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At a public hospital in Georgetown, Guyana, 44 patients seeking treatment for symptomatic, slide-confirmed malaria were given standard chloroquine (CQ) therapy and followed for 28 days. The patients apparently had pure infections with *Plasmodium falciparum* (14), *P. vivax* (13) or *P. malariae* (one), or mixed infections either of *P. falciparum* and *P. vivax* (17) or of *P. falciparum*, *P. malariae* and *P. vivax* (two). Each received supervised treatment with 10 mg CQ base/kg on each of days 0 and 1, and 5 mg/kg on day 2. On the day of enrollment (day 0), the patients complained of fever (100%), headache (100%), malaise (94%), myalgia (79%), nausea (67%), vertigo (49%) and vomiting (33%). Many (39%) were ill enough to confine themselves to bed. On day 4, fewer of the subjects complained of fever (15%), headache (15%), malaise (6%), myalgia (21%), nausea (6%), vertigo (24%) or vomiting (0%) despite the relatively high (>48%) risk of therapeutic failure. The cumulative incidence of parasitological failure against *P. falciparum* was 15% at day 4, 33% at day 7 and 48% at day 14. All of the *P. vivax* and *P. malariae* infections cleared before day 4 and none recurred by day 7. Two infections with *P. vivax* recurred later (on day 14 or 28) but in the presence of less than adequate, whole-blood concentrations of CQ plus desethyl-chloroquine (i.e. <100 ng/ml). Taken together, the results indicate a high risk of therapeutic failure of CQ against *P. falciparum* but also indicate that resistance to CQ in *P. vivax* occurs infrequently in Guyana.

The proliferation of drug-resistant strains of *Plasmodium* is complicating the development of national policies for the treatment of malaria in the developing world. Such policies often translate to widespread clinical practice because governments purchase and distribute the recommended antimalarials at subsidized costs. These prescribed medicines often define consumer preferences in the private sector. In the developed world, an array of antimalarials gives health-care providers options suited to individual patients and the probable sensitivity of the infections they have acquired. In contrast, patients in impoverished, rural, endemic areas almost always receive the drugs recommended

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by the government. Thus, treatment-policy decisions made by public-health officers in endemic regions directly impact the clinical management of malaria in the vast majority of people infected.

In Guyana, the government abandoned chloroquine (CQ) as first-line therapy against *P. falciparum* in the early 1990s. Complaints of frequent therapeutic failure from doctors prompted the decision to adopt the combination of quinine and pyrimethamine–sulfadoxine as first-line therapy. Recommended quinine therapy requires three doses daily for 7 days. The drug causes ringing in the ears of most of those treated, as well as vertigo and nausea. It is poorly tolerated and inadequate compliance with unsupervised therapy almost certainly occurs regularly. The risk of recurrent parasitaemia as a consequence of poor compliance with quinine must be weighed against that attributable to resistance to CQ. Reliable data characterizing the therapeutic response to CQ should drive treatment-policy decisions on alternative therapeutic strategies.

Phillips *et al.* (1996) described a *P. vivax* infection that had been acquired in Guyana but failed to respond to CQ therapy. As this case was reported at a time when CQ remained the first-line drug for *P. vivax* malaria in Guyana, it led to a review of the national policy for the treatment of *P. vivax* and the present trial of the CQ treatment of *P. vivax*. As no recent data from Guyana adequately described the therapeutic response of local *P. falciparum* infections to CQ, such infections were also investigated. The treatment policies for uncomplicated, *P. falciparum* and *P. vivax* malaria in Guyana, where malaria has become increasingly prevalent since the 1970s, were retrospectively evaluated. The study was based in Georgetown, on the northern coast, where malaria was virtually eradicated in the 1950s by spraying with DDT and the distribution of 'chloroquinized' salt (Giglioli, 1951; Giglioli *et al.*, 1976). Malaria on the northern coast remains relatively rare (Rambajan, 1994) and virtually all the cases seen in Georgetown are in adults who are either local residents who have recently visited the 'frontier' interior or residents of the interior who are visiting Georgetown.

