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Effectiveness of Antimalarial Drugs

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REVIEW ARTICLE

DRUG THERAPY

Effectiveness of Antimalarial Drugs

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THE OPENING OF THE PANAMA CANAL IN 1914 INITIATED AN ERA IN which efforts to control malaria were aimed at the anopheline mosquito. The World Health Organization's Global Malaria Eradication Campaign in the 1950s and 1960s marked the apex of these efforts. The use of dichlorodiphenyltrichloroethane (DDT) rid vast areas of endemic malaria virtually everywhere except in sub-Saharan Africa. The eradication strategy was abandoned in 1969, because it came to be considered logistically, socially, and politically impractical, especially given public concern about the effects of DDT on the environment. It took two decades and a global resurgence of malaria before a new strategy emerged, one that was focused on treatment rather than prevention.[1] This treatment strategy is currently being debated, and its efficacy is unproved.[2,3]

Both the broad collapse of preventive efforts and the waning efficacy of standard antimalarial drugs[4,5] account for the global resurgence of malaria. New therapies are available, but the use of older drugs persists for social, economic, and clinical reasons, despite resistance of the organisms to the older drugs. Efforts to use new antimalarial drugs may be hampered by regulatory requirements or economic obstacles as well as by important questions about safety for the large numbers of patients who treat themselves. Public health agencies continue to support the distribution of older therapies, despite strong criticism from scientists conducting research on the disease and its treatment and prevention.[6]

In addition to inadequate drug efficacy, new therapies may fail because of inappropriate use, inadequate absorption, poor adherence, contraindications, intolerability, the use of counterfeit drugs or improper manufacture of drugs, or prohibitive cost. Chloroquine and sulfadoxine–pyrimethamine, which for several decades were the foundation of malaria therapy, had a low risk with respect to this array of problems. However, the emergence and consolidation of resistance to these drugs eroded their clinical usefulness.

PLASMODIA

The coccidian genus plasmodium contains 172 species that infect birds, reptiles, and mammals. Four species infect humans — *Plasmodium falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. *P. falciparum* and *P. vivax* account for the vast majority of the 300 million to 500 million infections that occur each year. Endemic transmission takes place in most tropical latitudes and reaches into temperate zones seasonally (Fig. 1). Although each type of infection causes debilitating febrile illness, only *P. falciparum* carries a substantial risk of death; 1 million to 3 million deaths occur each year in regions of holoendemic infection in sub-Saharan Africa, most of them among infants and young children.

For plasmodia, humans are not the "definitive host," a concept defined by parasitologists as the site where sexual recombination occurs. Instead, many species in the genus anopheles have that distinction. From the perspective of the parasite, humans are

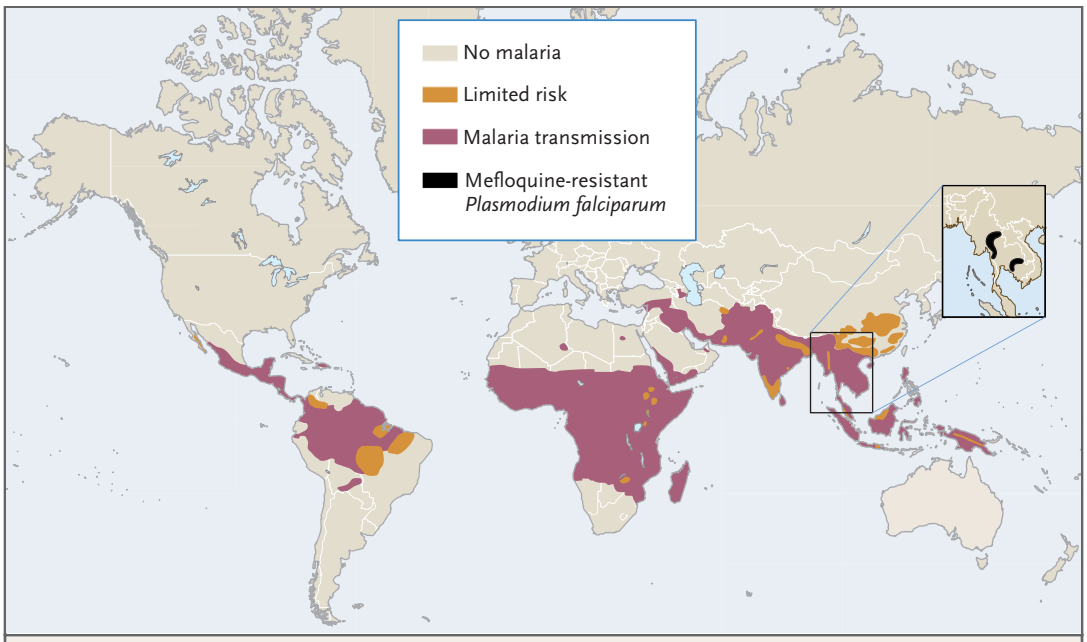

Figure 1. Risk of *Plasmodium falciparum* Malaria Worldwide.
Adapted from the Public Health Mapping Group, Communicable Diseases, World Health Organization, November 2002.

