  - indirect effects due to parasite kill, antigen release
    - fever, pruritus, urticaria, rashes, arthralgia, myalgia
    - in neurocysticercosis: meningismus, seizures
    - contraindicated in ocular cysticercosis

Niclosamide

- second line for tapeworms
- used as a single 2 g dose
- minimal absorption
  - adult worms (but not ova) are rapidly killed → theoretical risk of cysticercosis if viable ova released
  - no secondary inflammatory response in occult cysticercosis
- not available in the USA and Hungary

Levamisol

- clinical use
  - **anthelminthic**
    - excellent activity in **ascariasis**
    - less activity in hookworm, *T. trichiura* (whipworm)
  - immunomodulator (was)
    - seemed beneficial in *rheumatoid arthritis (*nowadays not used)
    - was used in combination with 5-FU as adjuvant in Dukes C *colorectal cancer*
- adverse effects
  - minor GI / headache at anthelminthic single low dose
  - agranulocytosis at prolonged high dose used for immunotherapy

Adverse effects

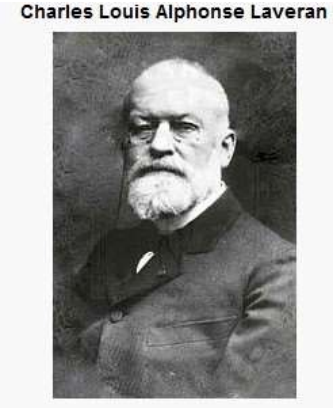
drug name	important adverse reactions
benzimidazoles	short term – **almost free of AE**, mild GI high dose – hypersensitivity, agranulocyt.
diethylcarbamazine	mild, transient – headache, nausea, dizzi. **release of protein from dying microfilaria** – fever, rash, cough, chest pain
ivermectin	**Mazzotti reaction** – fever, headache, rash, muscle pain, lymphadenitis, edema eye lesions - corneal opacities
pyrantel	rare, mild, transient – nausea, diarrhea liver enzyme elevations
praziquantel	common, mild, transient – headache, dizzin., nausea, diarrhea, liver enzyme↑
niclosamide	rare, mild, transient – nausea, diarrhea avoid alcohol consumption
levamisole	vasculitis, hyperthermia, **agranulocytosis**

Other narrow spectrum / alternative

(rarely used)

- bithionol
  - fascioliasis (sheep liver fluke) / paragonimiasis (lung fluke)
- triclabendazole
  - fascioliasis (sheep liver fluke)
- metrifonate
  - only for *Schistosoma hematobium* (bilharziasis)
  - organophosphate prodrug (nonenzymatic → dichlorvos)
- oxamniquine
  - only for *Schistosoma mansoni* (intestinal bilharziasis)

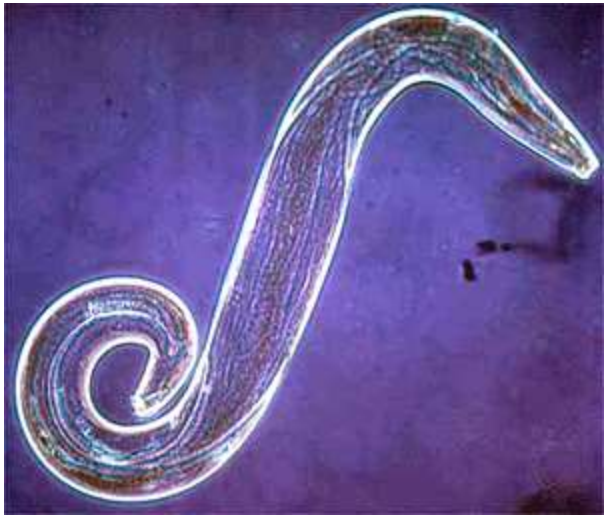
Chemotherapy of malaria



- ≈40% of the world's population is at risk of malaria
- ≈200 - 300 million infections in each year
- ≈1 million deaths (445000 (2016), 446000 (2015))
  - sub-Saharan Africa
  - most in infants and children
- **management is under constant review**
- **drug resistance is a major problem**
- measures to control malaria
  - protection from mosquito bites
  - **prophylaxis** with antimalarial drugs
  - prompt **treatment** of any infection that develops
  - vector control
- **prompt** **diagnosis** and **effective treatment** are crucial

