COST CONSIDERATIONS OF MALARIA CHEMOPROPHYLAXIS INCLUDING USE OF PRIMAQUINE FOR PRIMARY OR TERMINAL CHEMOPROPHYLAXIS

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Abstract. The costs of mefloquine, chloroquine, doxycycline, primaquine, and atovaquone/proguanil are calculated for various durations of exposure to malaria. The cost is included for detecting glucose 6-phosphate dehydrogenase (G6PD) deficiency before administering primaquine for primary or terminal prophylaxis. For durations of exposure ranging from 3 to 730 days, if no terminal prophylaxis is given, doxycycline (generic) is the least expensive regimen. Compared with doxycycline hyclate, chloroquine costs three to four times more, and primaquine, after screening for G6PD, costs about eight times more. Atovaquone/proguanil is less expensive than mefloquine for a 3-day exposure, but more expensive for 7 or more days. When terminal chemoprophylaxis with primaquine for 14 days is used in addition to doxycycline, mefloquine, chloroquine, or atovaquone/proguanil, primaquine alone is the least expensive regimen for exposures of <10 days. Thereafter, doxycycline plus 14 days of primaquine is most economical. For subsequent exposures when G6PD status is already known, primaquine alone is the least expensive regimen for up to 9 days of exposure, but doxycycline is less expensive thereafter. In general, generic doxycycline hyclate is the least expensive regimen. Primaquine alone is economically attractive. Mefloquine, doxycycline monohydrate, and atovaquone/proguanil, the most expensive regimens, are similar in cost for a 7-day exposure, but thereafter, atovaquone/proguanil is much more expensive.

INTRODUCTION

Among the considerations for chemoprophylaxis of malaria are convenience, safety profile, side effects, cost of screening tests, cost of primary drug used, and cost of terminal prophylaxis against late onset or relapsing forms of malaria, Plasmodium vivax and Plasmodium ovale. The costs of the medication(s) used include the number of doses required (before, during, and after exposure), the cost per dose, the cost of any laboratory testing required, and the cost of medication used for terminal prophylaxis. Indirect costs might include the cost of notifying patients of required laboratory results, the cost of treatment of any serious side effects, and the cost of treating any chemoprophylaxis failures, including relapsing malaria, resulting from poor compliance, resistance, or lack of terminal prophylaxis. However, the direct costs of the medication and laboratory testing are more easily measured.

Five medications are commonly used by physicians licensed in United States to prevent malaria: mefloquine, doxycycline, atovaquone/proguanil, chloroquine, and under special circumstances, primaquine. Mefloquine, chloroquine, and doxycycline work only on the erythrocytic stage of malaria. However, in the United States and Israel, about one third of cases present late (=2 months after returning from a malarious area). These cases are largely P. vivax or P. ovale that result from hypnozoites in the liver. Therefore, an optimal regimen is one that prevents the erythrocytic phase and eliminates the hypnozoites of P. vivax or P. ovale.

Primaquine is useful for prevention of malaria while in a malarious area (primary or causal prophylaxis), for terminal prophylaxis when leaving an area with P. vivax or P. ovale, and for radical cure of clinical cases of P. vivax and P. ovale malaria that might relapse if hypnozoites were not eliminated. The latter two situations are also known as anti-relapse therapy. Primaquine has causal activity against both P. falciparum and P. vivax with shown ability to prevent development or destroy the liver stages of malaria. Therefore, no terminal prophylaxis is required. However, pretreatment screening for glucose 6-phosphate dehydrogenase (G6PD) is required. Atovaquone/proguanil has causal activity against P. falciparum, but it is not known if it has causal activity against other species.

In this paper, I computed the direct costs of chemoprophylaxis for three scenarios: chemoprophylaxis without terminal prophylaxis and screening for G6PD only for those taking primaquine for primary prophylaxis; chemoprophylaxis and screening for G6PD of all persons and terminal treatment with primaquine in all groups, except those taking primaquine for primary prophylaxis, and chemoprophylaxis and terminal treatment with primaquine in persons already screened for G6PD.