simply a means of getting into mosquitoes, where sexual recombination can occur. A full description of the extraordinary complexity of this cycle is beyond the scope of this review. Figure 2 illustrates the essential features of the cycle and the terminology of antimalarial therapies.

EXTRINSIC DETERMINANTS OF DRUG EFFECTIVENESS

AVAILABILITY

Most developing nations license and make available only the antimalarial drugs that are provided through national health programs.[7] This approach often excludes relatively expensive or risky therapies, even for patients who may be able to afford a given drug and have access to medical supervision. The main factor affecting availability is economic — the ability or inability to purchase a drug for broad distribution and the potential reluctance to use an agent because of an inability either to screen users or to monitor its quality.

Chloroquine and sulfadoxine–pyrimethamine cost less than 15 percent of the cost of the least expensive alternative agents and approximately 1 to 2 percent of the cost of many of the agents marketed in the developed world (Table 1). The developing world requires distribution strategies for effective therapies that overcome the availability of cheap but ineffective drugs. The U.S. National Academies made a core recommendation[8] that governments and international financial institutions should commit $300 million to $500 million per year within five years to subsidize artemisinin-combined therapies (an emerging family of antimalarial drugs, including artemether, artesunate and dihydroartemisinin) to achieve prices for the end user in the range of 10 to 20 cents. Unless this recommendation is followed, market forces will continue to drive the use of ineffective therapies.

ADHERENCE

Most people taking antimalarial drugs live in rural regions of the developing world and are not supervised by health professionals. A study conducted among 1640 febrile patients with malaria in Burkina Faso[9] showed that 69 percent were self-treated, and in a study in Ethiopia, among 630 febrile patients with malaria, 67 percent were self-treated.[10] Complex, inconvenient, or poorly tolerated antimalarial regimens carry a substantial risk of inadequate adherence.[11] Among 414 Brazilian patients, the risk of

recurrent malaria correlated with self-reported poor adherence,[12] whereas among 632 Nigerian children strict adherence correlated with clinical recovery.[13] Convenient and easily understood packaging and education of the patients alleviate poor adherence. Owing to lengthy and complex regimens, currently used therapies such as quinine and primaquine and new combined therapeutic strategies[14] challenge the ease of adherence.

COUNTERFEIT AND SUBSTANDARD DRUGS

Counterfeit antimalarial drugs pose a serious threat in regions where the trade in pharmaceuticals is not rigorously regulated. A survey conducted in Cameroon found insufficient or inactive ingredients in 38 percent of preparations labeled chloroquine, 78 percent of those labeled quinine, and 12 percent of tablets labeled as an antifolate agent.[15] A survey in Southeast Asia involving 104 purchases of artesunate tablets found that 38 percent of the tablets contained no drug.[16] The trade in counterfeit drugs undoubtedly results in many deaths, but it is lucrative and carries little risk of imprisonment.[17] The inadvertent marketing of substandard pharmaceuticals poses another threat. In a survey of eight authorized wholesalers in Tanzania selling combined sulfadoxine–pyrimethamine tablets, 11 percent of the tablets failed industry standards for content, and 44 percent failed dissolution testing.[18]

INTRINSIC DETERMINANTS OF DRUG EFFECTIVENESS

STAGE SPECIFICITY

Plasmodia pass through distinct stages of form, function, location, clinical consequence, and susceptibility to antimalarial drugs (Fig. 2 and Table 1). Drug activity ranges from narrow (e.g., the activity of quinine against asexual blood stages) to broad (e.g., the activity of primaquine against sexual and asexual forms in the blood and liver). Moreover, the range of stage-specific susceptibility differs among species of plasmodia — for example, chloroquine kills the gametocytes of *P. vivax* but exerts no effect against those of *P. falciparum*. These intrinsic properties define the recommended uses of antimalarial drugs.

