A quantitative approach to recommendations on malaria prophylaxis

M. PAPPAIOANOU,1 H. O. LOBEL,2 & C. C. CAMPBELL3

In order to develop recommendations for malaria prophylaxis, a quantitative method is needed to balance the risk of Plasmodium falciparum malaria infections against the toxicity of antimalarial drugs. Using decision analysis, we estimated the expected mortality associated with three alternative regimens of prophylactic drugs for visitors to three areas with different risks of infection with chloroquine-resistant P. falciparum. The model used took into account the risks of malaria and of adverse reactions to antimalarial drugs. Estimates of the parameters used in the analysis were based on observations made on U.S. travellers. Reducing the risk of malaria infection was found to have a far greater impact on lowering the expected mortality than that of increasing the chemoprophylactic efficacy of the drugs used, thereby emphasizing the need for travellers to use anti-mosquito measures in malarious areas. The analytical method described can be used to define optimal malaria prevention strategies.

A systematic, quantitative approach is needed to develop recommendations for the prevention of malaria in travellers. Such recommendations must balance the risk of malaria infections caused by Plasmodium falciparum against the toxicity of antimalarial drugs. In the past, malaria chemoprophylaxis was assumed to provide effective protection against the disease without serious risk. Thus, chemoprophylaxis was recommended to travellers regardless of their potential for exposure to malaria infection, thereby ensuring that all travellers would be adequately protected. This assumption that the recommended drugs effectively protected against the disease, that their use was not associated with risk of severe adverse reactions, and that most travellers would use the drugs as prescribed. Unfortunately, chloroquine, a drug with an established record of safety and efficacy (1), has become less effective because of the spread of chloroquine-resistant P. falciparum (CRPF), and several alternative drugs have become associated with serious side-effects (2–7). In addition, some travellers do not use antimalarial drugs (8).

Recently, information obtained from studies of the knowledge, attitudes, and practices of U.S. travellers towards malaria prophylaxis (9) made it possible to use quantitative methods (decision analysis (10, 11)) to evaluate and compare different outcomes associated with alternative chemoprophylaxis regimens. In a previous study (12) this method was used to analyze disparate data sets and provided estimates of the risk of a fatal malaria infection to individual travellers. Here, in contrast, we report the application of decision analysis to quantify the expected mortality from malaria among the population of U.S. travellers for each of three alternative chemoprophylaxis regimens under different conditions of risk of infection and levels of drug use.

METHODS

For a hypothetical cohort of U.S. travellers to areas with CRPF in East Africa, West Africa, and southeastern Asia, we calculated the expected mortality associated with each of the following three malaria chemoprophylaxis regimens: pyrimethamine/sulfadoxine+chloroquine (regimen A); chloroquine alone (regimen B); and mefloquine (regimen C). These regimens were selected because they represent a range of probable efficacy and toxicity.

Design of the decision tree

The decision tree (Fig. 1, Table 1) models event-related sequences of the following parameters: the proportion of travellers using no prophylaxis; the

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Fasudan* Use of trade names is for identification only and does not constitute endorsement by the Public Health Service or the U.S. Department of Health and Human Services.
proportion using various drugs with a chemoprophylactic regimen; the risk of death from adverse reactions to antimalarial drugs; the risk of infection with *Plasmodium falciparum*; the prophylactic efficacy of antimalarial drugs; and the case-fatality rate of *Plasmodium falciparum* infections in the USA.

Mortality rates for each branch, i.e., path, of the decision tree were determined from the product of the various proportions and rates along the individual branches. The expected number of deaths was calculated from the product of the mortality rate and the number of travellers to each area.

**Estimates and assumptions**

Estimates used in the analysis are derived from data from the U.S. National Malaria Surveillance System, traveller statistics, surveys of U.S travellers, investigations of adverse drug reactions, and drug efficacy trials.

