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Primaquine Therapy for Malaria

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REVIEW ARTICLE

Primaquine Therapy for Malaria

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Primaquine is the only available drug for preventing relapse of malaria, and confusion surrounds its use. This review examines the wide range of clinical applications of primaquine described in the medical literature between 1946 and 2004. The risk of relapse of *Plasmodium vivax* malaria without primaquine therapy ranged from 5% to 80% or more, depending largely upon geographic location. Supervision of therapy profoundly impacts the risk of relapse, and almost all reports of malaria resistant to primaquine are associated with lack of such supervision. We nonetheless suspect that there is widespread resistance to the standard course of primaquine therapy, which is 15 mg primaquine base daily for 14 days. Clinical evidence confirms that a course of 15 mg daily for just 5 days, a regimen widely used in areas where malaria is endemic, has no discernible efficacy. This review supports a recommendation for a regimen of 0.5 mg/kg primaquine daily for 14 days, on the basis of superior efficacy and good tolerability and safety in nonpregnant persons without glucose-6-phosphate dehydrogenase deficiency.

Malaria causes an acute, debilitating febrile syndrome that ends in death for 1.5–2.7 million of the ~500 million infected annually [1]. Just 100 years ago, malaria infected millions of people in North America, Europe, Australia, and other subtropical and temperate regions [2]. Chloroquine, primaquine, and dichlorodiphenyltrichloroethane (DDT) helped eradicate malaria from temperate latitudes and control it in the tropics [3]. Those gains have deteriorated substantially, and outbreaks occur even in the United States [4–7].

Primaquine, introduced in 1950, prevents relapse and sterilizes infectious sexual plasmodia, but confusion surrounds its use. Among the several widely used regimens, none has been adequately evaluated. Tolerance of primaquine by *Plasmodium vivax* occurs in Southeast Asia and Oceania, but the risk of therapeutic failure has been rarely documented anywhere. Poor adherence to primaquine therapy and resistance to companion drugs like chloroquine, compounds the confusion. Worse still, abbreviated regimens of primaquine without proven clinical efficacy are also widely used. Finally, available evidence refutes primaquine's reputation for being toxic and poorly tolerated. This review examines these issues.

BIOLOGY

The protozoa that cause malaria belong to the apicomplexid coccidian family Plasmodiidae, genus *Plasmodium*. The genus contains 172 species, but only 4 routinely infect humans: *Plasmodium falciparum, P. vivax, Plasmodium malariae,* and *Plasmodium ovale*. Other plasmodia infect mammals, birds, and reptiles, and these rarely infect humans [8]. The plasmodia follow a similar life cycle (figure 1). The most important distinction between the 4 different *Plasmodium* species that bears on therapy is that 2 can cause relapse—parasitemia originating from hypnozoites in the liver that occurs from 16 days to several years after the primary infection. Only *P. vivax* and *P. ovale* form hypnozoites. Latent blood stages of the parasite account for the chronicity of malaria due to *P. malariae*, and malaria due to *P. falciparum* typically exhibits no chronic latency.