MATERIALS AND METHODS

Doses of medication and prophylaxis regimens recommended by the Centers for Disease Control are used to determine the number of doses of medication required for prevention of malaria. The average wholesale price of generic and brand-name medications is obtained from the Drug Topic Redbook. For mefloquine and chloroquine, the regimens are one dose weekly beginning 2 weeks before exposure, weekly during, and for 4 weeks after exposure. Doxycycline, atovaquone/proguanil, and primaquine are administered daily beginning 2 days before, each day during and for 28, 7, and 7 days, respectively, after leaving the malarious area. Because primaquine is recommended for adults at a daily dose of 30 mg base (52.6 mg salt), two tablets daily of the 15 mg base medication are required. (This dose is twice the Food and Drug Administration [FDA]-approved dose and is therefore “off-label”). For calculation purposes, the least expensive option per dose is used based on Table 1.

The cost of testing for G6PD is variable depending on whether a qualitative test is done followed by quantitative confirmation of those with suspected deficiency or whether a quantitative test is done at a commercial laboratory on all persons. A qualitative screening test is performed by incubating a small amount of blood with glucose-6-phosphate and
nicotinamide adenine dinucleotide phosphate (NADP). Drops of the mixture are removed at 5-minute intervals, spotted on filter paper, and viewed under long-wave ultraviolet light (Fischer Scientific, Hampton, NH). Fluorescence is clearly evident in mixtures prepared from normal blood, whereas G6PD-deficient samples yield little or no fluorescence. A kit for this assay is available (Trinity Biotech, St. Louis, MO). The reagents, controls, and materials cost one government laboratory less than $2.00 per sample when 10 tests are done. An easy to use NADH+ Spot Test is available from Sigma Chemicals for less than $1.00 per test. One commercial laboratory quotes a list price of $57.25 for a quantitative test with a discount to less than $20 per test for one government agency. For purposes of this study, a middle cost for G6PD screening for adequate G6PD. The reader may substitute their own costs into the formula: Number of doses of antimalarial × cost per dose + cost of G6PD screening + cost of primaquine for terminal prophylaxis.

RESULTS

Table 1 shows the average wholesale costs of antimalarial medications. A generic brand of mefloquine is slightly less per tablet than Lariam (Roche, Nutley, NJ) brand of mefloquine. However, generic doxycycline hyclate is only $0.25 per tablet compared with $4.51 for one brand of doxycycline monohydrate. The price for primaquine is based on two tablets of 15 mg base (26.3 mg salt) each. Likewise, hydroxychloroquine phosphate requires two 200-mg tablets daily for adults.

No terminal prophylaxis scenario. Table 2 and Figure 1 shows the relative cost of anti-malarial medications for various durations of exposure without terminal prophylaxis.Generic doxycycline is the least expensive regimen for each interval in a malarious zone, even considering that it must be taken for 28 days after leaving. This advantage is lost if the more expensive doxycycline monohydrate is used. In areas with chloroquine-sensitive malaria, generic chloroquine is the next most economic choice. Primaquine, even with testing for G6PD, is the third most economic choice up through 6 weeks of exposure. At 8 weeks of exposure, mefloquine, which is taken weekly, is more economical than primaquine, which is taken daily. Except for a short exposure of 3 days or less, atovaquone/proguanil is the most expensive regimen.

Terminal prophylaxis scenario. Because most malarious regions, other than the island of Hispaniola (Haiti and the Dominican Republic), have relapsing malaria, terminal prophylaxis may be warranted, especially for extended stays. When the cost of screening for G6PD and the cost of 14 days of primaquine are added to the cost of doxycycline, atovaquone/proguanil, mefloquine, or chloroquine, a different economic picture emerges (Table 3; Figure 2). Primaquine plus screening for G6PD is now the least expensive regimen for <10 days of exposure. Thereafter, generic doxycycline is the least expensive, even with the added cost of screening for G6PD and 14 days of primaquine. Atovaquone/proguanil remains the most expensive regimen, except for a 3-day visit. Terminal prophylaxis when adequate G6PD has previously been documented. For subsequent malaria exposures when screening for G6PD has already been accomplished, primaquine is the least expensive regimen for exposures <10 days (Table 4; Figure 3). Thereafter, doxycycline is the least expensive. For exposures up to ~19 weeks, primaquine is less expensive than mefloquine. For exposures <7 days, atovaquone/proguanil is less expensive than mefloquine. However, atovaquone/proguanil is the most expensive regimen for exposures of 7 days or more.