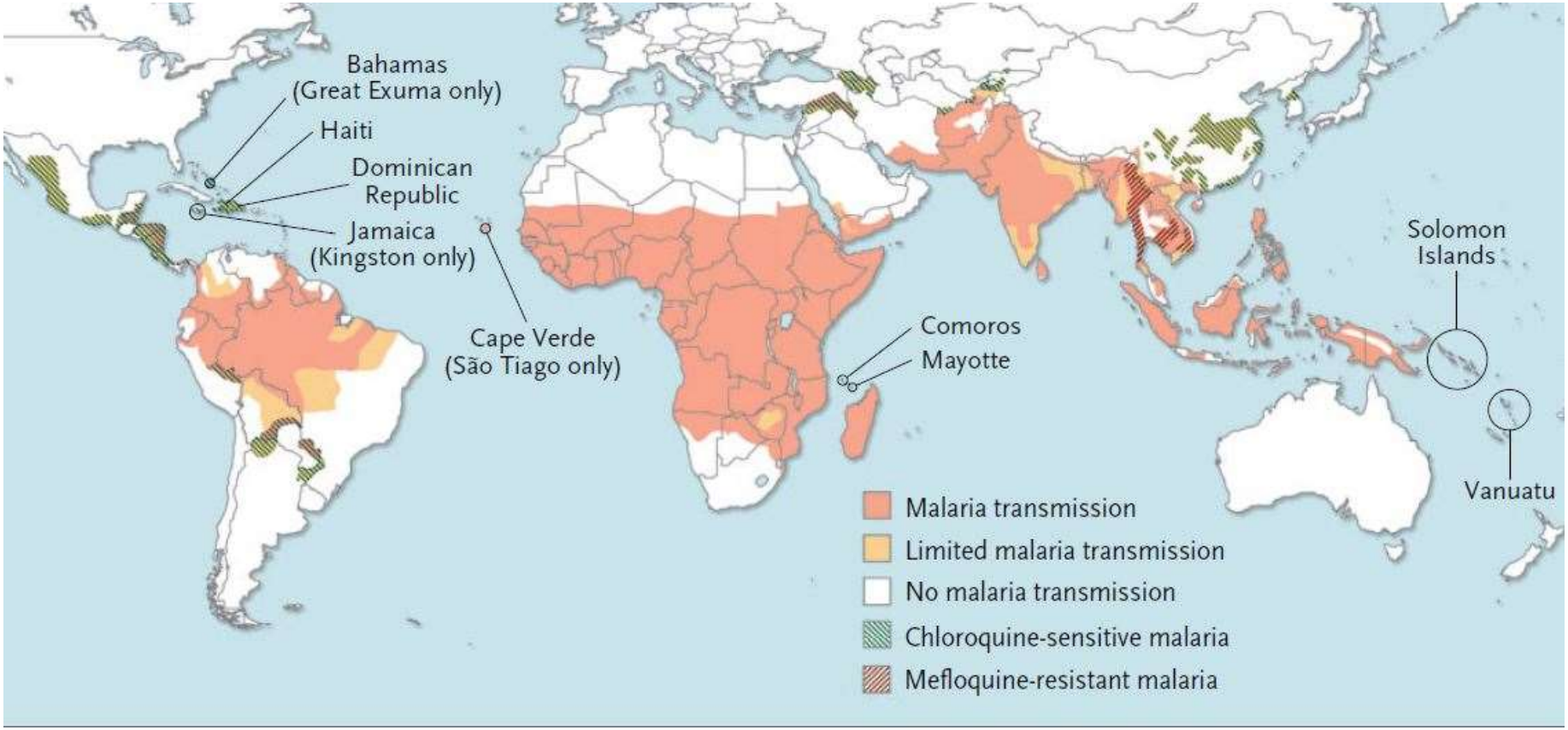
The cause of human malaria

- mostly **four species** cause human malaria
  - ***Plasmodium falciparum***
    - malignant **tertian** malaria
  - *Plasmodium vivax*
    - benign tertian malaria, **persistence**!
  - *Plasmodium malariae*
    - quartan malaria (72 hour cycle)
  - *Plasmodium ovale*
    - ovale tertian, rare, **persistence!**
  - *+* recently *Plasmodium knowlesi*
    - monkey malaria, rare, mostly uncomplicated



- complex life cycle
  - sexual (in mosquito) and asexual phase (in man)