PARASITE BURDEN

Most patients with malaria carry a burden of 10^8 to 10^{13} parasites.[19] Effective chemotherapy induces a constant fractional decline with each asexual cycle,[20] at a rate that varies according to the susceptibility of the parasite to a given drug. For example, artemisinin derivatives induce reductions of 10^4, whereas tetracycline achieves a reduction by only a factor of 10 with each cycle. The duration of exposure to a drug that is needed to eliminate infection hinges on the intrinsic rate of decline and, more important, on the initial parasite burden.[21] High levels of parasitemia, as compared with a low burden, require longer exposure to effective drug levels and have a relatively higher risk of treatment failure.[22]

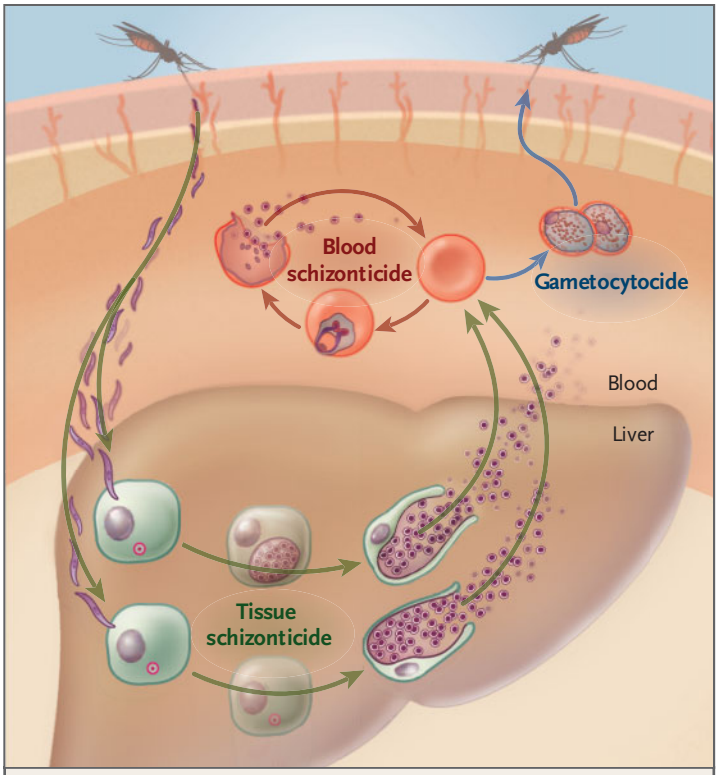

Figure 2. Antimalarial Drug Activity in the Life Cycle of Plasmodia.

Tissue-stage schizonticides kill the asexual stages developing in the liver, including liver schizonts (all species) and quiescent hypnozoites (*Plasmodium vivax* and *P. ovale*), thus preventing primary or secondary attacks (relapses) of clinical malaria. Blood-stage schizonticides interrupt asexual schizogony (mitotic division) in red cells, preventing or terminating clinical attacks of malaria. Gametocytocides kill or sterilize sexual stages in the blood, thus preventing infection of mosquitoes and transmission of the disease. Another class of drugs, the sporontocides (which kill forms developing in the mosquito, including the sporozoites that infect humans), is not represented here, because none are available for clinical use.

PHARMACOKINETICS

A variety of factors affect the pharmacokinetics of antimalarial drugs. Variant alleles of the human

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

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

* Unless otherwise indicated, the cost shown is the cost, in 2003 U.S. dollars, of medication for one adult treatment regimen, purchased in bulk, according to the International Drug Price Indicator Guide (IDPIG) (http://erc.msh.org/mainpage.cfm?file=1.0.htm&module=dmp&language=English).
† U.S. commercial sources were surveyed; the cost is not available from the IDPIG.
‡ The cost shown is from the IDPIG; the combination is available through the World Health Organization (WHO) to qualified purchasers at a cost of $2.40 per adult treatment regimen.
§ The cost shown is from the WHO.
¶ The cost shown is from Arrow et al.[8]

gene for cytochrome P-450 2C19 (CYP2C19), for example, correlate with slow or rapid metabolism of some antimalarial agents. For example, chloroguanide, metabolized through the activity of CYP2C19, was studied in 126 healthy, unrelated Nigerian subjects, of whom 5 percent had slow metabolism of the drug (8 percent of the normal rate).[23] A study of Thai subjects taking oral contraceptives reported that metabolism of chloroguanide was decreased by 34 percent,[24] a finding that may be explained by inhibition of CYP2C19 activity by estrogen. Certain foods may also profoundly affect the bioavailability (and toxicity) of certain antimalarial drugs — for example, fatty foods affect the bioavailability of halofantrine and of the combination of lumefantrine and artemether.

SAFETY AND TOLERABILITY

In rural health care centers, staff with relatively little formal training may be responsible for taking care of patients with malaria. The patients often have no written medical history, and the centers have minimal capacity for laboratory screening for contraindications to particular medications. Worse still, most of these people with malaria treat themselves with antimalarial agents acquired over the counter or passed from household to household.