P. vivax is pantropical, but it is largely absent from Africa. Black Africans lack an erythrocyte surface pro-

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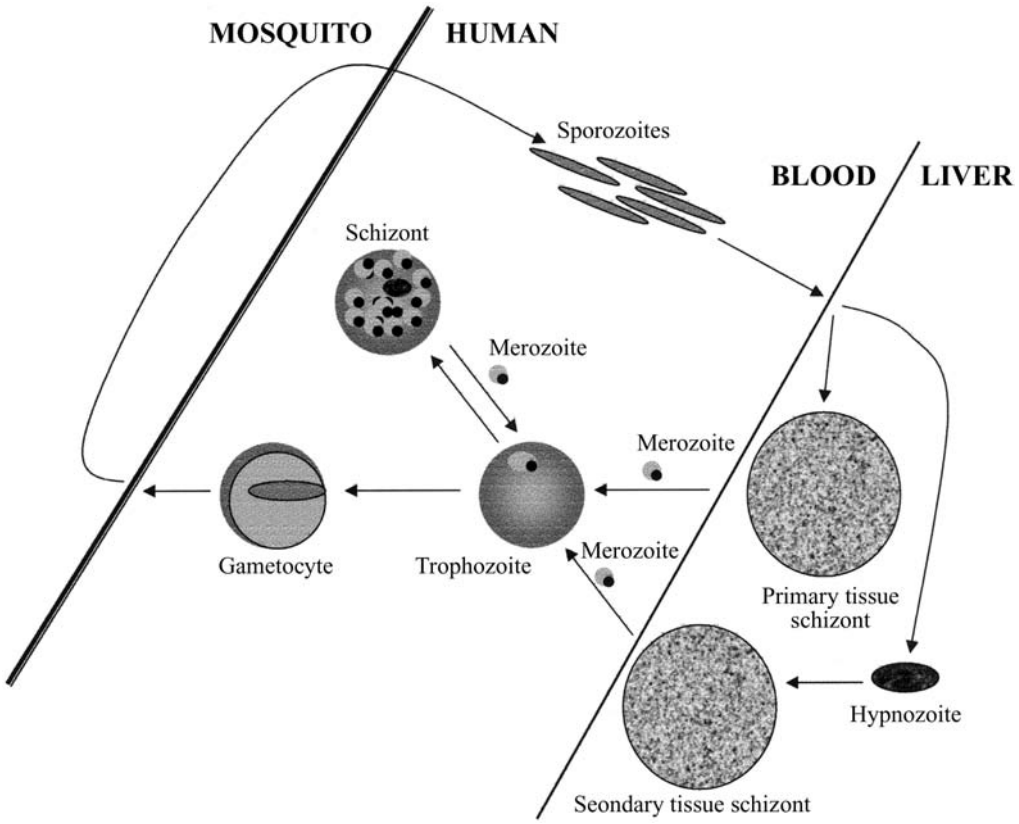

Figure 1. Life cycle of *Plasmodium* species in human beings. *Plasmodium vivax* and *Plasmodium ovale* produce both primary tissue schizonts and the hypnozoite that leads to a secondary tissue schizont, whereas *Plasmodium falciparum* and *Plasmodium malariae* produce only a primary tissue schizont. Parasitemia arising from hypnozoites is called a "relapse," and *P. vivax* and *P. ovale* malaria are called the "relapsing malarias." Primaquine treatment is often called "anti-relapse" therapy.

tein called Duffy factor that *P. vivax* merozoites require for invasion. Vivax malaria is especially common in India, Indochina, and the Philippine, Indonesian and New Guinean archipelagos. In the New World, vivax malaria occurs from northern Mexico to northern Argentina. Endemic *P. ovale* malaria occurs only in West Africa, The Philippines, Eastern Indonesia, and Papua New Guinea.

RELAPSE

Primaquine prevents relapse of malaria [9]. The pattern and probability of relapse in the absence of primaquine therapy varies by geographic origin. *P. vivax* malaria in temperate regions relapses at long intervals (>6 months) [10]. Among 1021 soldiers infected with *P. vivax* in Korea, 32% had relapse [11–14]. In India, the 12-month relapse rate ranged from 9% to 19% [15, 16]. All 180 subjects challenged with the North American St. Elizabeth strain of *P. vivax* had relapse 6–12 months later [17]. Experimental challenge notwithstanding, in temperate regions, the odds of relapse of *P. vivax* malaria are approximately 1 in 4 (table 1).

Infection with tropical strains of *P. vivax* is associated with a higher probability of relapse, relapse that occurs sooner, and, typically, multiple relapses. Among 54 American soldiers infected in the Pacific, all experienced relapse within 3 months [19]. Similar cohorts including a total of 562 subjects had a 5-month relapse rate of 72% [20, 21]. Of 213 subjects experimentally challenged with the Chesson strain of *P. vivax* from New Guinea [27], 99% had relapse within 8 months, most within 1 month after the primary parasitemia [17, 18]. Among 333 subjects infected with *P. vivax* from the tropical Pacific, the median time of relapse was day 22 after onset of the primary parasitemia [28]. No relapse occurred before day 16.