**Rates of use of chemoprophylactic drugs (nodes 2–4).** In 1984, estimates of the proportions of U.S. travellers using various chemoprophylactic drugs were obtained from questionnaire surveys of individuals returning on direct flights to the USA from East and West Africa (9) and from rural areas of south-east Asia, i.e., Thailand, Malaysia, Indonesia, and the Philippines (H. O. Lobel, unpublished observations, 1985). More than 74% of all travellers spent less than 1 month abroad.

Of 1209 travellers surveyed from East Africa, 47% had used pyrimethamine/sulfadoxine + chloroquine regularly and 23% chloroquine alone; in contrast, 30% had used no chemoprophylaxis. Accordingly, the usage rate of chloroquine alone for regimens A and C was estimated as 25%, while that of pyrimethamine/sulfadoxine + chloroquine (regimen A) or of mefloquine (regimen C) was 50%. For regimen B, use of chloroquine alone was estimated to be 75%; 25% of travellers were assumed not to have used chemoprophylactic drugs for each of the three recommended regimens. Because the impact of risk of exposure on fatal outcomes in areas with CRPF could be assessed more readily if the same drug usage rates were used by travellers to different areas, the rates used for East Africa were also employed for the cohort of travellers to West Africa.

Of 1231 travellers surveyed from south-east Asia, 4% had used pyrimethamine/sulfadoxine + chloroquine and 4% chloroquine alone, while 92% had used no chemoprophylaxis. Accordingly, in the analysis, usage rates of 5% for pyrimethamine/sulfadoxine + chloroquine and 5% for chloroquine alone, were used, together with a non-usage rate of 90%.

**Mortality associated with drugs used for prophylaxis (node 13).** The risk of a fatal reaction associated with the prophylactic use of pyrimethamine/sulfadoxine has been estimated to range from 1 per 11 000 to 1 per 25 000 (3). To protect against underestimation of such fatalities in the analysis, we assumed

<table>
<thead>
<tr>
<th>Table 1. Estimated proportions and risks for various destinations and decision tree nodes for U.S travellers (see text for details)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proportion of travellers using:</strong></td>
</tr>
<tr>
<td><strong>Node</strong></td>
</tr>
<tr>
<td>No prophylaxis</td>
</tr>
<tr>
<td>Chloroquine alone</td>
</tr>
<tr>
<td>3, 4</td>
</tr>
<tr>
<td>Pyrimethamine/sulfadoxine + chloroquine</td>
</tr>
<tr>
<td>Mefloquine</td>
</tr>
<tr>
<td><strong>Risk of:</strong></td>
</tr>
<tr>
<td>Death from reaction to pyrimethamine/sulfadoxine</td>
</tr>
<tr>
<td>Infection with <em>Plasmodium falciparum</em></td>
</tr>
<tr>
<td><strong>Probability of prophylaxis failure of:</strong></td>
</tr>
<tr>
<td>Chloroquine alone</td>
</tr>
<tr>
<td>Pyrimethamine/sulfadoxine + chloroquine</td>
</tr>
<tr>
<td>Mefloquine</td>
</tr>
<tr>
<td>Case-fatality rate</td>
</tr>
</tbody>
</table>

* Figures in this column refer to the corresponding node in Fig. 1.
Efficacy of chloroquine, pyrimethamine/sulfadoxine, and mefloquine in preventing Plasmodium falciparum malaria (nodes 18–20). The efficacy of malaria prophylactic regimens for non-immune U.S. travellers depends on: the risk of exposure to the malaria parasite; the prevalence of drug-resistant P. falciparum in an area; and the usage level of prophylaxis. Direct estimates of prophylactic efficacy are not available for most areas. Consequently, the probable prophylactic efficacy is generally derived from therapeutic efficacy trials (7). Results of in vivo studies of chloroquine sensitivity in East and West Africa, and south-east Asia provided estimates of the relative efficacy of chloroquine and pyrimethamine/sulfadoxine against CRPF infections (2, 14, 15). Among chloroquine users, 40% of malaria infections acquired in East Africa were presumed to be resistant to this drug, as were 10% in West Africa and 80% in south-east Asia. The proportion of infections resistant to the combination pyrimethamine/sulfadoxine + chloroquine among travellers taking these drugs for prophylaxis was presumed to be 5% in East and West Africa and 80% in south-east Asia. In comparison, 1% of infections were presumed to be resistant to mefloquine.