SUBJECTS AND METHODS

Study Site and Subjects

A treatment trial was initiated in September 1998 using the fever clinic at Georgetown Public Hospital in Georgetown, Guyana. This clinic served as a referral centre for patients suspected of having malaria. The clinic typically processed 30–50 patients/day, and 30%–50% of these usually proved slide-positive for *P. falciparum* or *P. vivax* malaria (with approximately twice as many *P. falciparum* infections as *P. vivax*). Thick bloodsmears were stained with Giemsa and screened, under oil immersion at $\times 1000$, by Ministry of Health microscopists in the clinic. Only patients with uncomplicated, slide-proven malaria were screened for enrollment in the trial; those with severe or complicated malaria were referred for admission to the hospital. Eligible volunteers were at least 5 years old and agreed to remain in the vicinity of Georgetown during the 28 days of post-treatment follow-up. The requirement to remain available during follow-up caused the majority of the otherwise eligible subjects to decline to participate. Informed consent was provided in accordance with U.S. Navy regulations governing the use of human subjects in medical research (SECNAVINST 3900.39B), and as approved by sanctioned committees for the protection of human subjects at the Ministry of Health in Guyana, and the Naval Medical Research Center in Bethesda, Maryland. Subjects were examined by a physician and submitted to venipuncture for collection of 12-ml samples of whole blood. These samples were used for the cryopreservation of parasites, the nested PCR of small-subunit ribosomal RNA (ssrRNA) for confirmation of diagnosis (see below), and routine tests for deficiency in glucose-6-phosphate dehydrogenase (G6PD).

Confirmation of Screening Diagnosis

The screening diagnoses based on the examination of Giemsa-stained thick bloodsmears were later checked in the laboratory using blood samples collected at enrollment. Confirmation included examination of Giemsa-stained thin bloodsmears (for all 49 subjects enrolled) and a PCR-based assay for the 18srRNA gene (for the 30 samples identified under the microscope as positive for *P. vivax*). For the assay, DNA was extracted, from blood samples spotted onto FTA® gene cards (Life Technologies, Rockville, MD), using a Chelex method (Kain and Lanar, 1991). The DNA was then subjected to two rounds of PCR using the primers and amplification conditions described by Snounou *et al.* (1993). In brief, the first round of PCR employed two *Plasmodium*-specific primers to amplify the DNA of any *Plasmodium* sp. present. In the second round, aliquots of product from the first round were placed into four separate reaction vessels, each containing species-specific primers for unique 18srRNA sequences (Snounou *et al.*, 1993). In a slight deviation from the published procedure, the first and second rounds of PCR were run for 30 and 40 cycles, respectively. The assays were performed in a 96-well format that included genomic DNA from *P. falciparum* and *P. vivax* (in distilled water) as positive controls. Electrophoresis of each of the nested products of the second round of PCR was performed in gels of either 3% NuSieve agarose (FMC BioProducts, Rockland, ME) or 2% SeaKem agarose (FMC BioProducts). The gels were stained with ethidium bromide.

Treatment

As part of the enrollment procedure on day 0, each subject was given uncoated tablets of chloroquine phosphate (Resochin™; Bayer, Leverkusen, Germany) in the clinic, at a dose 10 mg base/kg bodyweight. Each subject was watched for 30 min after treatment and dosing was repeated if vomiting occurred. The next day a member of the research team administered another 10 mg/kg in the subject's home or workplace. A final dose, of 5 mg/kg, was likewise administered on the following day.

HPLC was used to estimate CQ concentrations in whole-blood samples from subjects with suspected CQ-resistant *P. vivax* (Baird *et al.*, 1997*b*).

