Combination therapy is one method of overcoming the global challenge of drug-resistant \textit{Plasmodium falciparum} malaria. We conducted a hospital-based 28-day \textit{in vivo} test comparing chloroquine/doxycycline to doxycycline alone for treating \textit{P. falciparum} and \textit{Plasmodium vivax} malaria in Irian Jaya, Indonesia. Eighty-nine patients with uncomplicated falciparum malaria were randomized to standard dose chloroquine (n = 30), doxycycline (100 mg every 12 hours [7 days], n = 20), or chloroquine with doxycycline (n = 39); corresponding numbers for vivax malaria (n = 63) were 23, 16, 24. Endpoints were parasite sensitivity (S) or resistance (RI/RII/RIII). Of the 105 evaluable patients, chloroquine/doxycycline cured (S) 20/22 (90.9% [95% CI 78.9–100%]) patients with \textit{P. falciparum} malaria; 2/22 (9.1% [0–21%]) were RIII resistant. Doxycycline cured 11/17 (64.7% [42.0–87.4%]) patients, and chloroquine 4/20 (20% [2.5–37.5%]). Against \textit{P. vivax}, chloroquine/doxycycline cured (S) 12/17 (70.6% [48.9–92.2%]) patients, doxycycline 4/12 (33.3% [6.6–59.9%]), and chloroquine 4/12 (33.3% [6.6–59.9%]). Chloroquine/doxycycline was effective against \textit{P. falciparum} but only modestly effective against \textit{P. vivax}. These findings support the use of chloroquine/doxycycline as an inexpensive alternative to mefloquine for treating chloroquine-resistant \textit{P. falciparum} but not chloroquine-resistant \textit{P. vivax} in this setting.

INTRODUCTION

Drug-resistant \textit{Plasmodium falciparum} is a serious global problem making treatment increasingly difficult.\cite{1} In Indonesia, chloroquine is the recommended drug of first choice for treating malaria\cite{2} despite its poor efficacy against falciparum malaria\cite{3–5} and the recent emergence of chloroquine-resistant \textit{Plasmodium vivax}.\cite{6–8}

Using combination treatment of currently available drugs is a rational approach to combating drug resistance and avoids the long wait for antimalarial drugs in development.\cite{9} Drugs with different mechanisms of action may enhance their respective efficacies and extend their therapeutic “life spans,” a major public health consideration for developing countries whose need for effective drugs is pressing. Sulfadoxine/pyrimethamine (S/P) is widely used in malaria-endemic countries and has replaced chloroquine as first-line treatment for uncomplicated falciparum malaria in several African countries.\cite{10} However, S/P will not be the definitive answer to chloroquine resistance because its life span in Thailand was only five years\cite{11} and resistance to S/P has been reported in several countries.\cite{1,11}

Drug combinations have demonstrated improved efficacy over single agents against uncomplicated falciparum malaria. In Gabon, clindamycin improved the efficacy of a 3-day course of quinine from 32% to 88%, and that of standard dose chloroquine from 9% to 70%.\cite{12} Mefloquine/artsunate cured 98% of patients with highly resistant falciparum malaria acquired on the Thai-Burmese border and atovoquone/proguanil was 100% effective in Thai adults.\cite{13} Chloroquine-resistant vivax malaria is currently less problematic and can be treated with mefloquine,\cite{15} halofantrine,\cite{15,16} and often with chloroquine combined with primaquine.\cite{16}

Doxycycline and tetracycline have modest antimalarial activity against vivax or falciparum malaria.\cite{17–20} However, combining either drug for seven days with quinine, mefloquine, or artesunate resulted in treatment efficacies exceeding 94% against falciparum malaria in Thailand.\cite{21–24} and the addition of three days of doxycycline to standard-dose chloroquine improved the cure rate of chloroquine from 36% to 75% in Gabonese adults with falciparum malaria.\cite{25} Doxycycline has now replaced tetracycline for use in combination with quinine against falciparum malaria\cite{13} because of its therapeutic advantage of twice-daily dosing and low cost (US$ 3.14/100 generic capsules in Indonesia).