Case-fatality rates (nodes 21–24). The case-fatality rate observed in reported P. falciparum infections in U.S citizens is 4% (16). Although reporting of malaria-related deaths is almost complete in the USA, only 50% of non-fatal cases are reported (H. O. Lobel, unpublished observations, 1986). An adjusted case-fatality rate of 2% was therefore used to account for under-reporting of cases.

Numbers of travellers. Each year approximately 50 000 U.S. citizens travel to East Africa and 25 000 to West Africa. Accordingly, we used hypothetical cohorts of 50 000 travellers to East and West Africa to facilitate comparability of results. In contrast, an estimated 400 000 U.S citizens travel annually to south-east Asia (17).

Sensitivity analysis

Sensitivity analysis involves systematically changing the values assigned to one or more variables in the decision tree and calculating the outcome produced (11). In this way, the effects of different risks of infection and drug usage rates on the expected mortality for different levels of CRPF prevalence were estimated by varying the rates and calculating the outcome. The number of deaths associated with the three regimens was obtained for two levels of risk of infection (1% and 4%), two rates of non-use of prophylaxis (10% and 25%), and four rates of prevalence of CRPF (10%, 40%, 80%, and 100%).
Validation of results

The results for regimens A and B in East Africa were compared with reported malaria- and drug-related fatalities among U.S. travellers to this area in 1984 and 1986, when use of regimens A and B, respectively, had been recommended (17, 18).

RESULTS

East Africa

On the basis of the estimated risks and proportions used in the calculations, 6.25 deaths per year would be expected per 50,000 travellers to East Africa for a chemoprophylaxis regimen that includes the concurrent use of pyrimethamine/sulfadoxine + chloroquine (Table 2, regimen A). Of these deaths, adverse reactions to pyrimethamine/sulfadoxine would account for 2.5 deaths and malaria for the remainder. Regimen B (chloroquine alone) would result in 5.5 deaths, an increase in malaria-related mortality relative to that of regimen A, but a decrease in the number of deaths overall. Regimen C (mefloquine) was associated with the fewest deaths (3.55).

West Africa

Results showed that regimen A (pyrimethamine/sulfadoxine + chloroquine) would be expected to result in 14.5 deaths, of which 2.5 would arise from adverse reactions to pyrimethamine/sulfadoxine and the remainder from malaria (Table 2). Regimens B (chloroquine alone) and C (mefloquine) would result in 13.0 and 11.2 malaria-related deaths, respectively. In West Africa, despite a lower prevalence of CRPF (10%), the 4% risk of infection would be expected to result in 2-3 times more deaths than that calculated for East Africa for all three regimens.

South-east Asia

For south-east Asia, the risk of a P. falciparum infection is low because most travellers visit only urban areas. Despite a large number of U.S. visitors to the region and presumptive high levels of drug-resistant P. falciparum parasites, the three regimens would be associated with fewer than one malaria-related death per annum (Table 3). If it is assumed that 5% of travellers use pyrimethamine/sulfadoxine + chloroquine for prophylaxis, 2 deaths per 400,000 travellers per annum would be expected from adverse reactions to pyrimethamine/sulfadoxine.

Sensitivity analysis

Changes in the risk of infection had the greatest impact on expected mortality for all three regimens (Table 4). As shown in the table, an increase in risk of infection from 1% to 4% would result in a two- to fourfold increase in the expected mortality within each level of CRPF prevalence. For example, with a

Table 2. Expected number of deaths per annum for a hypothetical cohort of 50,000 short-term* U.S. travellers to East and West Africa, by rates of drug usage for three prophylaxis regimens