Follow-up

Smears were prepared of blood samples collected from the subjects on each of days 0–6, 11, 14, 18, 21 and 28 (for those infected with *P. falciparum*) or on days 0, 2, 4, 7, 11, 14, 18, 21 and 28 (for those infected with *P. vivax*). The level of any parasitaemia (parasites/μl) was estimated by counting parasites against 200 leucocytes, on the thick smear, and multiplying the count by 40 (assuming each subject had 8000 leucocytes/μl). A member of the research team visited each subject at his or her home or workplace to collect each post-enrollment sample and check on the subject's general health. Subjects complaining of illness were brought to the clinic for prompt evaluation by the physician on the research team. Subjects with slide-confirmed parasitaemia after day 3 received alternative therapy with quinine and pyrimethamine–sulfadoxine. For subjects without recurrent parasitaemia, follow-up ended on day 28.

Statistical Analysis

Life tables were used to estimate the risks of CQ therapeutic failure for *P. falciparum* and *P. vivax* (Baird *et al.*, 1997*a*). Recurrent parasitaemia was taken as evidence of therapeutic failure, regardless of clinical signs and symptoms. Rescue therapy prompted by an inter-current parasitaemia (i.e. with a *Plasmodium* sp. different to that observed on day 0) constituted a loss to follow-up. Mixed infections contributed to the analysis of each species. The rationale for interpreting the *in-vivo* test of CQ resistance in *P. vivax* was described by Baird *et al.* (1997*a*).

RESULTS

Subjects

Table 1 summarizes the demographic and parasitological characteristics of the study population. Overall, 49 subjects, all but nine of them male, were enrolled. Although children were eligible, only one child (a girl with *P. falciparum*) was enrolled. None of the subjects had G6PD deficiency. The results of the thin-smear examinations and PCR-based assays indicated that, at enrollment, the subjects had pure infections with *Plasmodium falciparum* (14), *P. vivax* (13) or *P. malariae* (one), or mixed infections either of *P. falciparum* and *P. vivax* (17) or of *P. falciparum*, *P. malariae* and *P. vivax* (two).

Diagnosis

Comparison of the results of subsequent examinations of thick and thin bloodsmears and of the PCR-based assay with those of the screening diagnosis demonstrated shortcomings in the initial thick-smear screening as the primary instrument of diagnosis (Table 2). In brief, many (62%) of the 26 infections initially considered to be solely of *P. vivax* were found to be mixtures of *P. vivax* and *P. falciparum*. Five infections initially identified as solely of *P. vivax* and showing nested-PCR results consistent with *P. vivax* (or a mixture of *P. vivax* and *P. falciparum*) presented morphological characteristics considered incompatible with a microscopical diagnosis of *P. vivax*. These infections showed: pigmented trophozoites; schizonts containing six to 14 merozoites each; variation in the sizes of the infected erythrocytes, from smaller to larger than normal; and bizarre, grossly enlarged erythrocytes (with diameters two or three times those of the uninfected erythrocytes), each containing a multinucleated form of the parasite. For these infections, the PCR-based diagnosis of *P. vivax* was taken to be correct for the purpose of reporting therapeutic responses to CQ, and the presentation of results in this report reflects this approach. Wherever discrepancies occurred between the thin-smear-based diagnosis and the results of the nested-PCR analysis, the latter were assumed to be correct when estimating the risks of therapeutic failure.

Responses to Treatment

Plasmodium falciparum

Six of the 33 subjects recorded as *P. falciparum* infections were lost to follow-up (i.e. they could not be located at home or work) prior to day 4, but all of the remaining 27 reached the end-point of recurrent parasitaemia or day 28 of follow-up. Of these 27 subjects (see Table 3), four failed to clear their *P. falciparum* parasitaemias by day 4 and were therefore given alternative treatment. Another 11 subjects cleared their parasitaemias by day 4 but had to be given alternative treatment because of recurrent *P. falciparum* parasitaemia by day 7 (five), between days 8 and 14 (four) or on days 17 (one) or 28 (one). Thirteen of the 27 subjects diagnosed with *P. falciparum* did not have

TABLE 1. *Demographic and parasitological characteristics of the study population*

Initial diagnosis	No. of subjects				Mean age and (range) (years)	Mean day-0 parasitaemia and (range)* (parasites/μl)
	Studied	Male	Female	With mixed infection		
P. falciparum malaria	33	27	6	19	26 (10–63)	7380 (40–92,240)
P. vivax malaria	32	25	7	19	31 (18–55)	3980 (120–17,120)
P. malariae malaria	3	3	0	2	38 (33–42)	3880†

*Mean counts exclude the mixed infections.
†The count for the sole mono-infection.