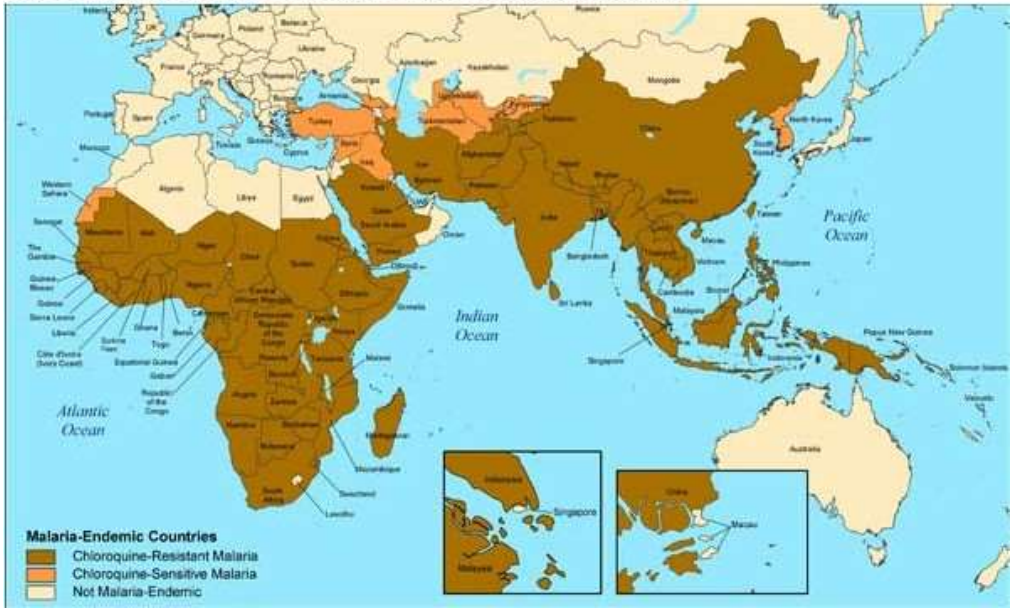
Malaria endemic areas - 2008



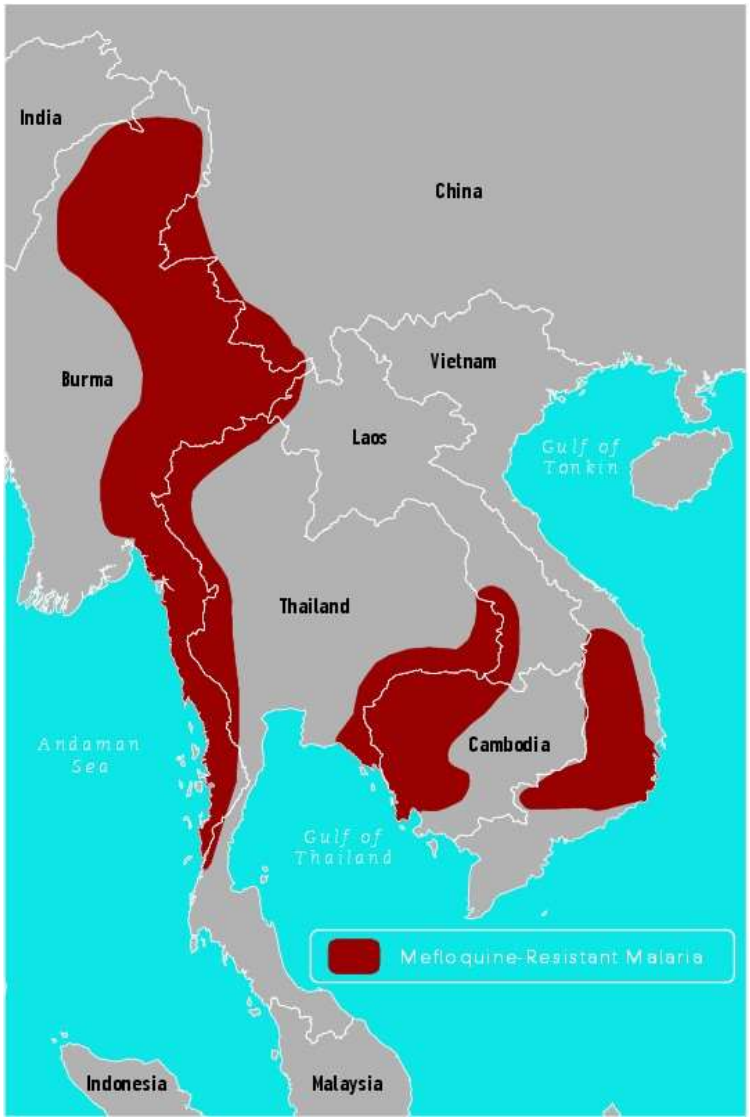
transmission is area dependent, sometimes very focal

Map 2-7. Malaria-endemic countries in the Western Hemisphere.

Map 2-8. Malaria-endemic countries in the Eastern Hemisphere.



Mefloquine resistant malaria



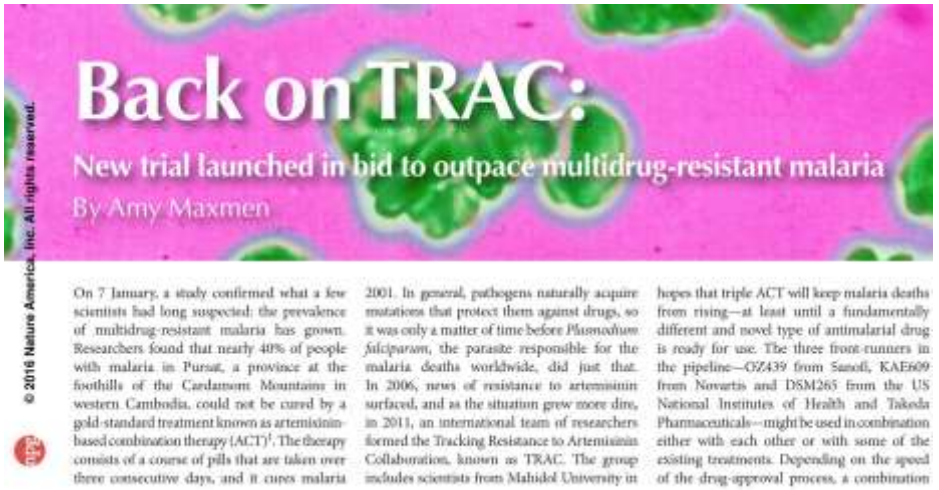
Singnificance of resistance (2016)

Comment

Colistin resistance: a major breach in our last line of defence

In hospital practice, clinicians have been buoyed by the recent development of new antibiotics active against multidrug resistant Gram-negative bacilli. However, recently approved antibiotics like ceftazidime-avibactam or ceftolozane-tazobactam do not provide activity against all Gram-negative bacilli, with notable gaps in their coverage, including the notorious New Delhi metallo-β-lactamase 1-producing organisms and many strains of carbapenem resistant Acinetobacter baumannii. For this reason, the polymyxins (colistin and polymyxin B) remain the last line of defence against many Gram-negative bacilli. Colistin-resistant and even pan-drug-resistant Gram-negative bacilli have already been reported.[1,2] Typically, colistin resistance is due to chromosomally mediated modulation

Liu and colleagues[3] present data from China showing that *E coli* from pigs at slaughter and from retail chicken and pork have high rates of plasmid-mediated colistin resistance. The same mechanism was found in *E coli* and *K pneumoniae* isolates from Chinese patients in hospital. These findings suggest that the links between agricultural use of colistin, colistin resistance in slaughtered animals, colistin resistance in food, and colistin resistance in human beings are now complete. One of the few solutions to uncoupling these connections is limitation or cessation of colistin use in agriculture. This will require substantial political will and we call upon Chinese leaders to act rapidly and decisively. Failure to do so will create a public health problem of major dimensions.