<table>
<thead>
<tr>
<th></th>
<th>Regimen A</th>
<th>Regimen B</th>
<th>Regimen C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>East Africa</td>
<td>West Africa</td>
<td>East Africa</td>
</tr>
<tr>
<td>Estimated prevalence of chloroquine-resistant Plasmodium falciparum</td>
<td>40%</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>Travellers with malaria:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prophylaxis taken</td>
<td>2.50</td>
<td>10.00</td>
<td>2.50</td>
</tr>
<tr>
<td>Chloroquine failure</td>
<td>1.00</td>
<td>1.00</td>
<td>3.00</td>
</tr>
<tr>
<td>Pyrimethamine/sulfadoxine + chloroquine failure</td>
<td>0.25</td>
<td>1.00</td>
<td>—</td>
</tr>
<tr>
<td>Mefloquine failure</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No. of deaths from malaria</td>
<td>3.75</td>
<td>12.00</td>
<td>5.50</td>
</tr>
<tr>
<td>No. of fatal adverse reactions to pyrimethamine/sulfadoxine</td>
<td>2.50</td>
<td>2.50</td>
<td>—</td>
</tr>
<tr>
<td>Total number of deaths expected</td>
<td>6.25</td>
<td>14.50</td>
<td>5.50</td>
</tr>
</tbody>
</table>

* Travel to an area for <3 weeks
* Usage levels: pyrimethamine/sulfadoxine + chloroquine (50%), chloroquine (25%), no prophylaxis (25%)
* Usage levels: chloroquine (75%), no prophylaxis (25%).
* Usage levels: mefloquine (50%), chloroquine (25%), no prophylaxis (25%).
Table 3. Expected number of deaths* per annum for a hypothetical cohort of 400,000 short-term U.S. travellers to south-east Asia, by rates of drug usage for three prophylaxis regimens

<table>
<thead>
<tr>
<th>Regimen A</th>
<th>Regimen B</th>
<th>Regimen C</th>
</tr>
</thead>
<tbody>
<tr>
<td>No prophylaxis taken</td>
<td>0.072</td>
<td>0.072</td>
</tr>
<tr>
<td>Chloroquine failure</td>
<td>0.003</td>
<td>0.006</td>
</tr>
<tr>
<td>Pyrimethamine/sulfadoxine failure</td>
<td>0.003</td>
<td>—</td>
</tr>
<tr>
<td>Mefloquine failure</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>No. of deaths from malaria</td>
<td>0.078</td>
<td>0.078</td>
</tr>
<tr>
<td>No. of fatal adverse reactions to pyrimethamine/sulfadoxine</td>
<td>2.000</td>
<td>—</td>
</tr>
<tr>
<td>Total number of deaths expected</td>
<td>2.078</td>
<td>0.078</td>
</tr>
</tbody>
</table>

* Calculated assuming 80% failure of chloroquine to prevent Plasmodium falciparum malaria.

Validation of results

Malaria surveillance carried out by the Centers for Disease Control (CDC) documented eight deaths among U.S. civilians in 1984 from *P. falciparum* infections (19), for which year CDC had advised use of regimen A for malaria prophylaxis. Three of the deaths occurred among travellers to East Africa (3.75 deaths expected; Table 1). Of these, one had taken no prophylactic drugs (2.5 deaths expected); one had taken chloroquine alone (1.0 death expected); and one had an unknown prophylaxis history. In addition, two travellers from East Africa died in 1984 from adverse reactions to pyrimethamine/sulfadoxine (2.50 deaths expected) ($\chi^2$ test for goodness of fit, 2 degrees of freedom, $P>0.2$, not significant).

In 1986, when regimen B was advised, three U.S. citizens died from *P. falciparum* infections acquired in East Africa (5.50 deaths expected). Of these, two had taken chloroquine alone (3.00 deaths expected), while one had used no prophylaxis (2.50 deaths expected) ($\chi^2$ test for goodness of fit, $P>0.2$, not significant). No deaths were associated with adverse reactions to pyrimethamine/sulfadoxine (no deaths expected).