Inexpensive, alternative treatments to chloroquine are needed for chloroquine-resistant falciparum and vivax malaria in northeastern Irian Jaya.\cite{26,27} We report the results of treating uncomplicated \textit{P. falciparum} and \textit{P. vivax} malaria with chloroquine/doxycycline, chloroquine alone, and doxycycline alone.

MATERIALS AND METHODS

\textbf{Study design, study site, and participants.} This was an open-label, randomized, clinical trial comparing chloroquine combined with doxycycline to chloroquine alone or to doxycycline alone for treating uncomplicated falciparum or vivax malaria. The study took place from October 1995 to January 1998 in the Jayapura Public and Indonesian Navy hospitals in Jayapura, northeastern Irian Jaya. This area has moderate transmission\cite{25,26} of multidrug-resistant falciparum malaria\cite{24–26} and chloroquine-resistant vivax malaria.\cite{27,28} Chloroquine is first-line treatment in this area\cite{2} and has documented failure rates of 54% against uncomplicated \textit{P. falciparum} and up to 78% against \textit{P. vivax}.\cite{29} Patients were recruited from Jayapura and Arso (the rural area around Jayapura); they were either life-long residents or recent arrivals.
from other parts of Indonesia. We obtained written informed consent from all patients. The study was conducted according to the Indonesian Ministry of Health, the Indonesian Navy, and the United States Navy and Army regulations governing the protection of human subjects.

**Sample size.** The sample size calculations were based on the assumption that the frequencies of resistance (RI/RII/RIII) were 0.5 for chloroquine alone (C) and 0.05 for the combination arm (CD). Using a two-sided alpha of 0.05, sample sizes of 18 per arm (C versus CD) would detect these resistance frequencies with a probability of 0.89. Although not the primary aim of the study, a comparison of D versus CD, with the same sample size of 18 per arm and anticipating a resistance frequency of 0.4 for doxycycline alone and 0.05 for the combination, would provide a power of 0.73.

**Patient assessment and selection.** Potential subjects were referred to our team by local physicians and medically screened: (i) medical history, (ii) physical examination, (iii) malaria smear, (iv) urine pregnancy test (β HCG test pack, Abbott, IL), and (v) qualitative glucose-6-phosphate dehydrogenase (G6PD) activity (G6PD spot test, Sigma). Eligible subjects were healthy males or non-pregnant females aged 15 to 50 years with either acute uncomplicated falciparum malaria or vivax malaria. Specific exclusions included mixed infections, symptoms or signs of severe and complicated malaria, malaria treatment within 7 days of presentation, and known study drug hypersensitivity.

**Conduct of clinical trial.** Enrolled patients were admitted to the hospital and sequentially randomized to treatment (C, CD, or D); this was later changed to a system of using labelled tickets that were selected “out of a hat” by the team physician. Patients with acute uncomplicated falciparum malaria were arbitrarily classified as “mild” (≤ 0.25% parasitemia = parasite density ≤ 12,500/μL), or “moderate” (parasitemia > 0.25% to < 3% = parasite density > 12,500–< 150,000/μL). This artificial division was designed so that no randomized “moderate” patients would receive doxycycline alone, due to concern over its slow onset of action. Patients randomized to chloroquine (Malarex, Dumex, Indonesia) were treated with chloroquine base: 10 mg/kg once on Days 2, 4, and 7. Daily administration of chloroquine (Pﬁzer) was 100 mg every 12 hours for 7 days (D and CD arms). All drugs doses were administered and documented by ward nurses. Patients were hospitalized for 28 days. The ward windows were screened with mosquito mesh and subjects slept under mosquito nets. Symptoms were recorded daily. Oral temperatures were taken every 8 hours for the first week, and daily thereafter. Treatment failures were treated with quinine (10 mg/kg thrice daily for 4 days) and doxycycline (100 mg twice daily for 10 days). Patients with vivax malaria were given primaquine base (30 mg/day for 14 days) at the time of hospital discharge, provided they were not G6PD deﬁcient.