DISCUSSION

While several factors should be considered by the prescribing physician and the patient with regard to malaria prophylaxis, cost is often one major consideration. In some situations, the organization that is working in an area with malaria bears the cost of antimalarial medication for those it sends to these regions. Military, government agencies, World Bank,
Peace Corps, and non-profit organizations may provide medication for persons occupationally exposed to malaria. Organizations may provide required laboratory testing and the cost of care for any adverse events. Individual travelers may have a different perspective on voluntary travel. Some are interested in the least expensive regimen, whereas others opt for the most convenient regimen or a regimen based on side effect profiles.

For all durations of travel, generic doxycycline hyclate is one of the most economical regimens. However, if doxycycline monohydrate generic ($2.13 per 100-mg. tablet) is used, the cost is similar to that of mefloquine. In a recent study comparing doxycycline, atovaquone/proguanil, daily chloroquine/proguanil, and mefloquine, doxycycline monohydrate and atovaquone/proguanil were the best-tolerated regimens overall. Sun sensitivity and vaginal candidiasis are reported with tetracycline use, but in this study, rates of these side effects were no higher than other regimens. Like chloroquine and mefloquine, doxycycline has the drawback of requiring 4 weeks of therapy after potential exposure to suppress erythrocytic stages and has no activity against hypnozoites that may cause late-onset *P. vivax* or *P. ovale*.

Chloroquine is the next most economical regimen compared with doxycycline hyclate. However, its use is limited to areas with chloroquine-sensitive malaria. These are, however, areas where many people travel including Mexico, Central America, Hispaniola, northern Argentina, and areas of the Middle East. In these areas, chloroquine is the preferred drug because of its convenient once-weekly dosing. Hydroxychloroquine is an option for those who do not tolerate chloroquine phosphate and is somewhat less expensive than chloroquine phosphate ($3.78 versus $4.79–6.04 per dose). Terminal prophylaxis with primaquine may be desirable in these areas to decrease the risk of *P. vivax* or *P. ovale*.

Primaquine, after G6PD screening, is the third most economic regimen for exposures < 8 weeks. However, if terminal prophylaxis after screening for G6PD is provided after other regimens, primaquine is the most economical regimen for exposures of up to 9 days. For some organizations, such as the US military, US Foreign Service, and US Peace Corps, testing for G6PD is built in to the entrance physical and laboratory work. The US Army tests with a quantitative assay before administering primaquine (Memorandum dated Feb. 18, 2004). Testing for adequate G6PD can be done using a screening test that is simple and quick. Persons with a possible deficiency based on the screening test are further tested by a commercial laboratory that does quantitative testing at a reasonable cost. Results are placed in the patient’s medical record for easy availability. Therefore, for these organizations, pre-screening before use of 8-aminoquinoline drugs such as primaquine and tafenoquine (under development) for primary or terminal prophylaxis or radical cure of patients with relapsing malaria is built in to the system. The cost of screening for G6PD for individuals may be variable depending on the test done (qualitative versus quantitative) and the laboratory test pricing arrangements.

### Table 3

Cost of chemoprophylaxis if terminal prophylaxis is used for all regimens (except primaquine) using primaquine 30 mg base/day for 14 days at a cost of $28.98 after screening for G6PD ($25)

<table>
<thead>
<tr>
<th>Days of exposure</th>
<th>Doxycycline</th>
<th>Chloroquine</th>
<th>Mefloquine</th>
<th>Primaquine</th>
<th>Atovaquone/proguanil</th>
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### Table 4

Cost of malaria prophylaxis including terminal prophylaxis ($28.98) (except primaquine) for subsequent exposures after G6PD status is known

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<tr>
<th>Days of exposure</th>
<th>Doxycycline</th>
<th>Chloroquine</th>
<th>Mefloquine</th>
<th>Primaquine</th>
<th>Atovaquone/proguanil</th>
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<td>$3,697.25</td>
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</tbody>
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### Figure 1

Cost of anti-malarial medications by duration of malaria exposure without “terminal prophylaxis.”