DISCUSSION

Since no available drug for malaria chemosuppression is both totally safe and effective (7), efforts to improve the prospects for prophylaxis have focused on developing new antimalarials that are both effective and safe. An important and unexpected finding of our analysis is that the impact of the risk of infection on expected mortality is much greater than that of chemoprophylaxis. The differences in expected mortality between East and West Africa and between Africa and south-east Asia indicate that reducing the risk of infection is potentially the best option for minimizing the total number of expected deaths from malaria. This might be accomplished by the regular use of protective clothing, insect repellents, and bed nets. However, in order to promote the appropriate and widespread employment of such measures their use would have to be incorporated into established prophylaxis recommendations.

Our analysis also demonstrated the relative protective efficacy of the combination pyrimethamine/sulfadoxine against malaria-related mortality in areas with CRPF; unfortunately, this effect was offset by deaths caused by adverse reactions.
Table 4. Expected number of deaths in a hypothetical cohort of 50,000 travellers, by regimen, risk of falciparum malaria, rate of non-usage of drugs, and prevalence of chloroquine-resistant *Plasmodium falciparum* (CRPF)*

<table>
<thead>
<tr>
<th>Risk of infection</th>
<th>Prevalence of non-use of drugs</th>
<th>Prevalence of CRPF</th>
<th>Expected malaria deaths in non-users</th>
<th>Regimen A</th>
<th>Regimen B</th>
<th>Regimen C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pyrimethamine/sulfadoxine + chloroquine</td>
<td>Chloroquine</td>
<td>Total</td>
<td>Chloroquine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(b)</td>
<td>(b)</td>
</tr>
<tr>
<td>1%</td>
<td>10</td>
<td>2.5</td>
<td>0.25</td>
<td>0.25</td>
<td>5.50</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
<td>0.25</td>
<td>1.00</td>
<td>6.25</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td></td>
<td>0.25</td>
<td>2.00</td>
<td>7.25</td>
<td>6.00</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td></td>
<td>0.25</td>
<td>2.50</td>
<td>7.75</td>
<td>7.50</td>
</tr>
<tr>
<td>10%</td>
<td>10</td>
<td>1.0</td>
<td>0.25</td>
<td>0.40</td>
<td>4.15</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
<td>0.25</td>
<td>1.60</td>
<td>5.35</td>
<td>3.60</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td></td>
<td>0.25</td>
<td>3.20</td>
<td>7.00</td>
<td>7.20</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td></td>
<td>0.25</td>
<td>4.00</td>
<td>7.75</td>
<td>9.00</td>
</tr>
<tr>
<td>4%</td>
<td>10</td>
<td>10.0</td>
<td>1.00</td>
<td>1.00</td>
<td>14.50</td>
<td>3.00</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
<td>1.00</td>
<td>4.00</td>
<td>17.50</td>
<td>12.00</td>
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<tr>
<td></td>
<td>80</td>
<td></td>
<td>1.00</td>
<td>8.00</td>
<td>21.50</td>
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<td></td>
<td>100</td>
<td></td>
<td>1.00</td>
<td>10.00</td>
<td>23.50</td>
<td>30.00</td>
</tr>
<tr>
<td>25%</td>
<td>10</td>
<td>1.0</td>
<td>1.00</td>
<td>1.60</td>
<td>9.10</td>
<td>3.60</td>
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<td></td>
<td>40</td>
<td></td>
<td>1.00</td>
<td>6.40</td>
<td>13.90</td>
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<td></td>
<td>80</td>
<td></td>
<td>1.00</td>
<td>12.80</td>
<td>20.30</td>
<td>28.80</td>
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<tr>
<td></td>
<td>100</td>
<td></td>
<td>1.00</td>
<td>16.00</td>
<td>23.50</td>
<td>36.00</td>
</tr>
</tbody>
</table>

* The following prophylaxis probabilities were held constant: efficacy of pyrimethamine/sulfadoxine + chloroquine = 95%; efficacy of mefloquine = 99%. Case-fatality rate = 2%.

* Includes death among non-users, malaria-related deaths, and 2.5 deaths associated with adverse reactions to pyrimethamine/sulfadoxine.

* The rates of drug usage assumed were as follows: Regimen A: pyrimethamine/sulfadoxine + chloroquine (50%), chloroquine alone (25%). Regimen B: chloroquine (75%). Regimen C: mefloquine (50%), chloroquine (25%).