Any antimalarial drugs that are to be distributed in such regions need to be safe and well tolerated, and the risks associated both with the indicated use and with contraindicated or inappropriate uses should be considered. Clinical studies supporting the licensing of new antimalarial drugs rarely include highly vulnerable groups such as infants, young children, and pregnant women.[25] Thus, safety issues often drive the decision to continue distributing chloroquine or sulfadoxine–pyrimethamine, despite substantial parasite resistance. Key data with regard to the safety and tolerability of the most commonly used antimalarial drugs are summarized in Table 2.

IMMUNITY

The intersection of immunity to plasmodia and antimalarial drug activity is poorly understood. In a study of Brazilian patients, self-reported poor adherence correlated with a risk of recurrence among nonimmune persons (i.e., those with a first infection) but not among semi-immune persons (i.e., those with >4.8 years' exposure to plasmodia).[12] Among 80 Lao patients, the level of humoral immunity to *P. falciparum* and the risk of therapeutic failure were correlated with the parasite count on admission to the hospital and the length of time to

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

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

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

the resolution of fever.[29] Djimde et al.[30] showed that the clearance of *P. falciparum* organisms carrying a mutant transporter gene, *pfcrt* K76T, that was linked with resistance to chloroquine correlated with acquired immunity in subjects in sub-Saharan Africa. In subjects with relatively little immunity who were infected with mutant parasites, the chloroquine therapy failed more frequently than in those infected with the same genotype of *P. falciparum* organisms who had clinical immunity. However, such correlations do not directly link immune effectors with drug activity; acquired immunity independently reduces the parasite burden, which is a well-known determinant of antimalarial effectiveness.

The acquired immunity that occurs throughout regions of holoendemic infection in sub-Saharan Africa may explain the relatively late increase in resistance in that region. Most people at risk in South America and Asia lack immunity and consequently carry substantially higher parasite burdens than do most Africans. Moreover, their symptomatic infections are generally treated far more often than are asymptomatic infections among Africans. In Asia and South America, these factors substantially increase the probability of the selection of resistant genotypes.[14]

RESISTANCE

The parasites causing malaria exhibit a range of susceptibility to antimalarial agents. Several distinct phenomena explain this range, including species-specific innate resistance (e.g., asexual blood stages of *P. falciparum* lack susceptibility to primaquine, whereas those of *P. vivax* appear to be sensitive to it[31]); strain-specific innate resistance (e.g., that of asexual liver stages of *P. vivax* from the island of New Guinea against primaquine[32]); and acquired resistance. Of these, acquired resistance is the most important, because failure may occur even in the presence of complete adherence to the recommended therapies. Studies in Senegal suggest that resistance to chloroquine contributed to an increase by a factor of 2 to 11 in mortality from malaria.[33] In western Kenya, case fatality rates were markedly higher among children receiving chloroquine than among those receiving other therapies.[34]

Most of the data on the responses of *P. falciparum* to therapy reflect this emphasis on acquired resistance. Nonetheless, *P. vivax* profoundly affects public health outside Africa,[35] and data are also available that cover its resistance to chloroquine. *P. malariae* and *P. ovale* infect relatively few people, and little is known about acquired resistance in these

species. Resistance to chloroquine in *P. malariae* was reported from Indonesia[36] but is apparently debatable.[37]

Genetic mutations among strains of plasmodia have been linked with phenotypes of clinical resistance. Some studies challenge specific links between genotype and phenotype in certain settings, but putative markers have emerged (Table 3); the extensive literature on this topic has been reviewed.[38-43] Validated genetic determinants of resistance would vastly improve surveillance and, thus, the effectiveness of resources for the treatment and control of malaria.

DRUG RESISTANCE

The risk of resistance varies according to species, strain, and drug. Estimates of risk are often confounded by the determinants already described. Methods of estimating risk also vary. The following estimates of the risk of treatment failure were distilled from many studies and should not be construed as quantitative region-specific risks, because patterns of resistance vary tremendously, even within nations. Protocols that evaluate efficacy generally follow the guidelines of the World Health Organization, which recommend a follow-up period of 7, 14, or 28 days.[44] The timing of recurrent parasitemia or disease reflects the degree of resistance — earlier failure represents higher-grade resistance. Late recurrence may be confounded by reinfection, especially in regions of intense transmission. Investigators in sub-Saharan Africa thus favor an in vivo test with a duration of 7 or 14 days, whereas those in other regions tend to favor a 28-day test or even 63-day test. Comparison of genotypes of the strains causing original and recurrent parasitemias can be used to address confounding by reinfection, but relatively few reporting clinics or laboratories have the capacity to conduct such testing. Tests conducted in Africa tend to report both parasitologic failure (i.e., recurrent parasitemia after treatment, independent of clinical presentation) and the clinical failure of treatment, whereas investigators elsewhere focus on parasitologic failure.[44]