### Figure 2

Cost of anti-malarials plus G6PD screening ($25) plus terminal prophylaxis with primaquine.
Screening for G6PD is especially important in men. As an X-linked gene, severe deficiency is fully expressed in men and is rare in women. The two types most commonly encountered in the United States are relatively mild G6PD<sup>−</sup> found in ∼16% of Afro-American men and the rare but more severe G6PD<sup>MED</sup> found in persons of Mediterranean descent.

Using primaquine for primary prophylaxis offers the advantage of eliminating the need for terminal prophylaxis. Primaquine is known to prevent the development of hypnozoites. Therefore, there is no need for terminal prophylaxis to prevent late onset, relapsing type malaria that comprise a large segment of civilian<sup>2,3</sup> and military<sup>6,9</sup> malaria. If primaquine is considered, it is better to begin prophylaxis with primaquine rather than switching to it later, because its main action is on liver stages rather than erythrocytic stages. Changing from mefloquine, doxycycline, or chloroquine to primaquine would require suppressive therapy of erythrocytic stages that may be patent before starting primaquine.

Mefloquine is moderate in cost, especially for longer-duration exposure. It is convenient, requiring once weekly administration only. Like chloroquine, it should be started up to 2 weeks before entering a malarious area and requires four weekly doses after leaving the malarious region to suppress erythrocytic stages of malaria. Neither chloroquine, doxycycline, nor mefloquine has effects on hypnozoites. These regimens therefore require co-administration of primaquine to prevent late-onset malaria in those with significant exposure to <i>P. vivax</i> or <i>P. ovale</i>. In general, mefloquine is well tolerated by most travelers despite the impression given by the lay press.<sup>10</sup> Women and those with lower body mass may experience more side effects than men.<sup>11</sup>

Atovaquone/proguanil is the most expensive regimen for preventing malaria over a long period of time. However, for periods of exposure up to 7 days, it compares favorably in cost to mefloquine. It is convenient, with a dosing regimen similar to primaquine (2 days before, each day during, and 7 days after leaving an area). It is approved for prevention of <i>P. falciparum</i> malaria only, although it is fairly effective against <i>P. vivax</i>.<sup>4</sup> The side effect profile is generally good, although serious side effects such as Stevens-Johnson syndrome have been reported.<sup>12</sup> Resistance has been reported.<sup>13</sup> Whether atovaquone/proguanil prevents the development of hypnozoites of <i>P. vivax</i> and <i>P. ovale</i> is unknown, and therefore, terminal prophylaxis with primaquine is recommended. Therapy of <i>P. vivax</i> or <i>P. ovale</i> malaria with atovaquone/proguanil must be accompanied by primaquine to prevent relapses. Use of atovaquone/proguanil for primary prophylaxis removes it from use as a convenient and effective treatment of proven or presumed malaria.

An approach proposed by some is to carry a standby treatment dose of atovaquone/proguanil. The cost of the 12-tablet treatment (four tablets per day for 3 days) is $59.16, equal in cost to a 3-day exposure. In other countries, a combination of lumefantrine and artesunate is marketed for standby therapy. This approach requires the patient to self-diagnose malaria using a rapid diagnostic kit or to rely on symptoms such as fever and chills. Neither of these approaches is sensitive or specific, with many false diagnoses of malaria.

This paper deals mainly with the direct costs of medication costs and laboratory screening. It does not consider the potential indirect costs of adverse events. Proper screening and education concerning G6PD deficiency, neuropsychiatric symptoms, sun sensitivity, and <i>Candida vaginitis</i>, psoriasis, and eczema, and other conditions may prevent well-known adverse events of primaquine, mefloquine, doxycycline, and chloroquine, respectively.<sup>14</sup>

When cost is a primary consideration, doxycycline hyclate or primaquine are two choices that should be considered. Both are well tolerated. Persons in the U.S. Armed Forces, Foreign Service, and Peace Corps are routinely tested for G6PD as part of the medical program. Atovaquone/proguanil is a reasonably economical and convenient choice for those exposed for 7 days or less. For exposures of a week or more, including long-term exposure, chloroquine (where malaria remains sensitive) or mefloquine is convenient, generally well tolerated, and cost-competitive compared with atovaquone/proguanil.

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