* The rates of drug usage assumed were as follows: Regimen A: pyrimethamine/sulfadoxine + chloroquine (50%), chloroquine (40%). Regimen B: chloroquine (90%). Regimen C: mefloquine (50%), chloroquine (40%).
actions to pyrimethamine/sulfadoxine. For low
prevalences of CRPF, fewer deaths are expected with
regimen B (chloroquine alone) than with regimen A
(pyrimethamine/sulfadoxine + chloroquine). In con-
tast, when the prevalence of CRPF approaches
100% the use of regimen B would be expected to
result in more deaths than that of regimen A. Meflo-
quine offered the best chemoprophylactic option for
minimizing malaria- and drug-related fatalities for
travellers visiting areas with CRPF; however, use of
this drug is not yet widespread and the risk of its
associated adverse reactions is not fully known.
Furthermore, despite its high level of prophylactic
efficacy, the number of expected deaths under con-
tions of intense transmission, such as in West
Africa, remained high.

In addition to mortality, morbidity from malaria
and adverse drug reactions are also important out-
comes to be taken into consideration in assessing
optimal chemoprophylaxis regimens. In further cal-
culations, we incorporated into the decision tree
a 0.05% risk of a non-fatal adverse reaction that
required hospitalization in persons taking pyrimetha-
mine/sulfadoxine + chloroquine, chloroquine, or
mefloquine (R. Steffen, personal communication,
1987). The results obtained showed that the number
of travellers expected to be affected by drug- and
malaria-related morbidity combined did not differ
substantially for the three regimens. Because of
under-reporting of both malarial infections and non-
fatal reactions to drugs as well as of differences in
severity of malaria infections and severe drug re-
actions, data for morbidity were considered to be less
precise than those for mortality. Incorporating the
risk of morbidity into the decision tree did not facili-
tate defining the optimal prophylaxis regimen, and
mortality alone was therefore chosen as the outcome
to be studied. Furthermore, there is reasonable cer-
tainty that all malaria-related deaths among U.S.
travellers are detected through the CDC malaria sur-
veillance system and that all deaths associated with
the prophylactic use of pyrimethamine/sulfadoxine
for 1984–86 were identified (3)—criteria that are
important for validating the results of the analysis.
The financial cost of malaria infections and adverse
drug reactions are also important, quantitatively
calculable outcome variables that could be evaluated
in future studies.

The impact on expected mortality associated with
changes in drug usage rates and risks of infection for
various levels of CRPF prevalence was determined in
the sensitivity analysis. Changes in the case-fatality
rate also influence mortality; such changes were not
included in the analysis, however, because the case-
fatality rate is independent of the use of chemop-
 prophylaxis. The risk of infection, and the level of
CRPF.

Decision analysis is therefore a valuable method of
integrating into a systematic evaluation process the
multiple factors that affect the risks of malaria-related
morbidity and mortality among U.S. travellers and
provides a rational basis for developing optimal
recommendations for prevention of malaria among
such individuals.

RÉSUMÉ

RECOMMANDATIONS RELATIVES À LA PROPHYLAXIE
DU PALUDISME. APPROCHE QUANTITATIVE

On a rapporté dans cet article les résultats d’une étude
dans laquelle on a utilisé des méthodes d’analyse décision-
nelle pour quantifier la mortalité prévisible chez les
voyageurs des États-Unis, dans diverses conditions de
risque d’infestation et d’importance de la prophylaxie
employée, pour trois schémas chimio prophylactiques: Fan-
sider et chloroquine (schéma A); chloroquine seule (schéma
B); et méfloquine (schéma C). Autrefois, on pensait que la
chimio prophylaxie du paludisme procurait une protection
efficace contre le paludisme, sans risque important. Mal-
heureusement, la chloroquine, une substance dont l’inno-
cuité et l’efficacité sont bien établies, a perdu de son intérêt
en raison de l’extension des P. falciparum chloroquino-
résistants. En outre, plusieurs autres médicaments ont été
associés à des effets secondaires potentiellement mortels.
Aussi les recommandations en matière de chimio prophylaxie
formulées par les autorités sanitaires à l’intention des
voyageurs doivent-elles tenir compte de la proportion
de voyageurs qui emploient les médicaments recommandés,
de la toxicité de ces médicaments, du risque d’infestation
par P. falciparum. de l’efficacité prophylactique de ces
substances et du taux de létalité des infestations à
P. falciparum.