Back on TRAC:

New trial launched in bid to outpace multidrug-resistant malaria

By Amy Maxmen

On 7 January, a study confirmed what a few scientists had long suspected: the prevalence of multidrug-resistant malaria has grown. Researchers found that nearly 40% of people with malaria in Pursat, a province at the foothills of the Cardamom Mountains in western Cambodia, could not be cured by a gold-standard treatment known as artemisinin-based combination therapy (ACT)[1]. The therapy consists of a course of pills that are taken over three consecutive days, and it cures malaria

2001. In general, pathogens naturally acquire mutations that protect them against drugs, so it was only a matter of time before *Plasmodium falciparum*, the parasite responsible for the malaria deaths worldwide, did just that. In 2006, news of resistance to artemisinin surfaced, and as the situation grew more dire, in 2011, an international team of researchers formed the Tracking Resistance to Artemisinin Collaboration, known as TRAC. The group includes scientists from Mahidol University in

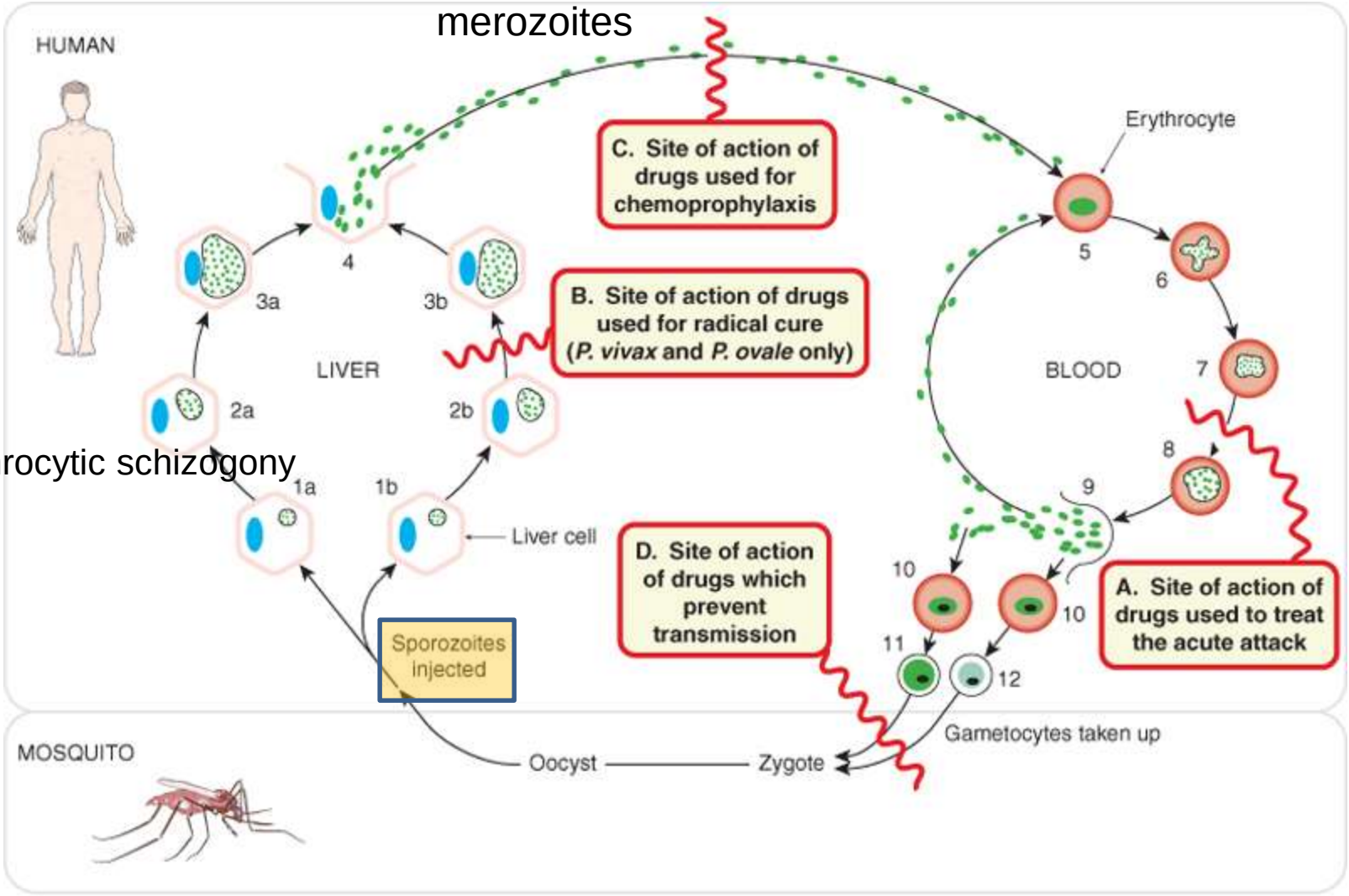
hopes that triple ACT will keep malaria deaths from rising—at least until a fundamentally different and novel type of antimalarial drug is ready for use. The three front-runners in the pipeline—OZ439 from Sanofi, KAE609 from Novartis and DSM265 from the US National Institutes of Health and Takeda Pharmaceuticals—might be used in combination either with each other or with some of the existing treatments. Depending on the speed of the drug-approval process, a combination

"**plasmid-mediated colistin resistance** for the first time"
"**readily passed** between Escherichia coli strains"
"the plasmid could be passed to *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* strains"

"It therefore seems inevitable that plasmid-mediated transfer of colistin resistance **will seriously limit the lifespan of the polymyxins** as the backbone of regimens against multiply resistant Gram-negative bacilli."