The probability of relapse is high (>1 in 5), regardless of where the infection is acquired, and potential exposure to infection indicates use of terminal prophylaxis (i.e., presumptive primaquine therapy). Indeed, failure to prescribe or comply with post-exposure prophylaxis accounts for most cases of vivax malaria in travelers [29]. Schwartz et al. [30] found that late onset (>2 months after exposure) occurred in 62% of 1321 vivax malaria cases, and in 63% of these cases, there was adequate adherence

Table 1. Summary of reports of relapse of *Plasmodium vivax* malaria not treated with primaquine therapy.

Reference(s)	Geographic location	*P. vivax* strain	No. of patients	Duration of follow-up	Percentage of patients with relapse
[17, 18]	New Guinea	Chesson	213	2 w to >8 mo	99
[19]	New Guinea	Wild	54	2 w to 3 mo	100
[20, 21]	Pacific	Wild	562	2–5 mo	72
[12–14]	Korea	Wild	1021	>4 mo	32
[16]	India	Wild	264	2–8 mo	19
[15]	India	Wild	5528	12 mo	11
[22]	India	Wild	222	12 mo	9
[23]	Pakistan	Wild	250	12 mo	52
[24]	Thailand	Wild	342	2 mo	63
[25]	Ethiopia	Wild	29	3 mo	50
[17]	North America	St. Elizabeth	180	12 mo	100
[26]	Global	Wild	68	NR	25

NOTE. Mo, months; NR, not reported; w, weeks.

to prescribed suppressive prophylaxis (i.e., against blood stages of the parasite). Most cases of vivax malaria among travelers are relapses and are preventable with primaquine, the only currently available drug for therapy to prevent relapse.

PRIMAQUINE THERAPY

Development. War in the Pacific in 1941 created an urgent strategic need in the United States for a drug to prevent relapse of malaria. Studies during and after World War II focused on 8-aminoquinolines, because, in the 1920s, pamaquine (the prototypical 8-aminoquinoline) had proven effective but too toxic. Thousands of compounds were screened in animals, and 21 went to clinical trials. Isopentaquine and primaquine proved superior [31]. Primaquine became available to American troops during the Korean War.

A total dose of 200 mg primaquine base (all doses of primaquine in this article refer to base, exclusive of weight of the typical diphosphate salt formulation) achieved cure, and a dose of 15 mg was well tolerated, so a 14-day regimen was adopted. According to Schmidt et al. [32], "the use of this regimen should not be construed as synonymous with necessity" (p. 1127). Provided an adequate total dose was delivered, schedule did not impact efficacy. A single 45-mg dose administered once per week for 8 weeks (360 mg) was as effective as 30 mg daily for 14 days (420 mg) or 60 mg daily for 7 days (420 mg) [33] and was more effective than 15 mg daily for 14 days (210 mg) [34].

Pharmacokinetics. Primaquine is rapidly absorbed in the gastrointestinal tract and concentrated in the liver, brain, heart, lungs, and skeletal muscle. It crosses the placenta. The mean volume of distribution is 3 L/kg. It peaks in plasma within 1–3 h, at ~70 mg/mL. It is rapidly excreted in urine, with a plasma half-life of 4–9 h. Its metabolism is complex and poorly understood [35]. Among the many known or suspected metabolites, none has been definitively linked to activity against the *Plasmodium* parasite.

Standard therapy. Primaquine therapy is given after the diagnosis of *P. vivax* or *P. ovale* malaria and should coincide with blood schizonticidal therapy. Others recommend commencing primaquine therapy after blood schizonticidal therapy, on the basis of immunosuppressive activity observed in vitro [36–38]. In vivo studies have failed to corroborate those findings [39]. Primaquine appears to be more effective when given concurrently with blood schizonticides [40–42] (table 2). Indonesians who took 30 mg daily for 1 year showed no effects on cellular immunity to tetanus toxoid [43] or on susceptibility to malaria [44].