Giemsa-stained malaria smears were read daily until negative; thereafter, three times per week until Day 28. A positive smear was deﬁned as one or more asexual forms seen after examining 200 thick smear ﬁelds under ×1,000 magniﬁcation. The parasite count (number/μL) was quantiﬁed as the number of asexual parasites/200 white cells on the thick ﬁlm × 40.31

Filter paper (No. 1 Whatman, Fairﬁeld, NJ) blots for chloroquine drug levels were made on Days 0, 3, and 28, or on the day of recurrent parasitaemia. One hundred μL of whole blood were drawn from a ﬁnger stick into a capillary tube and spread evenly onto the ﬁlter paper. Blots were air dried and stored in individual plastic bags at ambient temperatures until analysed. Chloroquine and its main active metabolite, desethylchloroquine, were measured in whole blood by HPLC.32 The sum of chloroquine and desethylchloroquine is reported as the total whole blood chloroquine concentration (ng/ml).

**End points.** The parasitological end points were classiﬁed as sensitive (S) or resistant (RI/RII/RIII). Sensitive: complete and sustained clearance of asexual parasitaemia by Day 7 to Day 28; RI: complete clearance of asexual parasitaemia by Day 7 but recrudescence within 28 days of starting treatment; RII: marked reduction (≥ 75%) of asexual parasitaemia within 48 hours but no clearance by Day 7; and RIII: no marked reduction of asexual parasitaemia by 48 hours.33 For vivax malaria, we classiﬁed RI cases as RII/relapse because clinical differentiation between recrudescence or relapse (from liver hypnozoites) during follow-up may be problematic. Genotyping by the polymerase chain reaction (PCR) was performed on the recurrent and original (Day 0) parasitaemias by a method previously described.34,35 A matching genotype between primary and recurrent isolates indicates a > 90% probability of a RI treatment failure or a vivax relapse caused by the same clone as the original infection.34,35 A non-matching genotype suggests a new infection or a vivax relapse caused by an antecedent infection.

Secondary clinical end points were (i) the fever clearance time (FCT/hours): the time taken for the patient to become and remain afebrile (oral temperature ≤ 37°C recorded at least four consecutive times); (ii) the parasite clearance time (PCT/days): the number of days taken for a malaria smear to become negative for at least two consecutive days; and (iii) the proportion of symptomatic patients (reporting either fever, chills, headache, myalgia, weakness, anorexia, or nausea) on Days 2, 4, and 7.

**Statistical analysis.** Data were double-entered and validated using Epi Info 6.04b (Centers for Disease Control and Prevention, Atlanta, GA). Signiﬁcance testing of proportion- al data (Chi squared), and calculating the 95% conﬁdence intervals (CI) of continuous data were performed using SPSS for Windows 8.0 (SPSS, Chicago, IL). Relative risks and conﬁdence intervals around proportions were calculated using Epi Info 6.04b. Normally distributed data were compared using the student’s t-test or ANOVA or the corresponding non-parametric tests, Mann-Whitney U or Kruskall-Wallis, for skewed data. All statistical tests were two sided and a P value of ≤ 0.05 was considered statistically signiﬁcant. Only patients who completed the study were ana- lysed for the parasitological end points.

**RESULTS**

Of 164 screened patients, 152 patients entered the study: 89 P. falciparum and 63 P. vivax malaria (Figure 1); 28 of 152 were excluded from analysis because of violation of the randomization system by one physician who allocated treatment using clinical judgement. These 28 excluded study sub- jects included all patients who were enrolled during the time
period of this physician’s participation, in order to eliminate any possibility of bias. Patients in the treatment groups had similar baseline characteristics except for the *P. falciparum* cases randomized to doxycycline alone who had significantly less residential time in Irian Jaya. Parasite counts of both malaria species were similar between treatment groups (Table 1). Reasons for non-completion of study were mixed: 1) Reasons for non-completion of study were mixed.