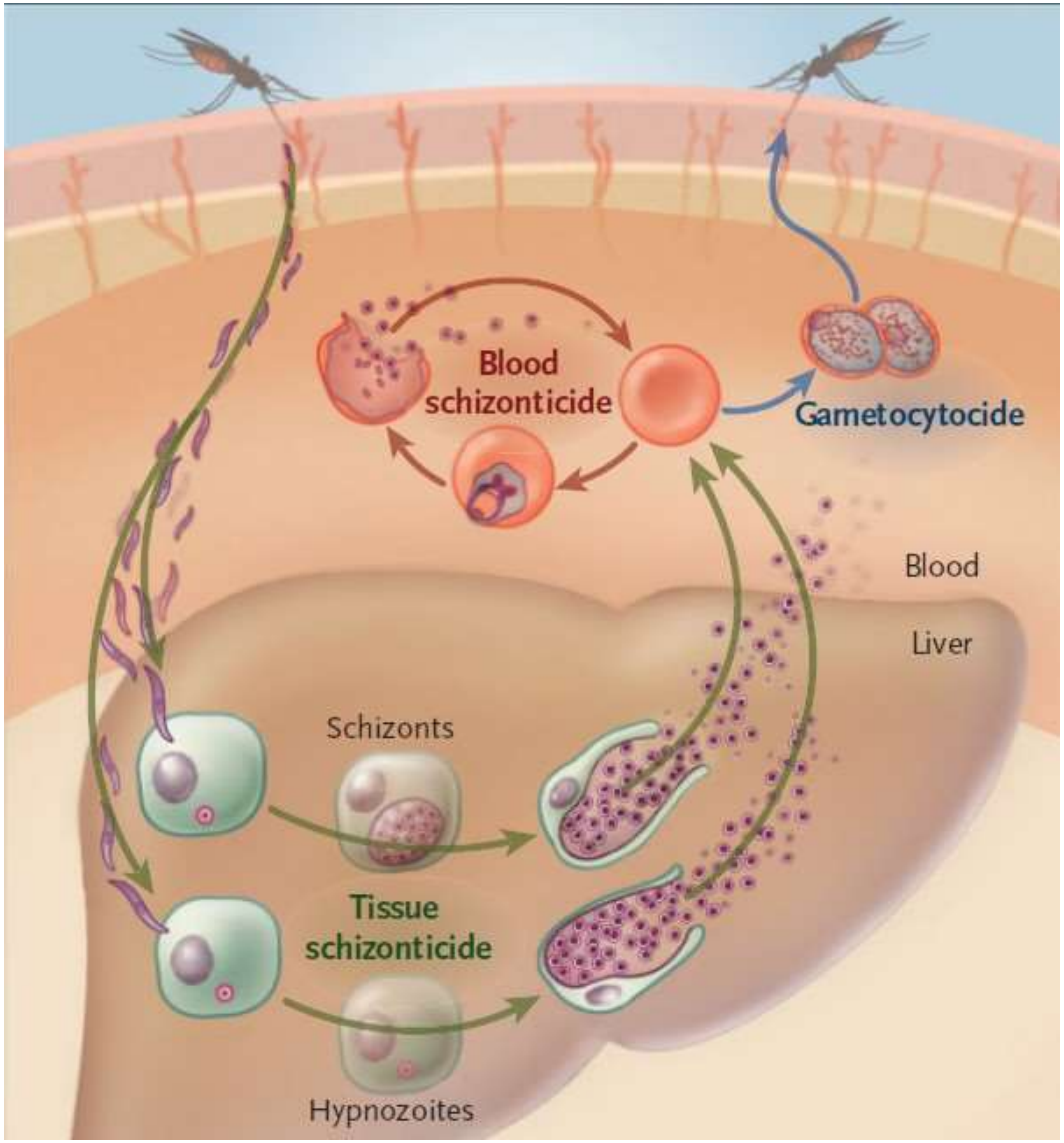
"On 7 January, a study confirmed what a few scientists had long suspected: the prevalence of **multidrug-resistant malaria** has grown. Researchers found that nearly **40% of people with malaria** in Pursat, a province at the foothills of the Cardamom Mountains in western Cambodia, **could not be cured by a gold-standard treatment** known as artemisinin-based combination therapy."

merozoites



preerythrocytic schizogony

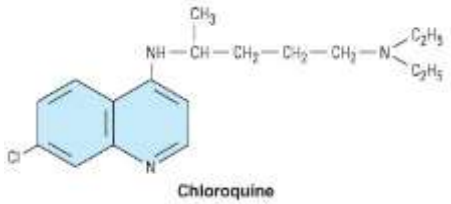
Antimalarial drug activity in the life cycle of plasmodia

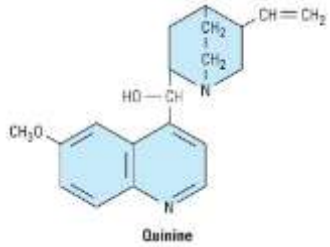


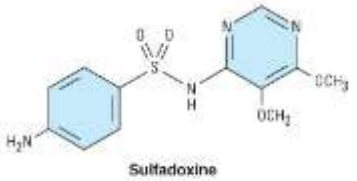
- **tissue schizonticides**
  - in liver
    - schizonts - causal prophylaxis
    - hypnozoites - anti-relapse
- **blood schizonticides**
  - in red cells
- **gametocytocides**
  - in blood
- sporontocides
  - in mosquito