A few studies during the past 25 years gauged therapeutic efficacy of standard primaquine therapy [45–55]. Reports up to 1977 confirmed the excellent efficacy of supervised therapy against *P. vivax* infection in regions other than New Guinea and Thailand (table 3). Of 1344 patients given supervised therapy, only 14 (1%) experienced relapse, whereas, of 2061 patients given unsupervised therapy, 449 (22%) had relapse (relative risk, 0.05; 95% CI, 0.03–0.09; $P < .0001$). Similarly, the relative risk of relapse with supervised therapy among 469 soldiers returned from Vietnam was 0.23 (95% CI, 0.12–0.46; $P < .0001$). Relapse after unsupervised therapy [56, 58–67] does not prove resistance.

Nonetheless, primaquine does not remain universally effective. During the past 10 years, we heard from clinicians around the world complaining of more frequent failures of primaquine therapy. Even though no unambiguous evidence of resistance yet exists, experience teaches us to heed such warnings. We routinely advise against using the standard regimen and instead

Table 2. Summary of relapse rates after standard primaquine therapy in early reports of infection with the Chesson strain of *Plasmodium vivax*.

Reference	Primaquine dosage	Concurrent blood schizonticidal therapy	No. of patients	Duration of follow-up, months	Percentage of patients with relapse
[41]	15 mg/day for 14 days	None	19	12	79
[18]	15 mg/day for 14 days	Quinine	24	12	21
[34]	15 mg/day for 14 days	Chloroquine	79	12	27
[18]	22.5 mg/day for 14 days	None	5	12	80
[18]	22.5 mg/day for 14 days	Quinine	31	12	3
[18]	30 mg/day for 14 days	Quinine	5	12	0
[33]	60 mg/day for 7 days	Chloroquine	11	1–14	0
[34]	45 mg/week for 8 weeks	Chloroquine	71	12	8

recommend the alternative of 0.5 mg/kg daily for 14 days. This now concurs with recommendations by the Centers for Disease Control and Prevention (unpublished data, CDC).

Failure of standard therapy. Evidence for failure of the standard primaquine regimen emerged from early experimental challenge with the Chesson strain of *P. vivax* isolated from an American soldier infected in New Guinea in 1944 [27]. Table 2 summarizes that work of 50 years ago. Relapse occurred in 26 of 103 subjects treated with chloroquine or quinine and the standard primaquine regimen of 15 mg, whereas only 1 of 36 subjects treated with primaquine regimens of 22.5 or 30 mg daily for 14 days had relapse. The relative risk associated with the higher dose was 0.11 (95% CI, 0.02–0.78; $P < .005$). More recent trials in Thailand demonstrated similar findings: 7 (18%) of 81 patients given a standard dosage of chloroquine and a 15-mg primaquine regimen had relapse within 6 months, whereas only 1 of 86 treated with a 22.5-mg regimen had relapse [46]. In the other study [47], 10 (17%) of 60 patients given standard primaquine therapy had relapse. The relative risk of relapse associated with the 22.5-mg regimen, compared with the 15-mg regimen, was 0.1 (95% CI, 0.01–0.71; $P < .005$). A trial found that a regimen of 30 mg daily for 14 days combined with atovaquone and proguanil (Malarone; GlaxoSmithKline) was efficacious against *P. vivax* infection in 46 Thai patients, of whom 35 were followed up for 12 weeks, and there were just 2 cases of recurrent parasitemia (94% efficacy) [68]. Jelinek et al. [59] demonstrated that infection acquired on the island of New Guinea had a 12-fold higher risk of relapse after primaquine therapy. Only 3 of 44 who did not travel to New Guinea experienced relapse, whereas 4 of 5 persons who did travel to New Guinea experienced relapse (OR, 11.7; 95% CI, 1.6–100; $P < .001$). Duarte et al. [69] report the only recent study of therapeutic response to standard primaquine therapy among patients with vivax malaria in the New World: 7 (14%) of 50 patients given supervised therapy had relapse within 6 months.