**P. falciparum** (Table 2). The cure rate (S) of chloroquine/doxycycline (70.6%) was significantly higher than that of chloroquine alone (29.4%), (RR = 2.4 [1.08–5.33], *P* = 0.016) but not significantly different compared to doxycycline alone (33.3%), (RR = 2.12 [0.90–4.99], *P* = 0.067). Doxycycline and chloroquine had similar cure rates (RR = 1.13 [0.38–1.13], *P* = 1.0). RI/relapse and RII/RIII resistance were present in the chloroquine arm, RI/relapse and RIII resistance in the doxycycline arm, and RI/relapse only in the CD arm. PCR data were available for 11 cases of recurrent parasitemia (by arm: C = 5, CD = 4, D = 2). Ten had matching and one had mismatching genotypes compared to their respective Day 0 parasitemias. The recurrent parasitemias occurred between Days 11–23 (C arm), and Days 22–25 (CD and D arms). Mean FCTs in all three treatment groups were similar but the mean PCT was significantly higher on Day 7 for the doxycycline arm compared to the combination and chloroquine arm (1/15 [6.7%], *P* = 0.023).

**Chloroquine levels.** The Day 3 whole-blood total chloroquine levels in patients given chloroquine or chloroquine/doxycycline ranged from 315–1,545 ng/ml, median 719 ng/

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**Table 1**

Patient characteristics at enrollment

<table>
<thead>
<tr>
<th></th>
<th>Falciparum malaria</th>
<th></th>
<th>Vivax malaria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C n = 30</td>
<td>CD n = 39</td>
<td>D n = 20</td>
<td>C n = 23</td>
</tr>
<tr>
<td>Male</td>
<td>28</td>
<td>33</td>
<td>19</td>
<td>22</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>6</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Mean (SD) age yr</td>
<td>24.5 (5.0)</td>
<td>23.7 (5.2)</td>
<td>24.9 (5.6)</td>
<td>23 (4.9)</td>
</tr>
<tr>
<td>Time in Irian Jaya†</td>
<td>17 (1m–40)</td>
<td>19 (4–30)</td>
<td>3 (3m–26)</td>
<td>2 (6m–24)</td>
</tr>
<tr>
<td>Previous malaria‡</td>
<td>2 (0–10)</td>
<td>3 (0–11)</td>
<td>3 (0–9)</td>
<td>5 (0–16)</td>
</tr>
<tr>
<td>No. (%) symptomatic</td>
<td>30 (100)</td>
<td>39 (100)</td>
<td>19 (95)</td>
<td>23 (100)</td>
</tr>
<tr>
<td>No. (%) febrile</td>
<td>25/29 (86.2)</td>
<td>35 (89.7)</td>
<td>15 (75)</td>
<td>19/22 (86.4)</td>
</tr>
<tr>
<td>No. (%) splenomegaly</td>
<td>11 (36.7)</td>
<td>21 (53.8)</td>
<td>6 (33.3)</td>
<td>9 (30.4)</td>
</tr>
<tr>
<td>Parasite count/µL§</td>
<td>5,280 (40–93,040)</td>
<td>7,040 (40–76,120)</td>
<td>1,740 (80–40,160)</td>
<td>3,320 (80–12,840)</td>
</tr>
</tbody>
</table>

*C* = chloroquine alone; *CD* = chloroquine and doxycycline in combination; *D* = doxycycline alone; *SD* = standard deviation.

† Includes one > moderate *P. falciparum* subject inadvertently given doxycycline.

‡ Median (range) number of reported attacks of clinical malaria within the last two years (history only). *Vivax* cases: *C* versus *CD*, *P* = 0.01 (Mann-Whitney U test).