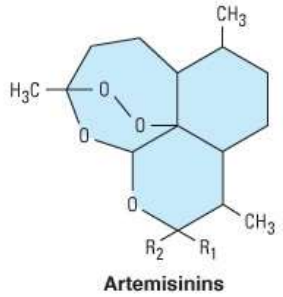
Classification : chemical structure

- 4-aminoquinolines
  - **chloroquine** / **amodiaquine / piperaquine**
- 4-methanolquinolines
  - **quinine / quinidine / mefloquine**
- 8-aminoquinoline
  - **primaquine**
- folate antagonists
  - **sulfadoxine/pyrimethamine** (Fansidar®)
  - **proguanil**
- others
  - **atovaquone (see Malarone®)**
  - doxyxcycline / clindamycin
  - **artemisinins**
    - **(artesunate / artemether / dihydroartemisinin)**
  - halofantrin
  - **lumefantrin**









Classification: life cycle

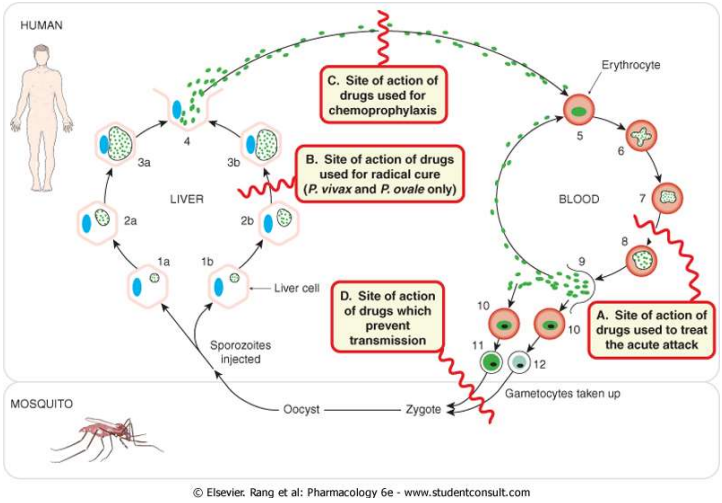
group	drugs		liver stages		blood stages	
		sporozoite	primary	hypnozoite	asexual	gametocyte
1	**artemisinins**	-	-	-	+	+
	chloroquine	-	-	-	+	+/-
	mefloquine	-	-	-	+	-
	quinine/quinidine	-	-	-	+	+/-
	pyrimethamine	-	-	-	+	-
	sufadoxine	-	-	-	+	-
	tetracyclines	-	-	-	+	-
2	atovaquone/proguanil	-	+	-	+	+/-
3	primaquine	-	+	+	-	+

not for *P.falciparum*

only *P. falciparum*

Classification: life cycle

- tissue schizonticides – **primaquine**, atovaquone+proguanil (Malarone®)
- blood schizonticides – e.g. artemisinins, chloroquine, mefloquine, quinine
- gametocytocides – primaquine, artemisinins



- **drugs used in chemoprophylaxis**
  - atovaquone+proguanil (Malarone®)
  - chloroquine (only if sensitive)
  - doxycycline
  - mefloquine
  - primaquine
    - *P. vivax* only
    - terminal prophylaxis

prophylaxis: before – during – after travel

Factors influencing the prophylactic drug choice

- resistance – chloroquine / mefloquine
- duration of the trip
- age and medical history
- pregnancy
- drug intolerance
- economic considerations

Drugs for malaria prophylaxis

drug	adult dose	use in children	use in pregnancy
atovaquone-proguanil	250/100 mg once daily	yes (> 11 kg)	no
mefloquine	250 mg once **weekly**	yes (> 5 kg)	**yes**
doxycycline	100 mg once daily	**no**	no
chloroquin	500 mg once **weekly**	yes	**yes**
primaquine	30 mg once daily	yes	no

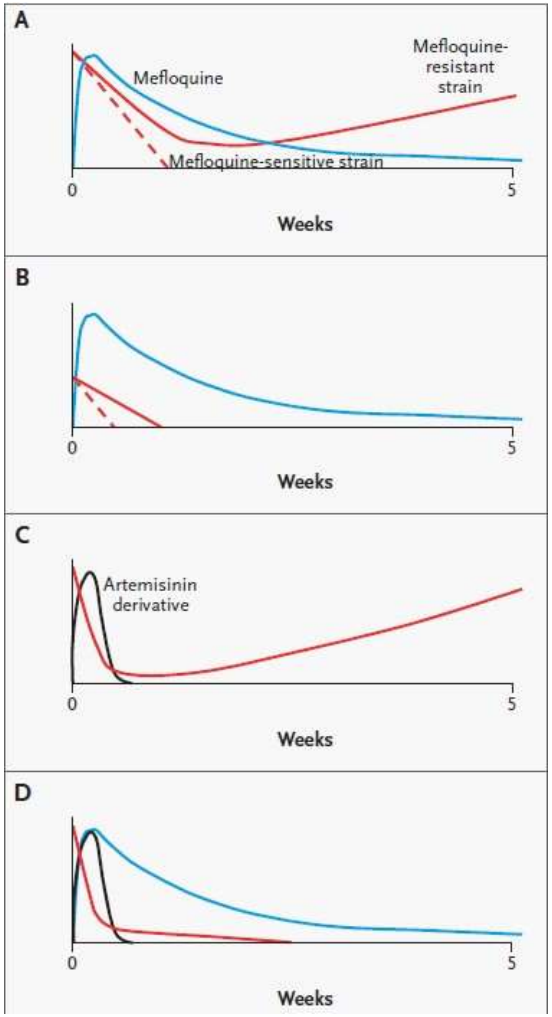
- malaria is more severe in pregnancy
- ↑ risks of adverse outcomes

recommendation for pregnant women: **do not travel to malaria endemic area**

Drugs in malaria prophylaxis

drug	adverse effects	dosing freq
atovaquone-proguanil	abdominal pain, nausea, vomiting, headache	daily
chloroquine	GI disturb, headache, dizziness, blurred vision, insomnia, pruritus, psoriasis exacerb, retinopathy (in high doses)	weekly
doxycycline	nausea or vomiting, photosensitivity, vaginal yeast infections	daily
mefloquine	psychoses or seizures, other psychiatric disord, headache, insomnia, visual and GI disturb	weekly
primaquine	GI upset if empty stomach (take with food), in G6PD def. fatal hemolysis	daily