Vivax malaria should be treated with a primaquine regimen of $\geqslant$22.5 mg daily for 14 days (we favor 30 mg), or a total dose of $\geqslant$315 mg for as long as 8 weeks [29, 42, 43, 48, 49]. Schwartz and colleagues [70] demonstrated a high risk of relapse after standard "adult-dose" therapy (15 mg daily for 14 days) among Israeli patients weighing >80 kg. Medical officers of the New Zealand armed forces described the same phenomenon among troops who returned from East Timor (unpublished data). Patients heavier than 70 kg should receive at least 0.5 mg/kg daily.

For patients who are pregnant or who have well-documented failure of recommended primaquine therapy, no currently available alternative therapies exist. The risk of relapse in these patients should be managed with suppressive therapy with chloroquine or mefloquine for at least 4 weeks, preferably 8 weeks. These patients certainly should be counseled regarding their risk of relapse beyond 8 weeks.

Resistance to primaquine. Resistance to primaquine by blood stages of the *Plasmodium* parasite [71] is of little clinical consequence. Resistance in tissue stages dominates public health concern, and the absence of such resistance after 50 years seems incredible. There may be compelling physical, chemical, or biological reasons; for example, short plasma half-life or sterilization of gametocytes. Alternatively, clinical evidence of resistance to primaquine may be present but difficult to detect. We favor this explanation.

Proof of resistance requires addressing important confounding factors. Use of directly observed therapy administered by reliable people addresses the most important of these. Patients exposed to risk of infection after treatment should be excluded from analysis. Resistance to chloroquine by *P. vivax* [72–75] must be considered; recurrent parasitemia may be recrudescence of a chloroquine-resistant strain, rather than relapse due to a primaquine-resistant strain. Clinical trials designed to detect resistance to primaquine should use an effective blood schizonticide with a short plasma half-life, such as quinine, which will rule out the possibilities of suppression of early

Table 3. Summary of reports of relapse of *Plasmodium vivax* malaria after treatment with a standard regimen of primaquine therapy (15 mg per day for 14 days).

Type of therapy, geographic location	Year	No. of patients	Duration of follow-up, months	Percentage of patients with relapse	Reference(s)
Supervised					
Vietnam	1974	218	12	4	[45]
Thailand	1994	141	1–18	18	[46, 47]
Solomon Islands	1977	10	12	0	[48]
Korea	1953	914	4–20	<1	[49, 50]
Nicaragua	1953	145	4	0	[51]
Central America	1974	57	9–36	4	[52]
Unsupervised					
Vietnam	1970	251	12	18	[53, 54]
Brazil	1991	1347	3–12	25	[55]
Somalia	1997	60	NR	43	[29]
Global	1995	57	>18	13	[59]
Global	1987	175	NR	10	[26]
Global	1990	132	NR	9	[57]

NOTE. Mo, months; NR, not reported.

relapse by lingering traces of the drug in patients (i.e., false-negative responses) and recrudescence due to resistance to chloroquine (i.e., false positive responses). Table 4 summarizes key confounders of the diagnosis of infection with primaquine-resistant *P. vivax*. Collins and Jeffery [76] have reviewed resistance to and tolerance of primaquine in *P. vivax*.

Five-day regimen. A primaquine regimen of 15 mg daily for 5 days to prevent relapse of *P. vivax* malaria is national policy in many countries where the disease is endemic. In 1954, Singh et al. [77] found no cases of relapse among 50 patients treated with pyrimethamine and the 5-day regimen. Basavaraj [78] corroborated this in 1960, as did Mendoza in Mexico (World Health organization document WHO/MAL/527.65, cited by Contacos et al. [79]). Cedillos et al. [80] found reductions in the number of clinical episodes in communities where the 5-day regimen plus standard amodiaquine was given. Some studies showed low relapse rates (<10%) among large numbers of patients in India given the 5-day regimen [22, 81], but relapse rates for patients not treated with primaquine may be this low. Randomized and controlled studies are needed to prove the importance of this point.