CHLOROQUINE

After an analogue that had been developed in Germany was captured in 1943, during World War II, chloroquine quickly came into universal use as therapy for and prophylaxis against malaria.[45] Chloroquine was highly effective, easily administered, and inexpensive and had good safety and tolerability. However, resistance in *P. falciparum* appeared in the late 1950s in Thailand and Colombia and emerged in the 1970s in New Guinea and eastern sub-Saharan Africa. Today, resistance to chloroquine in malaria caused by *P. falciparum* occurs everywhere except in Central America (and Hispaniola) and in some regions of southwestern Asia.

In sub-Saharan Africa, the risk of parasitologic treatment failure with the use of chloroquine was almost uniformly greater than 40 percent, whereas the risk of clinical treatment failure tended to be higher in the eastern and central portions of the African continent (typically >30 percent and often >50 percent, respectively) than in the west (typically <20 percent).[8] Elsewhere, the rates of parasitologic failure at day 28 were 57 percent (of 209 evaluations) in southwestern Asia,[46-50] 46 percent (2280 evaluations) in southern Asia,[51-57] 85 percent (223 evaluations) in Southeast Asia,[58-66] and 66 percent (137 evaluations) in South America.[67-71] Prescribing chloroquine monotherapy against this parasite in any setting, except one in which its effectiveness has recently been demonstrated, should be considered irresponsible.

Resistance to chloroquine by *P. vivax* has emerged, apparently having originated in New Guinea, where failure rates now approach 100 percent.[63] In contrast, surveys in Thailand reveal uniformly sensitive vivax malaria (not shown in Fig. 1).[72] Chloroquine-resistant *P. vivax* may be characterized as endemic to the Indonesian archipelago, especially in the east (including New Guinea), sporadic in the rest of Asia, and rare in South America.[73]

SULFADOXINE–PYRIMETHAMINE

Sulfadoxine–pyrimethamine, which has potent efficacy against chloroquine-resistant and pyrimethamine-resistant *P. falciparum*, became available in 1971 and became the standard second-line therapy against chloroquine-resistant falciparum malaria. This combination acts synergistically against folate synthesis, inhibiting dihydropteroate synthase and dihydrofolate reductase. Although rare, idiosyncratic allergic reactions have occurred among users of sulfa drugs, sulfadoxine–pyrimethamine has otherwise offered superior safety and tolerability, along with the advantage of single-dose therapy. However, resistance to sulfadoxine–pyrimethamine was recognized at the Thai–Cambodian border in the 1960s, and failures occurred in refugee camps in Thailand in the 1970s.[38]

Table 3. Mutations in *Plasmodium falciparum* That Are Associated with Resistance to Antimalarial Drugs.

Gene	Product	Genetic Determinant*	Drug
pfcrt	Transporter	Thr76	Chloroquine
pfmdr 1	Transporter	Tyr86	Chloroquine, mefloquine, quinine, dihydroartemisinin†
		Copy number	Mefloquine, artesunate
dhps	Dihydropteroate synthetase	Gly437, Glu540, Gly581	Sulfadoxine
dhfr	Dihydrofolate reductase	Asn108, Arg59, Ile51, Leu164	Pyrimethamine
cytb	Cytochrome *b*	Ser268	Atovaquone

* The predominant determinants, according to available data, are listed.
† The mutation is associated with increased sensitivity to this drug.

The rates of parasitologic failure of treatment with sulfadoxine–pyrimethamine in sub-Saharan Africa were relatively high in southern regions of holoendemic infection (>50 percent) and low elsewhere (<5 percent, except in Cameroon, where the rate of failure was 10 percent). The rates of clinical treatment failure in sub-Saharan Africa were similarly distributed (<5 percent in the west and 8 to 34 percent in the east and south).[8] Studies in Southeast Asia indicated that the rates of parasitologic failure at day 7 and day 28 were 36 percent and 49 percent, respectively.[74-79] Good efficacy (80 percent) persisted elsewhere — in southwestern Asia and on the Horn of Africa, where no parasitologic failures were reported among 362 evaluations[80,81]; in southern Asia, where the failure rate was 18 percent (of 339 evaluations) by day 28[55-57]; and in South America, where the failure rate was 9 percent (of 50 evaluations) by day 7, 14 percent (of 42 evaluations) by day 14, and 6 percent (of 119 evaluations) by day 28.[82-84] The risk of resistance to sulfadoxine–pyrimethamine is relatively high in Southeast Asia and eastern Africa.