TABLE 2. *Comparison of the results of the screening, based on thick bloodsmears, with those of the subsequent examination of thin smears and the PCR-based assay, for all the subjects who were identified as having* Plasmodium vivax *infection in the initial screening and then investigated by the PCR-based assay**

Results of:			Parasitaemia†
Thick-smear screening	Thin-smear examination	Nested PCR	(trophozoites/μl)
P. falciparum + *P. vivax*	*P. vivax*	*P. vivax*	15,360
P. falciparum + *P. vivax*	*P. vivax*	*P. vivax*	120
P. vivax	*P. vivax*	*P. vivax*	6080
P. vivax	*P. vivax*	*P. vivax*	12,640
P. vivax	*P. vivax*	*P. vivax*	1280
P. vivax	*P. vivax*	*P. vivax*	640
P. vivax	*P. vivax*	*P. vivax*	1840
P. vivax	*P. vivax*	*P. vivax*	11,200
P. vivax	*P. vivax*	*P. falciparum* + *P. vivax*	1920
P. vivax	*P. vivax*	*P. falciparum* + *P. vivax*	1920
P. vivax	*P. vivax*	*P. falciparum* + *P. vivax*	9120
P. vivax	*P. vivax*	*P. falciparum* + *P. vivax*	4800
P. vivax	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	640
P. vivax	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	4000
P. vivax	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	720
P. vivax	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	160
P. vivax	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	560
P. vivax	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	1280
P. vivax	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	320
P. falciparum + *P. vivax*	*P. falciparum* + *P. vivax*	*P. falciparum* + *P. vivax*	1120
P. vivax	*P. vivax*	*P. falciparum*	1520
P. vivax	*P. malariae*	*P. malariae*	3880
P. vivax	*P. falciparum* + *P. malariae*	*P. vivax* + *P. malariae* + *P. falciparum*	560
P. vivax	*P. vivax* + *P. malariae*	*P. vivax* + *P. malariae* + *P. falciparum*	4960
P. vivax	Indeterminate	*P. vivax*	920
P. vivax	Indeterminate	*P. vivax*	2880
P. vivax	Indeterminate	*P. vivax*	6560
P. vivax	Indeterminate	*P. falciparum* + *P. vivax*	17,200
P. vivax	*P. falciparum* + *indeterminate*	*P. falciparum* + *P. vivax*	9760

*No PCR data were produced for another five subjects identified as having pure *P. vivax* infections (two) or mixed *P. vivax*/*P. falciparum* infections (three) at the initial screening.
†Estimated from counts on the thick bloodsmears.

recurrent parasitaemia during the 28 days of follow-up. None of the 27 subjects with *P. falciparum* infection at enrollment developed an inter-current *P. vivax* parasitaemia. The Figure illustrates the cumulative incidence of *P. falciparum* after the standard CQ therapy. The risk of the therapeutic failure of CQ against *P. falciparum* in Guyana was estimated at 33% by day 7 and 48% by day 14.

Of the subjects found to be infected with *P. falciparum* at enrollment, >75% reported relief from physical complaints within 4 days of their first dose of CQ (Table 4). Among those subjects who cleared their *P. falciparum* parasitaemias by day 4, >90% were free of all physical complaints except arthralgia and dizziness by day 4.