§ Mean (range). Only falciparum cases with parasitemia ≤ 12,500/µl were enrolled in the doxycycline arm alone.
TABLE 2
Results of evaluable patients with falciparum or vivax malaria

<table>
<thead>
<tr>
<th></th>
<th>Falciparum malaria</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C</td>
<td>CD</td>
<td>D</td>
</tr>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 22</td>
<td>n = 17</td>
</tr>
<tr>
<td>S</td>
<td>4 (20.0)*</td>
<td>20 (90.9)</td>
<td>11 (64.7)</td>
</tr>
<tr>
<td>RI†</td>
<td>8 (40.0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>RII</td>
<td>5 (25.0)</td>
<td>0 (0)</td>
<td>2 (11.8)</td>
</tr>
<tr>
<td>RIII</td>
<td>3 (15.0)</td>
<td>2 (9.1)</td>
<td>4 (23.5)</td>
</tr>
</tbody>
</table>

Mean (95% CI) FCT/hours: S, 41.2 (27.0–55.4), RII, 51.9 (43.4–74.9); RI, 61.6 (23.8–99.4).<sup>20</sup>

Mean (95% CI) PCT/days: S, 2.8 (2.0–3.6), RI, 3.4 (2.7–4.1); RII, 3.8 (2.6–5.1).<sup>20</sup>

C = chloroquine alone; CD = chloroquine and doxycycline in combination; D = doxycycline alone; S = sensitive; RI, RII, and RIII = resistance (see text for definitions). FCT = fever clearance time; PCT = parasite clearance time. CI = confidence interval.

* n (%) † RIII for Plasmodium vivax malaria.

ml. The median Day 3 levels were similar between (i) the CD and chloroquine arms: 723 ng/ml versus 703 ng/ml, respectively, \( P = 0.51 \), (ii) patients with resistant or sensitive falciparum infections: 698 ng/ml versus 706 ng/ml, respectively, \( P = 0.93 \), and (iii) patients with resistant or sensitive vivax infections: 702 ng/ml versus 719 ng/ml, respectively, \( P = 0.52 \).

**DISCUSSION**

This study has shown that the combination of chloroquine and doxycycline markedly improved the cure rate of uncomplicated, multidrug-resistant falciparum malaria in northeastern Irian Jaya. Against vivax malaria, there was only modest improvement over chloroquine alone.

Scant data exist on doxycycline or tetracycline monotherapy of falciparum or vivax malaria. Malaysian children with chloroquine-resistant falciparum malaria had higher cure rates with 7 days of doxycycline compared to four days, 22/26 (84.6%), and 4/9 (44.4%), respectively.\(^*\) Seven days of doxycycline cured 9/9 American volunteers with experimentally-induced, low parasitemic \( P. falciparum \) malaria whereas five days resulted in 4/4 cases of recrudescence.\(^*\) These seven-day cure rates are higher than in our falciparum patients (65%). We have identified only one study of tetracycline treatment of experimentally induced, Chesson strain vivax malaria, the strain from New Guinea.\(^*\) Of twelve American volunteers given tetracycline (2 or 4 gm/day for 7 or 14 days), only 4 subjects (33.3%) were fully sensitive; a cure rate consistent with our vivax data. Tetracycline or doxycycline monotherapy resulted in slow mean parasite and fever clearance times against \( P. falciparum \) (PCT 5 days, FCT 3–5 days)\(^*\) and \( P. vivax \) (PCT 7 days, FCT 6 days)\(^*\) malaria. Our study has re-documented the slow parasite clearance times of falciparum (8 days) and vivax malaria (8 = 5 days), but our mean fever clearance times were faster, just over 2 days for both species.