MEFLOQUINE

Mefloquine emerged as a successor to chloroquine in the 1980s. Resistance appeared in regions at the border between Thailand and Cambodia within a few years, perhaps owing to widespread use of quinine, to which it is structurally related.[38] Resistance in that border region remains high.[85] However, in nearby regions resistance to mefloquine remains relatively low. Smithuis et al.[62] reported that, of 75 patients, more than 90 percent in the region of the western border of Myanmar (Burma) responded to mefloquine (at a dose of 15 mg per kilogram of body weight). In another study, of 79 patients hospitalized in Bangkok and treated with mefloquine (25 mg per kilogram), 68 (86 percent) remained free of parasitemia after 28 days.[86] Similar efficacy was observed in Bangladesh.[56] However, a group of Dutch marines in Cambodia who were receiving mefloquine prophylaxis during the 1990s had high attack rates of falciparum malaria.[87] In contrast, the protective efficacy of mefloquine among Indonesian soldiers in western New Guinea — where the efficacy of chloroquine against *P. falciparum* and *P. vivax* approaches zero[63] — was 100 percent.[88] The risk of the prophylactic or therapeutic failure of mefloquine in Southeast Asia appears to be low outside the shared borders of Thailand, Myanmar, and Cambodia.

Few studies have evaluated the effectiveness of mefloquine against falciparum malaria in Africa. In the mid-1990s, Lobel et al.[89] examined mefloquine prophylaxis among 140 Peace Corps volunteers who were infected by *P. falciparum*. Poor adherence explained most of the infections, but in five cases the resistance appeared to be genuine (i.e., parasitemia was present with >620 ng of mefloquine per milliliter in plasma). Despite sporadic, well-documented failures of mefloquine among travelers to Africa, the drug remains effective there.

Studies conducted in coastal Peru and in the Amazon Basin among 153 subjects with *P. falciparum* malaria who were receiving mefloquine (at a dose of 15 mg per kilogram) revealed complete sensitivity.[68,90,91] Despite occasional reports of resistance in the Amazon basin, the available evidence shows a low risk of resistance throughout South America.

Mefloquine has received adverse attention in the media in recent years. The drug has been blamed for suicides, homicides, and other personal tragedies on the basis of anecdotal accounts, which, by their

nature, cannot establish cause and effect. Well-controlled trials consistently indicate that mefloquine given as prophylaxis is as well tolerated as other antimalarial drugs.[92] Nonetheless, the drug has been linked with a higher risk of insomnia, fatigue, and adverse neuropsychiatric effects (e.g., depression and anger) than other antimalarial drugs.[93-95] The risk appears highest among women, especially those taking the drug for the first time and those with a low body-mass index.[96]

QUININE

Jesuit priests in Peru in the 1500s learned from the Incas that powder from the bark of the cinchona tree relieved shivering with cold, and they supposed it would also offer relief from the chills of malaria. Its activity against the parasite, later shown to be due to quinine, was unknown to them. Resistance to quinine appears sporadically, and a moderate risk of treatment failure appears to be limited to some regions of Southeast Asia and New Guinea. Zalis et al.[97] suggested that there might be a link between poor in vitro responses to quinine and diminished clinical responsiveness in the Amazon basin, but without supporting clinical data. Recent well-controlled trials of quinine monotherapy showed variable rates of efficacy against *P. falciparum*: 92 percent in a group of 49 patients in Bangladesh,[56] 67 percent among 54 patients in western Thailand,[98] and 80 percent among 30 patients in a clinic in Bangkok.[99] A seven-day regimen was more than 95 percent efficacious in Venezuela[100] and Equatorial Guinea.[101] Rare reports of failure of intravenous quinine for the treatment of severe or complicated malaria have appeared sporadically.[102]

Oral quinine is used to treat uncomplicated malaria, generally over a period of three to seven days in combination with another blood-stage schizonticide, typically tetracycline or doxycycline. Although one study of 86 patients in Thailand showed the superiority of a seven-day regimen combined with tetracycline (a 100 percent efficacy rate) as compared with a five-day regimen combined with tetracycline (87 percent),[103] studies performed elsewhere have shown complete efficacy with shorter regimens combining quinine, doxycycline, and primaquine.[88,104]

Poor adherence carries a high risk of treatment failure, particularly because quinine causes a syndrome of adverse effects known as cinchonism, including primarily tinnitus, nausea, and vertigo. A randomized trial in Thailand recorded a 71 percent rate of adherence.[11] However, in Cambodian villages, the rate of compliance with the same regimen was far lower — 11 to 20 percent — even after an intervention to raise awareness about the need for compliance.[105]