Plasmodium vivax

Three of the 32 subjects initially infected with *P. vivax* were lost to follow-up before day 4 (Table 3). Another eight, all with mixed infections at enrollment, were withdrawn because they had to be treated for recurrent *P. falciparum* parasitaemia by day 14. Although two more subjects had (slide- and nested-PCR-confirmed) recurrent *P. vivax*

TABLE 3. *Life tables for the therapeutic failure of chloroquine against* Plasmodium falciparum *and* P. vivax*

Parasite	Interval (day)	*N*	*i*	*w*	IR	CI
Plasmodium falciparum	0†	33	0	6	0	0
	4	27	4	0	0.1482	0.1482
	7	23	5	0	0.2174	0.3334
	11	18	2	0	0.1111	0.4075
	14	16	2	0	0.125	0.4816
	18	14	1	0	0.0714	0.5186
	21	13	0	0	0	0.5186
	28	13	1	0	0.0769	0.5556
Plasmodium vivax	0†	32	0	3	0	0
	4	31	0	2	0	0
	7	29	0	2	0	0
	11	27	0	1	0	0
	14	26	1	3	0.0408	0.0408
	18	22	0	0	0	0.0408
	21	22	0	0	0	0.0408
	28	22	1	0	0.0454	0.0844

*N is the number of subjects at risk in the interval, I the number of incident cases of therapeutic failure, w the number of withdrawals due to loss to follow-up or parasitaemia with another species, IR the interval risk $\{i/[N-(w/2)]\}$, and CI is the cumulative incidence $\{1-[(1-\mathrm{IR_a})\times(1-\mathrm{CI_b})]\}$ in which $\mathrm{IR_a}$ is the current interval risk and $\mathrm{CI_b}$ the cumulative incidence of the prior interval.
†At enrollment.

TABLE 4. *Resolution of clinical complaints following chloroquine treatment of the subjects with* Plasmodium falciparum *infections*

Complaint	Day-0 frequency (%)	Day-4 frequency (%) among:	
		All subjects	Those aparasitaemic on day 4
Sick	100	18	9
Febrile	100	15	9
Headache	100	15	6
Malaise	94	6	3
Muscle ache	79	21	9
Joint ache	76	24	15
Nausea	67	6	3
Dizziness	49	24	15
Vomiting	33	0	0
Diarrhoea	21	10	10
Disturbed vision	12	12	9
Confined to home	39	12	6

parasitaemia on day 14 or 28, each had a whole-blood concentration of CQ plus desethyl-chloroquine on the day of recurrence (74 and 0 ng/ml) that was below the minimum effective concentration for *P. vivax*. These two cases of recurrent parasitaemia were therefore considered consistent with CQ-sensitive *P. vivax*.

DISCUSSION

This report documents a substantial risk of therapeutic failure of CQ among a small sample of subjects infected with *P. falciparum* in Guyana, South America. The sample only represented a small proportion of the patients reporting to the enrollment site because

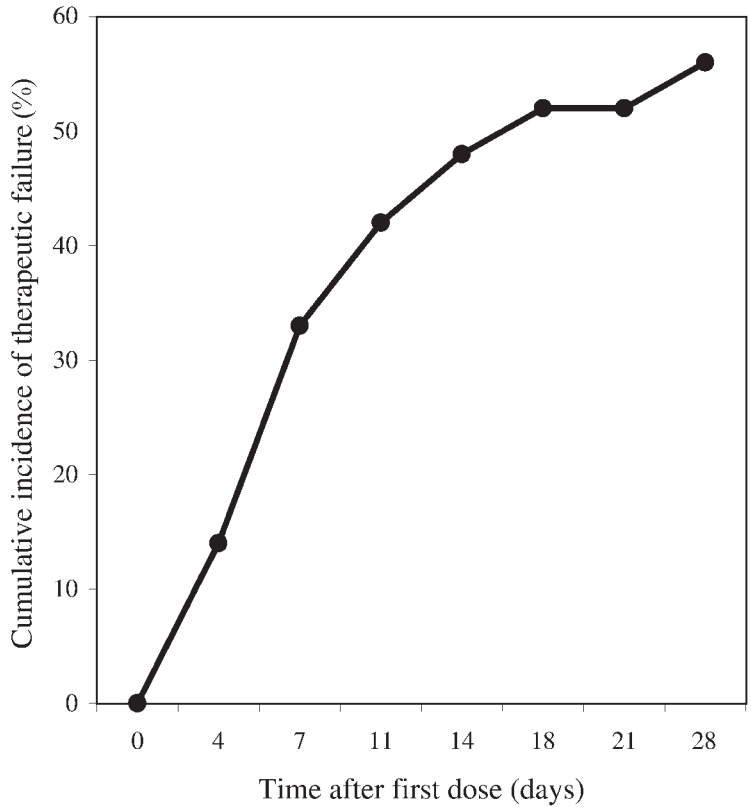

FIG. Cumulative risk of post-chloroquine, recurrent, *Plasmodium falciparum* parasitaemia in Guyana.