Combinations in the treatment of malaria



- earlier were not used
- more **common** nowadays
- **parasite burden** is important (A vs. B)
- short and effective course not necessarily eliminate
- **combination of short and long** is better

duration of administration: 3-4 days

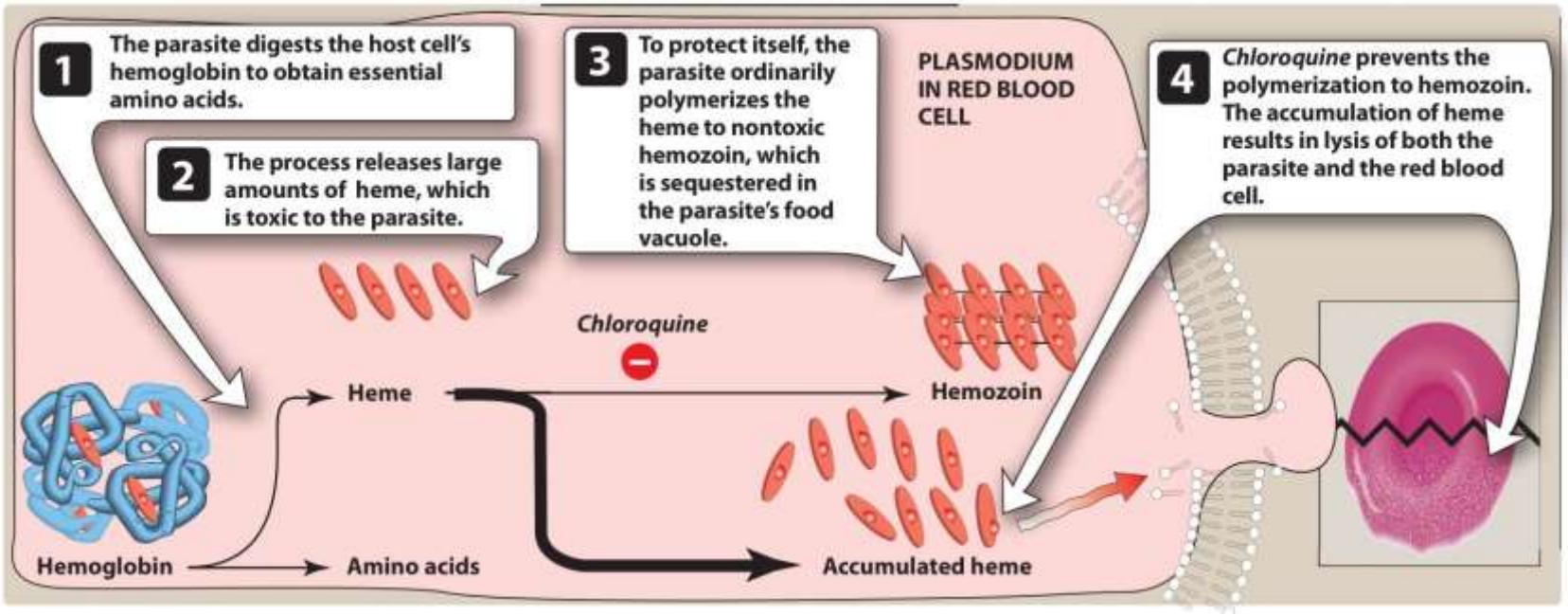
Combinations in the treatment of malaria

- **artemisinin-based combination therapies (ACTs)**
  - artemether-lumefantrine (Coartem®, Riamet®)
  - artesunate-amodiaquine (ASAQ®, Coarsucam®)
  - artesunate-mefloquine
  - dihydroartemisinin-piperaquine (Artekin®, Duocotecxin®)
  - artesunate-sulfadoxine-pyrimethamine
  - (artesunate-pyronaridine (Pyramax®))
- *other*
  - sulfadoxin-pyrimethamine (FANSIDAR®)
  - atovaquone-proguanil (MALARONE®)

Half lives of ACT partner drugs

drug	half life
lumefantrine	4-5 days
amodiaquine	9-18 days
mefloquine	13-24 days
piperaquine	~28 days
pyrimethamine	4 days
sulfadoxine	4-8 days
pyronaridine	8 days