PRIMAQUINE

Developed during World War II, primaquine remains the only licensed tissue-stage schizonticide (Fig. 2) for the prevention of relapse after infection (standard therapy) or as presumptive therapy against relapse after exposure to the risk of infection, without evidence of infection (terminal prophylaxis). Recently recommended for use as prophylaxis,[106] primaquine has a uniquely broad spectrum, killing liver stages, asexual blood stages (of *P. vivax*[31] but not *P. falciparum*[107]), and sexual blood stages. In endemic regions, primaquine is widely used as a gametocytocide to prevent infection of mosquitoes.

Despite more than 50 years of use in millions of people per year, primaquine is still shrouded in confusion and genuine mystery. At least four different regimens, some prescribed for only one week and others for as long as eight weeks, are aimed at the same objective of preventing relapse.[108] Three factors largely explain the lack of uniformity: first, the reluctance of health care programs to accept therapy that has a duration of two weeks; second, perceived issues of toxicity and tolerability; and third, the use of a total dose, rather than a dosing schedule, as the primary determinant of efficacy. How the same total dose of a rapidly eliminated drug kills organisms irrespective of whether it is delivered over a period of 7, 14, or 56 days defies explanation.

Resistance is not fully understood either. Resistance in asexual blood stages of *P. vivax* has long been known[109] but is of no clinical consequence. Reports of resistance to tissue-stage schizonticidal activity fail to consider or describe patients' adherence, to exclude the possibility of reinfection, or to address the possible recrudescence of chloroquine-resistant strains. Lack of evidence of resistance to primaquine in liver stages probably reflects a heavy burden of proof rather than an absence of resistance.[108]

COMBINED THERAPIES AGAINST RESISTANCE

Combined therapies, which constitute a widely practiced strategy in the treatment of diseases such as leprosy, tuberculosis, and infection with the hu-

man immunodeficiency virus and which have long been known to be effective against malaria,[110] have rarely been used in its treatment until recently.[111] The use of more than one agent successfully requires separate mechanisms of action against the same stage of the parasite. Thus, because both sulfadoxine and pyrimethamine are folate antagonists, they would not be considered a combined therapy. Similarly, combining a blood-stage schizonticide with primaquine is not considered combined therapy, because the drugs attack different stages of the parasite. The fixed combination of atovaquone–chloroguanide, which affects mitochondrial electron transport and folate metabolism in asexual blood stages, represents true combination therapy.[112]

Combined antimalarial therapies include old and new drugs — old drugs in new combinations (chloroquine and sulfadoxine–pyrimethamine), an old drug combined with a new drug (amodiaquine and artesunate), and new drugs in combination (lumefantrine and artemether).[113,114] Combination therapy that includes artemisinin appears to be potent and particularly useful in endemic regions; extracted from the weed *Artemesia annua*, the artemisinins (primarily artemether, artesunate, and dihydroartemisinin) were developed in China during the 1960s.

The artemisinins act very rapidly, reducing parasitemia by a factor of 10^4 with each cycle. Thus, for a parasite burden in the range of 10^{12}, only three cycles are required to abolish parasitemia. The artemisinins are rapidly eliminated, and daily administration for a period of seven days (three cycles) is required. Episodes of recrudescence follow briefer regimens, but a seven-day regimen is considered to be impractical. Therefore, treatment for a period of three days with artemisinin combined with a slowly eliminated companion blood-stage schizonticide has been adopted. This three-day regimen of artemisinin reduces the parasite burden by a factor of 10^8 (leaving only 0.000001 percent of parasites surviving to be abolished by mefloquine) (Fig. 3). The artemisinins also exert activity against gametocytes, reducing the probability of transmission.

The use of combination therapies with artemisinin does not preclude the onset of drug resistance, particularly since patients may not take the medication as directed. Thus, the multiple doses needed with such combined therapies (typically six doses over a period of three days) represent an important potential pitfall. The emergence of resistant strains may already be in progress. In vitro studies indicate