most such patients had been infected in the interior of the country while working for a living and wished to return to the interior as quickly as possible. That most of the subjects were adult males is probably evidence that travel to (or residence in) the forested interior is a dominant risk factor for infection among patients seeking treatment in Georgetown; infection among populations resident in the endemic interior occurs across all ages (Rambajan, 1994). The present subjects represented people who had incidentally planned on remaining in Georgetown for at least 28 days, usually for reasons related to family activities. It seems unlikely that this produced a sample bias with respect to risk of therapeutic failure.

Nearly half (48%) of the *P. falciparum* infections recurred within 14 days of the first dose of CQ, with relatively few recurrences after day 14 (the 28-day cumulative incidence was 55%). *Plasmodium falciparum* in Guyana appears polarized with respect to CQ susceptibility, with resistant and susceptible populations mixed in roughly equal proportions. Approximately one half of the infections recrudesced within 14 days, whereas the other half appeared completely susceptible to CQ. This unusual pattern may be a product of the termination, in the early 1990s, of the use of CQ as first-line therapy against *P. falciparum* in Guyana, which presumably diminished the survival advantage of resistance to the drug. In the absence of baseline data, however, this interpretation represents just one of several possible explanations.

The small sample of *P. vivax* evaluated in this study failed to reveal any therapeutic failure attributable to resistance to CQ. Among the 32 subjects with *P. vivax*, only two had recurrent *P. vivax* parasitaemia

during 28 days follow-up, and both of these had inadequate blood concentrations of CQ plus desethyl-chloroquine (< 100 ng/ml) at the time of the recurrence. If this sample were representative of *P. vivax* in Guyana, the risk of resistance to CQ would be less than one in 30 infections. Despite convincing evidence that CQ-resistant *P. vivax* occurs in Guyana (Phillips *et al.*, 1996), the results of the present (albeit small-scale) study indicate that, during late 1998, the risk of therapeutic failure because of such resistance was < 5%.

The primary therapy currently recommended for uncomplicated, *P. falciparum* malaria in Guyana is 7 days of quinine and a single dose of pyrimethamine–sulfadoxine. This was the regimen provided to the present subjects who failed to clear their infections with CQ. Unfortunately, many of these patients returned to the clinic within 2 weeks of their first dose of quinine, all with recurrent *P. falciparum* parasitaemia (data not shown). As failure to comply with the unsupervised regimen of quinine was the rule among these subjects, this therapeutic strategy suffers obvious shortcomings. However, there are few if any practical alternatives available to the local Ministry of Health. Neither the government nor most residents of Guyana possess the economic wherewithal to purchase highly effective and well-tolerated antimalarials such as Lariam® (mefloquine) or Malarone® (atovaquone–proguanil). Therapies involving artemisinin derivatives are not available. Uncomplicated, *P. falciparum* malaria in Guyana appears to receive inadequate therapy often.

Despite the high risk of parasitological failure with CQ against *P. falciparum*, most subjects infected with this parasite experienced almost complete clinical recovery within 4 days of their first dose of the drug (Table 4). This was especially true among those who managed to clear their parasitaemias by day 4. Most experienced rapid and substantial relief from illness despite the high risk of recurrence with symptoms (13 of 15 complained of being ill at the time of their recurrent parasitaemias). This finding corroborates similar observations in Africa and South–east Asia (Hoffman *et al.*, 1983; Khoromana *et al.*, 1986). However, CQ therapy in the face of even a relatively modest resistance has been associated with increased risk of malaria-attributable death (Zucker *et al.*, 1996; Trape *et al.*, 1998). The training of Ethiopian mothers to treat their young children with CQ reduced mortality in the children by 40% (Kidane and Morrow, 2000). In this case, 'self-treatment' with CQ was obviously better than no treatment, but effective alternative therapy would avoid the unnecessary risk of death resulting from parasitic resistance to CQ. The 'self-treating' poor may not appreciate such risk after clinical recovery, and they may fail to understand that CQ therapy may exacerbate the transmission of malaria by creating asymptomatic but infectious carriers. An effective alternative therapy that costs as little as CQ but has an equally good safety and tolerance profile would be required to undermine the economic forces that drive CQ use in the face of resistance.