Doxycycline was clearly inadequate against \( P. falciparum \), achieving a 20% cure rate and a high proportion (40%) of RII/RIII infections. The cure rate against \( P. vivax \) was marginally better (29%) but the proportion of high-grade resistance was lower at 12%. In Jayapura in 1984,\(^*\) 16 patients with falciparum malaria were treated with chloroquine in a 7-day *in vivo* test; only 9 (56.2%) were S/RI and the seven resistant cases were RI (3), RII (2), and RIII (2 [12.5%]). Twelve years on, our data and those of earlier studies continue to document the high degree of chloroquine resistance of both falciparum and vivax malaria in this area.\(^*\) 6,16,36

To date, only one randomized study comparing chloroquine/doxycycline with chloroquine for treating acute, uncomplicated falciparum malaria has been published. Adults from Gabon (median parasite count of 13,500/µl) received three days of concurrent doxycycline/chloroquine. The cure rate was 75% compared to 36% for standard-dose chloroquine alone.\(^*\) The cure rate may well have been higher had doxycycline been given for seven days, as in our study, and as suggested by the earlier trials of doxycycline monotherapy.\(^*\)

Chloroquine/doxycycline cured 90.9% of our patients with falciparum malaria. However, this good result is tempered by the occurrence of RIII resistance in two patients (9%). These patients remained asymptomatic and had rising parasite counts at 48 hours but were not seriously ill. In Thailand, a clinical trial assessing the efficacy of chloroquine/tetracycline against falciparum malaria was prematurely abandoned because two patients with RIII resistance became seriously ill. The investigators concluded that the chloroquine/tetracycline combination was potentially dangerous.\(^*\) Clinicians should be aware that RIII resistance is the most serious form of resistance because treatment has little or no effect in lowering the parasite count and patients may develop severe falciparum malaria. In Irian Jaya, RII chloroquine-resistant \( P. falciparum \) has been documented as 16.2% on the north coast,\(^*\) 22.8% in Arso,\(^*\) and 12.5% in Jayapura.\(^*\) Our figures were 15% for chloroquine and 9.1% for the chloroquine/doxycycline suggesting that the combination might have had a small beneficial effect against RII resistant parasites. However, overcoming RII resistance to chloroquine in this area will require more efficacious antimalarial drugs or drug combinations. Against vivax malaria, the high rate of initial parasite clearance was offset by the relatively high rate of apparent recrudescence, necessitating the use of alternative treatment. In our setting of drug-resistant falciparum and vivax malaria, optimal patient management would ideally require accurate speciation, targeted treatment, and follow-up; clearly a challenge under field conditions. The cure rates of the combination were achieved by administering doxycycline for seven days, a major drawback for patient compliance outside the research setting. Our results cannot be extended to two important vulnerable groups, young children and pregnant women in both of whom doxycycline is contraindicated.
Chloroquine/doxycycline had a higher cure rate against *P. falciparum* (90.9%) than *P. vivax* (70.6%), but this difference was not quite significant (P = 0.08). Intuitively, one would have expected a higher vivax cure rate because vivax malaria is a “benign” malaria. This finding underscores the importance of studies aimed at understanding the mechanisms of action and resistance of chloroquine and doxycycline in the two major species of human malaria. Our data suggest that different mechanisms of drug resistance may exist between *P. falciparum* and *P. vivax*.

In this study we have shown that the combination was effective against multidrug-resistant falciparum malaria and highly effective for the initial clearance of chloroquine-resistant vivax malaria. In Irian Jaya, it could offer a reasonable alternative to chloroquine, the current standard of care, which has a failure rate against *P. falciparum* well above the 25% level recommended by the World Health Organization (WHO) for a change in antimalarial treatment against this species.26 Seven days of generic doxycycline would increase the cost of chloroquine alone from approximately US$0.07 to 0.51. This compares to 13 cents for an adult course of S/P, and US$2.35 for an adult course of generic mefloquine of 15 mg/kg (five 250 mg tablets).

Chloroquine/doxycycline will not be the definitive answer to chloroquine-resistant falciparum or vivax malaria. However, it may have a role as an interim measure in malaria-control programs for treating either malaria species, provided *P. falciparum* III resistance is not a significant problem.

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