Mechanism of action of chloroquine

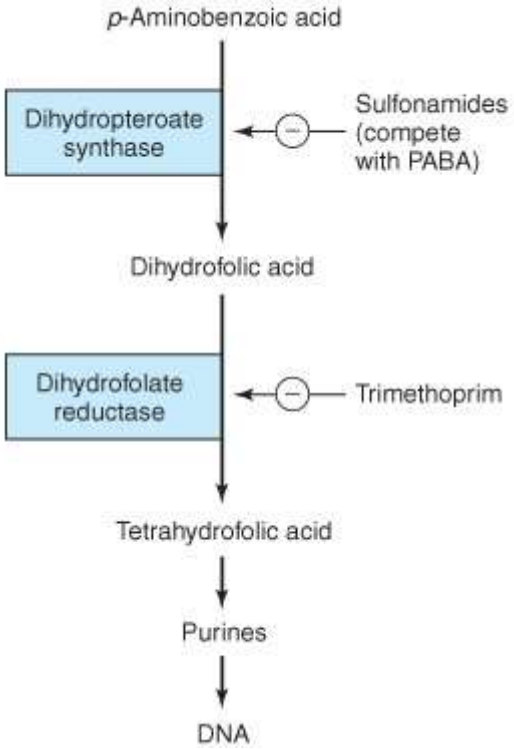


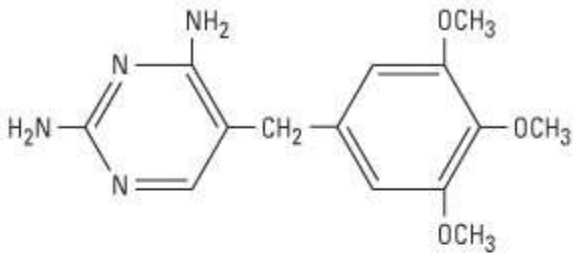
quinine, amodiaquine, mefloquine, lumefantrine: **similar**

artemisinins: cleave endoperoxide bridge in digestive vacuole → **free radicals**

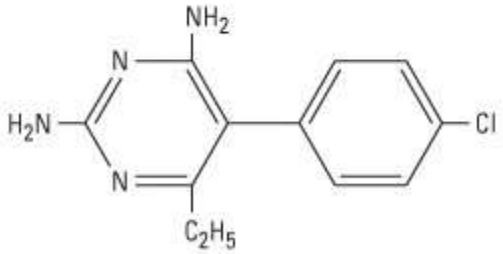
atovaquone: **disrupt mitochondrial electron transport**
(enhanced by nonmetabolized proguanil – see Malarone®)

Mechanism of action of sulfonamides/folate antagonists

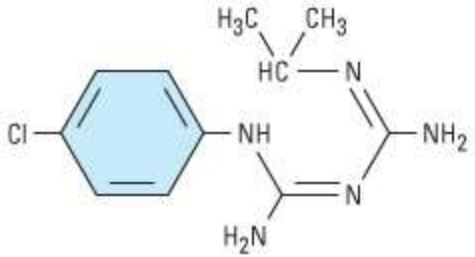




Trimethoprim



Pyrimethamine



Proguanil

Pharmacokinetics of antimalarial drugs

drug	some pharmacokinetic characteristics
chloroquine	complete oral abs; **V_d ~100-1000 L/kg; long half life (month)**
amodiaquine	oral; active metabolite with **long half life**
quinine	oral / i.v. ; **in malaria longer half life**
quinidine	i.v. ; shorter half life than quinine
mefloquine	oral only ; highly protein bound; **long half life (20 days)**
primaquine	good oral absorption ; rapid metabolism ; half-life 3-8 hours
sulfadoxine-pyrimethamine (Fansidar)	oral; pyrimethamine **$t_{1/2}$~3.5 days**; sulfadoxin ~ 170 hours
atovaquone-proguanil (Malarone)	proguanil is a prodrug (but in this comb. the nonactivated form causes the synergism)
doxycycline	oral (i.v.)
halofantrine	oral ; irregular absorption
lumefantrine	oral ; irregular absorption; comb. with artemether (Coartem)
artemisinins	artesunate – water-soluble (po, iv, rectal); artemether – lipid-soluble; (po, im, rectal); dihydroartemisinin – water-soluble (po); short $t_{1/2}$

Clinical use of antimalarial drugs

drug	treatment	prophylaxis	comment
chloroquine	yes	**yes**	only if sensitive
amodiaquine	yes	no	fixed combination with artesunate
quinine	yes	no	p.o. / i.v. *P falciparum*
quinidine	yes	no	i.v. severe *P falciparum*
mefloquine	yes	**yes**	*P falciparum*
primaquine	yes	**yes**	**only** *P vivax* / *P ovale;* dormant;G6PD!
sulfadoxine-pyrimethamine (Fansidar)	yes	no	chloroquine resistant *P falciparum*
atovaquone-proguanil (Malarone)	yes	**yes**	*P falciparum*
doxycycline	yes	**yes**	for treatment together with quinine
halofantrine	yes	no	*P falciparum*
lumefantrine	yes	no	fixed combination with artemether
artemisinins	yes	no	p.o. **combinations** / i.v. artesunate severe

Adverse effects of antimalarial drugs

drug	adverse effects
chloroquine	well tolerated; **pruritus**; rash; rare hemolysis in G6PD def.
amodiaquine	agranulocytosis / hepatotoxicity; rare (obs. in prophylaxis)
quinine	**cinchonism** (tinnitus; headache; nausea; visual dist.), **hypoglycemia,** blackwater fever
quinidine	similar to quinine
mefloquine	nausea/vomiting; seizures/**psychosis** (mainly when treatment)
primaquine	well tolerated ; nausea/GI pain; **hemolysis in G6PD def.**
sulfadoxine-pyrimethamine (Fansidar)	well tolerated ; GI symptoms, skin rash + sulfonamides
atovaquone-proguanil (Malarone)	well tolerated ; nausea/GI pain
doxycycline	GI upset; photosensitivity; contra <8 years
halofantrine	well tolerated; arrhytmias (QT prolongation)
lumefantrine	well tolerated; no risk of dangerous arrhytmias
artemisinins	generally well tolerated / neutropenia, allergy (rare)

Primaquine induced hemolytic anemia