Contacos et al. [79] treated 5 volunteers exposed to a Pakistani strain of *P. vivax* with the 5-day regimen, and all had relapse within 181 days. Miller et al. [52] also tried this regimen against the Salvador II strain of *P. vivax*, and the patient had relapse at day 223. Singh et al. [82] recorded a relapse rate of 11% among 995 patients treated with the 5-day regimen, and the relapse rate among 222 patients not treated with primaquine was 9%. Rowland and Durrani [23] reported *P. vivax* relapse rates of 52% and 51%, respectively, among 500 Pakistani patients randomized to receive treatment either with chloroquine alone or with the 5-day, 15-mg regimen combined with chloroquine. Gogtay et al. [83] and Yadav and Ghosh [84] reported essentially similar findings from India. Villalobos-Salcedo and colleagues [85] compared 60-day relapse rates among patients in Amazonia treated with chloroquine and 15 mg of primaquine daily given for 5 or 14 days: the odds of relapse among subjects who received the 5-day regimen was 5.3 (95% CI, 0.9–40; $P < .03$) (tables 5 and 6).

ACTIVITY AGAINST BLOOD-STAGE PARASITES AND *P. OVALE*

Blood schizonticidal therapy. Primaquine is not recommended as a stand-alone blood schizonticide, but its effect upon blood-stage parasites should be understood. Primaquine monotherapy was shown to be effective against *P. vivax* parasitemia in Thailand by Pukrittayakamee et al. [88], who administered 15 mg daily for 14 days to 30 patients, and parasitemia was cleared in all. Wilairatana et al. [89] treated 23 patients infected with *P. vivax* in Thailand with 30 mg of primaquine daily for 14 days, and all patients remained aparasitemic at day 28. These studies demonstrate the apparently potent blood schizonticidal activity of therapeutic doses of primaquine against *P. vivax*.

Therapeutic doses of primaquine do not affect the asexual blood stages of *P. falciparum*. In eastern Indonesia, we found no difference in activity of primaquine against *P. falciparum* in 25 subjects given chloroquine plus primaquine (30 mg daily for 28 days) and in 28 given chloroquine plus a placebo of primaquine [90]. In 1955, Arnold et al. [91] described complete therapeutic failure of a primaquine regimen of 30 mg daily against *P. falciparum* (Panama P-F-6 strain) in 6 volunteers.

Table 4. Key confounders of the diagnosis of infection with primaquine-resistant *Plasmodium vivax*.

Confounder	Ambiguity	Solution
Noncompliance to prescribed therapy	Adequacy of dose	Supervise of therapy
Emesis of dose	Adequacy of dose	Supervise of therapy and readminister vomited doses
Parasite tolerance	Resistance vs. tolerance	Determine baseline susceptibility or use 30-mg regimen
Chloroquine resistance	Recrudescence vs. relapse	Relapse can be discounted if recurrence is <1 month after the end of therapy; or use an alternative therapy (e.g. quinine)
Reinfection	Reinfection vs. relapse	Evaluate repatriated traveler or, if necessary, evacuate to an area where malaria is not endemic

Transmission-blocking therapy. A single dose of 45 mg of primaquine is routinely prescribed for *P. falciparum* malaria in areas where it is endemic, to reduce the risk of transmission. In experimentally challenged volunteers, primaquine markedly reduced the number of circulating gametocytes and sterilized those remaining [92, 93]. This was an important finding, because effective blood schizonticidal treatment may leave surviving gametocytes [94]. This result is especially problematic when slow-acting antimalarials are used, because the brief period of primaquine gametocytocidal activity precedes elimination of trophozoites that may differentiate to gametocytes. In practice, a single dose of primaquine may accomplish little [92, 93, 95]. Kaneko et al. [96] evaluated this regimen in a village in Sumatra and documented reduced numbers of gametocyte in patients treated with primaquine, but they did not assess transmission to mosquitoes. Standard primaquine therapy against *P. vivax* resulted in rapid (4–20 h) and complete loss of transmission to mosquitoes in 5 patients infected with *P. vivax* in Brazil [97].

