Factors Influencing the Pattern of Imported Malaria

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Background: Data on imported malaria in industrialized areas are known to be incomplete because of underreporting and lack of homogeneity. These facts and the complexity of factors influencing the transmission of malaria render their interpretation difficult. The relevance of various factors is usually not fully considered, although their impact on recommendations for chemoprophylaxis may be important.

Methods: All malaria cases imported from Kenya from 1988 to 1996 that were reported to the Federal Office of Public Health of Switzerland were analyzed. The reciprocal impact on data interpretation with regard to *Plasmodium* species, chemoprophylaxis, onset of first symptoms after return, male or female sex, seasonal fluctuation, duration of stay, nationality groups, and fatal outcome was analyzed.

Results: Multivariate analysis showed a significant impact of *Plasmodium* species, regular chemoprophylaxis, and long duration of stay on the latency of malaria attacks. African origin and repeated stays were confounders with regard to adherence to chemoprophylaxis. The local situation of malaria transmission and the development of tourist figures were found to influence the evolution of malaria rates. These factors must be analyzed simultaneously to prevent errors in data interpretation. A higher proportion of *tertian* malaria cases (caused by *Plasmodium vivax* or *Plasmodium ovale*) than in previous reports was recorded owing to the impact of chemoprophylaxis and longer outbreak latencies. Seventy-five percent of tertian malaria cases were diagnosed within 6 months after return.

Conclusions: Factors influencing the pattern of imported malaria must be assessed in relation to each other, especially if data from different countries and various chemoprophylaxis regimens are compared. Furthermore, regular malaria chemoprophylaxis with mefloquine given until 4 weeks after return from an endemic area is not adequate to prevent tertian malaria. Regular chemoprophylaxis was found to cause longer latencies for all malaria species.

With the spectacular growth in tourism worldwide, imported malaria and the associated case fatality rates remain a public health problem in industrialized countries. Travel medicine specialists try to reduce the risk for travelers by recommending antimosquito measures and drugs against malaria. Unfortunately, there is not yet worldwide consensus on the respective drug regimens. Furthermore, it is difficult to analyze the impact of chemoprophylaxis on imported malaria rates because of the complexity of influencing factors and because data of imported malaria are often based on crude epidemiologic figures. Muentener and colleagues demonstrated the heterogeneity of available data from various countries. Nevertheless, public health specialists use such data to compare trends and interpret the influence of various recommended chemoprophylaxis regimens on the basis of these figures.[1] Only a few case-controlled studies are available on the impact of chemoprophylaxis on imported malaria.[2,3] Other factors are known to influence the rates of imported malaria, but their respective importance is often marginally considered. In this context we analyzed the factors influencing the pattern of imported malaria and the impact they had on data interpretation. In Switzerland substantial data sets are collected by the Federal Office of Public Health relying on the federal mandatory declaration of malaria. The reporting system was optimized in 1988 by making the declaration mandatory for both medical doctors and laboratories, thus providing a double control (see <www.bag.admin.ch/infreporting/forms/f>).[4] Nevertheless, the underreporting is still estimated to be between 30 and 50%.

Using this data set, we analyzed all imported malaria cases from Kenya for the following reasons: (1) up to 50% of all declared malaria cases in Switzerland from 1988 to 1996 were imported from Kenya, one of the leading destinations of Swiss travelers[1,5,6]; (2) most of these travelers were tourists mainly visiting the coastal areas where malaria is holoendemic; (3) chemoprophylaxis is highly recommended for trips to these areas; (4) chemoprophylaxis recommendations by the Federal Office of Public Health were reviewed in 1988, and the declaration system for infectious diseases including malaria was optimized that same year. The recommendation of first choice was mefloquine; alternatively, sulfadoxine-pyrimethamine or chloroquine plus proguanil could be used. After 1994 sulfadoxine-pyrimethamine was no longer recommended for prophylactic use.

As the recommendations remained stable over the following 9 years, the profile of travelers was homogeneous,

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and the epidemiologic impact of the imported malaria cases from Kenya was important, we carried out a retrospective study on all reported malaria cases from Kenya to Switzerland from 1988 to 1996. We compared our data with that pertaining to tourists recorded by the World Tourism Organization (WTO) and data provided by the Kenyan General Consulate (tourist figures vs issued visas) to estimate malaria rates among Swiss travelers. These results were concordant. Further, we analyzed the collected data with regard to the origins of patients and their behavior concerning chemoprophylaxis and other protective measures. We also analyzed the species of *Plasmodium* involved and the pattern of illness, with a special regard to the latency period between the patients' return to Switzerland and the outbreak of disease.