Un arbre décisionnel figurant les séquences événemen-
tielles de ces paramètres a été analysé dans trois régions:
Afrique orientale, Afrique occidentale et Asie du Sud-Est.
On a calculé pour chaque branche de l’arbre des taux de
mortalité en faisant le produit des diverses proportions et
taux figurant le long de ces branches. Le nombre prévisible
de décès a été obtenu en faisant le produit du taux de mor-
talité par le nombre de voyageurs se rendant dans chaque
région. Les résultats sont basés sur des cohortes hypothé-
tiques de 50 000 voyageurs pour les modèles d’Afrique
orientale et occidentale, de 400 000 voyageurs pour le
modèle de l'Asie du Sud-Est, et l'on a pris les risques estimés et les proportions qui suivent pour les autres paramètres inclus dans ces modèles: a) une proportion de 25% de voyageurs n'employant pas de prophylaxie en Afrique orientale et occidentale et de 90% en Asie du Sud-Est; b) une proportion de voyageurs prenant soit l'association Fanimation-chloroquine (schéma A), soit la méfloquine seule (schéma C) de 50% en Afrique orientale et occidentale et de 5% en Asie du Sud-Est; c) une proportion de voyageurs ne prenant que de la chloroquine de 25% (schéma A ou C) ou de 75% (schéma B) en Afrique orientale et occidentale, et de 5% (schéma A ou C) ou de 10% (schéma B) en Asie du Sud-Est; d) un risque d'infestation par P. falciparum de 1% en Afrique orientale, de 4% en Afrique occidentale et de 0,001% en Asie du Sud-Est; e) un taux d'échec de la prophylaxie par la chloroquine de 40% en Afrique orientale, de 10% en Afrique occidentale et de 80% en Asie du Sud-Est; et f) un taux d'échec de la prophylaxie par le Fansionid et la chloroquine de 5% en Afrique orientale et occidentale et de 80% en Asie du Sud-Est. On a supposé dans les trois modèles un risque de décès provoqué par une réaction indésirable au Fansionid de 0,01%, un taux de fatalité du paludisme à falciparum de 2% et un taux d'échec de la prophylaxie par la méfloquine de 1%.

Dans le modèle d'Afrique orientale, on peut s'attendre à 6,25 décès par an (y compris 2,5 décès liés au Fansionid) pour 50 000 voyageurs ayant suivi le schéma chimiprophylactique Fansionid-chloroquine; à 5,5 décès avec une prophylaxie par la chloroquine seule, et à 3,55 décès avec une prophylaxie par la méfloquine. Dans le modèle d'Afrique occidentale, on peut s'attendre à 14,5 décès avec le schéma Fansionid-chloroquine, à 13,0 décès avec la chloroquine seule et à 11,2 décès avec la méfloquine. Dans le modèle de l'Asie du Sud-Est, on peut s'attendre à moins d'1 décès lié au paludisme et à 2 décès liés au Fansionid par an pour 400 000 voyageurs utilisant Fansionid+chloroquine, et à moins d'1 décès avec la chloroquine seule ou la méfloquine.

On a estimé les effets de chaque paramètre sur la mortalité prévisible en la recalculant après avoir fait varier les estimations. C'est la modification du risque d'infestation, le faisant passer de 4% à 1%, qui a eu le plus d'impact dans tous les cas, divisant par 2 à 4 la mortalité attendue pour les divers degrés de chloroquinorésistance. Ces résultats laissent à penser qu'une utilisation généralisée de mesures anti-moustiques appropriées pourrait constituer le meilleur moyen d'obtenir une diminution globale de la mortalité.

REFERENCES