P. ovale *infection.* This parasite occurs in West Africa, The Philippines, eastern Indonesia, and New Guinea. The foci in the Pacific have exceedingly low but consistent frequencies of infection [98]. Diagnosis of *P. ovale* infection should be supported by agreement among expert microscopists or by molecular biological evidence [99, 100]. Primaquine therapy for *P. ovale* infection is as for *P. vivax* infection. Therapeutic failure of primaquine against *P. ovale* has been reported [101], but only in patients who did not receive directly observed therapy.

TOLERABILITY AND TOXICITY

Gastrointestinal upset. We do not accept the view that primaquine is toxic and poorly tolerated. Compared with other antimalarials, it has good tolerability and safety in people considered good candidates to receive it. Lethal doses of 8-aminoquinolines in animals exhibited pronounced hepatotoxicity [31], and lesser doses showed hematological and gastrointestinal effects, primarily epigastric discomfort [17, 102]. However, studies of therapeutic doses demonstrate good tolerability and safety. Clayman et al. [103] observed abdominal distress in human subjects who had fasted and received a single dose of primaquine: it was reported by 5% of subjects who received a 15-mg dose, by 10% who received a 30-mg dose, 35% who received a 60-mg dose, and 100% who received a 90-mg dose. The drug was tolerated without complaint in subjects who had eaten, even at the highest doses administered.

The 15-mg dose of primaquine consistently shows good tolerability [12, 14, 18], and few complaints occur at higher doses. Clyde and McCarthy [33] administered 60 mg daily for 7 days to 11 men and described the adverse effects as "negligible in 9 men, and 2 others consisted of moderate abdominal cramps and nausea toward the end of the course" (p. 563). Baird et al. [42] administered two 60-mg and one 30-mg dose concurrent with chloroquine therapy to 22 subjects in Indonesia; physical complaints were no more frequent than among 23 other subjects receiving chloroquine and a placebo of primaquine. Among 5 subjects given a 14-day, 30-mg regimen, Edgecomb et al. [18] observed mild transient adverse effects in only 1 subject. In a trial of a regimen of 30 mg daily for prophylaxis in Indonesia, 43 men continued taking the regimen for 1 full year and had no more complaints that did 42 subjects who received placebo [104]. Kenyan children tolerated the same regimen for 12 weeks [105], as did another Indonesian group taking 30 mg every other day for 16–19 weeks [106].

Methemoglobinemia. Primaquine consistently elevates the methemoglobin level (typically <5 g%, and >12 g% is rare) [31]. Fletcher et al. [107] reported elevation to 6.1 g/L (level at baseline, 1.6 g/L) after a regimen of 15 mg daily for 14 days—essentially the same as the level of 5.8 g% observed in Indonesian subjects who received 30 mg daily for 52 weeks [105]. Methemoglobin levels of <20% are tolerated without symptoms or signs [108], and we are not aware of patients receiving primaquine who required treatment for methemoglobinemia. An inborn deficiency of methemoglobin reductase greatly increases the capacity for primaquine and other agents to induce clinically relevant methemoglobinemia [109].

Glucose-6-phosphate dehydrogenase (G6PD) deficiency and primaquine-induced hemolytic anemia. Primaquine causes acute hemolysis in people with inborn G6PD deficiency. Among G6PD-deficient Africans, treatment causes destruction primarily of senescent erythrocytes and is therefore mild and self-

Table 5. Rates of relapse of *Plasmodium vivax* malaria after primaquine therapy at a dosage of 15 mg daily for 5 days.