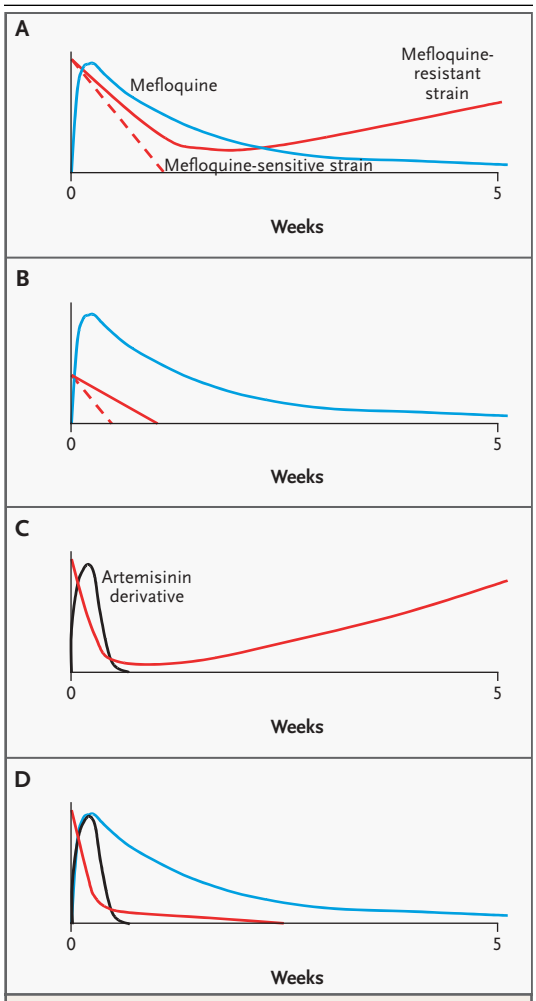

Figure 3. Combination Therapies with Artemisinin Derivatives.

The figure illustrates the rationale behind the use of an artemisinin derivative combined with a slowly excreted drug such as mefloquine for therapy against falciparum malaria over a period of five weeks. Panel A shows plasma levels of mefloquine (blue line) and relatively high levels of parasitemia caused by strains resistant to mefloquine (solid red line) and sensitive to mefloquine (dashed red line). Prescribed therapy eliminates the sensitive but not the resistant infection. Panel B shows the importance of parasite burden as a determinant of drug effectiveness, indicating the elimination of both sensitive and resistant infections at lower levels of burden. Panel C shows the quick inhibitory effect of a short regimen of an artemisinin derivative (black line), but, owing to its short plasma half-life, the drug cannot completely eradicate the parasite. Panel D shows the effect of combining an artemisinin derivative (black line) with a drug such as mefloquine (blue line): a quick "knockdown" of the parasite burden by the artemisinin derivative allows the slower-acting and more slowly excreted mefloquine to exert activity against a greatly diminished parasite burden.

diminished susceptibility to artesunate among Asian isolates.[41] Isolates from western Cambodia, where combination therapies with artemisinin derivatives are widely used, show diminished susceptibility to the combination of mefloquine and artesunate, as compared with isolates from eastern Cambodia.[115] In contrast, in the 1990s in some regions bordering western Thailand, combination therapies with artemisinin derivatives were deployed as first-line therapy with excellent efficacy (more than 90 percent), and this success appears to be stable.[116] Where more resources are available, including medications, resistant strains have been slower to develop. Where both medication and an effective health care infrastructure are present, resistance can be controlled. Such economic and personnel issues may explain the contrasting findings with regard to rates of resistance to combination therapies with artemisinin derivatives.[117] Thus, supplying these therapies in the setting of an adequate health care infrastructure would seem the best way to prevent the onset of resistance.

Patients with severe or complicated malaria often cannot take oral medication, and parenteral quinine has been the standard approach to therapy. Rectal artesunate may radically improve the care of such patients, especially across the geographic expanses of regions of endemic infection where parenteral medications are neither available nor practical. Clinical trials indicated that rectal artesunate (combined with another blood-stage schizonticide) cleared parasitemia more quickly than parenteral quinine and with equal efficacy.[118,119]

SUMMARY

A global public health threat due to the resurgence of malaria stems from a general collapse of vector-control operations and from resistance to chloroquine or sulfadoxine–pyrimethamine. Recent surveys show rates of treatment failure higher than 50 percent for chloroquine in most affected regions, as well as poor efficacy of sulfadoxine–pyrimethamine in sub-Saharan Africa and Southeast Asia. Quinine and mefloquine remain effective therapies everywhere except in some regions bordering Thailand. Resistance to primaquine — the only drug for preventing relapse — probably occurs but has not yet been confirmed. New drugs should be effective among the poor, self-treating rural populations in regions of endemic disease and should be provided through programs that address issues of availability and cost, convenience and adherence, safety and tolerability, and quality assurance. The combination therapies with artemisinin derivatives represent the present best efforts toward providing such therapeutic agents. These drugs deliver an inhibitory effect that substantially reduces the probability of selection for resistant parasites, as compared with traditional monotherapies. However, widespread distribution without complementary capabilities in the delivery of health care places the clinical usefulness of these critical drugs in doubt.

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