The data shown in Table 2 demonstrate considerable inaccuracy in the initial screening diagnosis based on the examination of thick bloodsmears. Given the high risk of CQ-resistant *P. falciparum* and the continued use of CQ as the first-line treatment for *P. vivax* infection in Guyana, the large proportion of mixed *P. vivax*/*P. falciparum* infections misdiagnosed as pure *P. vivax* infections (62%) is worrisome. Many individuals infected with *P. falciparum* must be receiving only CQ therapy on the basis of a *P. vivax* diagnosis at screening. The clinic where this study was conducted employed two or three, full-time microscopists who essentially worked non-stop during the hours of the clinic's operation, to keep up with the demand. The addition of thin-smear reading, to increase the chances of detecting *P. falciparum* in mixed infections, would very substantially increase the workload and, like PCR-based assays, would not be practical

with the available resources. The solution to the problems of poor compliance with quinine and poor differentiation of species by thick-smear-based diagnosis may be a single, well tolerated alternative therapy that is effective against both *P. falciparum* and *P. vivax*. Combined therapies merit exploration as possible solutions to this problem. Furthermore, administering 45 mg primaquine weekly for 8 weeks would not only achieve effective transmission-blocking but also kill the liver stages of *P. vivax*. A means of assuring compliance to this regimen would substantially improve protection of the gains made against malaria on the coast of Guyana.

The northern coast of Guyana, where $>75\%$ of the country's population of about 700,000 live, has been largely free of malaria since a campaign of DDT spraying and distribution of 'chloroquinized' salt during the 1950s and 1960s (Giglioli *et al.*, 1976; Rambajan, 1994). Nonetheless, the region remains receptive to endemic malaria. The primary vector, *Anopheles darlingi*, has demonstrated the ability to re-establish itself on the coast and trigger outbreaks from infections introduced by travellers from the interior (Rambajan, 1987, 1988, 1994). Although *An. darlingi* (an efficient vector) remains rare in the coastal region, the inefficient vector *An. aquasalis* occurs in abundance (S. Rawlins, unpubl. obs.). The ease of human travel between the malaria-free coastal region and the malaria-endemic interior constitutes an obvious threat, and one that is amplified by the apparent inadequacy of the available therapy. At least three of the present subjects apparently acquired their infections on the outskirts of Georgetown (data not shown). In the absence of effective, unsupervised therapy for malaria or a resumed application of residual insecticides, endemic, CQ-resistant, *P. falciparum* malaria threatens to reclaim the coastal region of Guyana.

In conclusion, the high risk of therapeutic failure of CQ against uncomplicated, *P. falciparum* malaria in Guyana supports the Ministry of Health's earlier abandonment of CQ as the first-line drug for such disease. At the time of the present study, CQ apparently remained effective for most *P. vivax* acquired in Guyana, but other evidence of CQ resistance in this species merits surveillance of the problem. In view of the high frequency of mixed infections of *P. falciparum* and *P. vivax* not detected by routine diagnostic procedures, an ideal therapeutic regimen would be effective against both species. Poor compliance with quinine therapy for *P. falciparum* and the high risk of undiagnosed *P. falciparum* mixed with *P. vivax* being treated with CQ alone merits reconsideration of the national treatment policy. Re-introduced endemic malaria threatens the heavily populated coastal region of Guyana and addressing the threat requires effective treatment strategies. A *Plasmodium* sp. in Guyana with an ssrRNA gene apparently indistinguishable from *P. vivax*, but having consistent morphological characteristics incompatible with that species, was identified.

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