Reference	Geographic location	Supervised therapy	No. of patients	Duration of follow-up, months	Percentage of patients with relapse
[52]	Central America	Yes	1	9	100
[79]	Pakistan	Yes	5	7–11	100
[23]	Pakistan	No	250	12	51
[22]	India	Yes	725	12	7
[81]	India	No	995	8	10
[82]	India	No	6393	12	1
[83]	India	Yes	62	6	27
[86]	India	No	15,240	12	16
[87]	India	No	5541	12	9

limited, with recovery (with reticulocytosis) even if primaquine therapy is continued [34]. The hemolytic effects in G6PD-deficient subjects were either less severe or altogether absent using either the 45-mg or 60-mg weekly dose for 8 weeks, compared with the 15-mg regimen [34].

Many G6PD variants have been identified [110]. Some are not associated with any hemolytic sensitivity, and others are associated with life-threatening hemolytic episodes, such as the Mediterranean B− variant [111]. Primaquine causes largely unpredictable degrees of severity of hemolysis among patients with other variants, which may occur in any ethnic group. G6PD variants associated with mild primaquine sensitivity, such as African A−, typically show 10%–20% of normal G6PD activity, whereas variants associated with severe sensitivity, such as Mediterranean A−, show less than 5% of the normal activity. Commercially available qualitative tests for G6PD deficiency make diagnosis relatively easy [112, 113]. The inability to routinely assess G6PD status of a fetus in utero explains why pregnancy is a contraindication for primaquine therapy.

G6PD catalyzes the rate-limiting step in the hexose monophosphate shunt, which drives reduction of glutathione. Diminished G6PD activity thus limits defenses against oxidative damage. However, primaquine-induced hemolysis involves more subtle effects than oxidative attack, because potent stimulation of the hexose monophosphate shunt by primaquine metabolites has been shown to occur independently of glutathione redox equilibrium [111, 114].

CONCLUSIONS

1. The risk of relapse for vivax malaria ranges from 5% to 80%.

2. The standard regimen of 15 mg daily for 14 days is often not effective. A regimen of 30 mg for 14 days should be

Table 6. Summary of reports from India, Pakistan, and Brazil showing the therapeutic efficacy of standard chloroquine in combination with 15 mg of primaquine daily for 5 or 14 days for treatment of *Plasmodium vivax* malaria.

Reference	Geographic location	Primaquine therapy given	No. of patients	Relapse rate, %	Therapeutic efficacy, % (95% CI)
[81]	India	None	222	9	…
[83]	India	None	60	12	…
[84]	India	None	723	9	…
[81]	India	15 mg for 5 days	995	11	−9.7 (−21 to 3)
[83]	India	15 mg for 5 days	62	27	…
[84]	India	15 mg for 5 days	759	7	2.2 (−3 to 7)
[83]	India	15 mg for 14 days	63	0	100 (95 to 100)
[23]	Pakistan	None	350	51	…
[23]	Pakistan	15 mg for 5 days	250	51	0 (−8 to 8)
[23]	Pakistan	15 mg for 14 days	100	32	37 (27 to 48)
[85]	Brazil	15 mg for 5 days	30	27	ND[a]
[85]	Brazil	15 mg for 14 days	31	7	…

[a] No data: relapse rate without primaquine therapy unknown.

prescribed, or 0.5 mg/kg daily for 14 days for infants or people weighing >70 kg.

3. Supervised compliance with prescribed therapy is necessary to prove resistance.

4. Taking primaquine with food greatly improves its gastrointestinal tolerability.

5. Primaquine-induced methemoglobinemia is mild and self-limited.

6. Therapeutic doses of primaquine are well tolerated and not toxic in people considered good candidates to receive the treatment.

7. Primaquine is dangerous with G6PD deficiency and should not used without knowledge of G6PD status or during pregnancy.

8. Standard primaquine therapy rapidly and completely prevents development of *P. vivax* in mosquitoes (i.e., transmission blocking).

9. A single 45-mg dose of primaquine adjunctive to therapy for *P. falciparum* infection may not block transmission.

10. The 5-day, 15-mg regimen of primaquine is not effective against relapse of *P. vivax* malaria.

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