Study Population and Methods

Imported malaria cases from Kenya reported to the Swiss Federal Office of Public Health from 1988 to 1996 were reviewed, analyzing all declaration forms. One case that had not been confirmed microscopically and one case of relapsing tertian malaria without new exposure were excluded.

The attribution of the chemoprophylaxis groups was done according to the physicians' information provided on a complementary declaration form, which was filled in either at the time of case declaration or after being recalled to do so by the Federal Office of Public Health. The cases were attributed to four groups according to whether they followed no, irregular, regular, or unknown chemoprophylaxis regimens. The cases with drug intake from 1 week before departure until 4 weeks after returning were attributed to the group with regular chemoprophylaxis. Cases with delayed, prematurely disrupted, or irregular drug intake were attributed to the group with irregular chemoprophylaxis. When the information about the chemoprophylaxis regimen was missing, the case was attributed to the group with unknown chemoprophylaxis. The various chemoprophylaxis regimens were grouped together because of the small numbers.

Cases were assigned to four groups according to duration of stay in Kenya. Cases involving a stay of > 5 weeks were attributed to the group with long stay duration. Those cases involving stays of 5 weeks or less were attributed to the group with short stay duration. All cases of patients who reported more than one stay were attributed to the group of repeated stays. The cases for which information about the duration of stay was missing were attributed to the group with unknown duration of stay.

Imported malaria rates among Swiss residents traveling to Kenya were calculated from the number of declared malaria cases from Kenya and corresponding figures of registered arrivals from Switzerland to Kenya provided by the WTO. These calculations were compared with the figures obtained using as the denominator the number of visas delivered by the General Consulate of Kenya in Zurich. The results did not differ significantly. For calculations of seasonal rates, only the figures from 1990 to 1992 were available.

To assess the impact of the various factors on latencies (beginning of symptoms after return, diagnosis after return, time between beginning of symptoms and diagnosis), a multivariate analysis was performed. Using the general linear model (GLM) procedure of the Statistical Analysis System (SAS) package, the latencies were regressed on various combinations of the available explanatory variables in the creation of a parsimonious model that adequately described the data.[7] A Box-Cox transformation of these dependent variables was used to better satisfy the underlying distributional assumptions concerning the error terms.[8] Model fit was assessed in terms of changes in the error sum of squares. Individual terms were assessed by means of the likelihood that the observed value had arisen by chance alone (the p value) and the absolute value of the associated regression coefficient.

Groups were compared using the chi-square and Wilcoxon/Kruskal-Wallis tests of the Epi-info 6.0 program.

Results

The total number of included cases was 315. The demographic breakdown is given in Table 1. Most reported cases involved Swiss citizens, but a growing proportion of malaria cases among people with African origin was recorded over the years. Almost three-quarters of all cases were falciparum malaria; 16% were tertian malaria cases (caused by *Plasmodium vivax* or *Plasmodium ovale*). An overview of chemoprophylaxis drugs is given in Figure 1.

Species

The comparison of the cases of malaria caused by different species showed that patients with tertian malaria had taken regular chemoprophylaxis more often than did patients with falciparum malaria ($p < .001$). Further analysis showed that the tertian malaria group had taken mefloquine more often than did the falciparum group ($p < .007$). There was no statistically significant difference in frequency of the causing species for other chemoprophylaxis drugs. The onset of first symptoms after return occurred later in the patients with tertian malaria than in those with falciparum malaria; the median time was 138 days versus 6 days ($p < 1 \times 10^{-6}$). There was a significant difference in the time between the first symptoms and diagnosis; however, this difference disappeared

when the species groups with the same chemoprophylaxis regimen were compared. The species itself caused no delay in diagnosis.

Chemoprophylaxis

The analysis of the different chemoprophylaxis groups showed that most of the patients who had taken no chemoprophylaxis also had not applied mosquito protection. However, those patients who reported a regular chemoprophylaxis drug intake applied regular or intermittent mosquito protection. Fifty-nine percent of the patients of European nationality with falciparum malaria who had taken regular chemoprophylaxis were hospitalized versus 76% of those who had not taken any chemoprophylaxis ($p = .028$).

Ten deaths were reported. There was no death reported in the group with regular chemoprophylaxis. Two patients who died had taken irregular chemoprophylaxis.

In the group with regular chemoprophylaxis, all latencies were delayed compared with the groups with irregular or missing chemoprophylaxis (Figure 2). The longest latencies (up to 5.5 yr) were found in the group with tertian malaria who had taken regular chemoprophylaxis. The latencies of tertian and falciparum malaria are shown in Figures 3 and 4, respectively. The patient with a latency of 6 months in the falciparum group without chemoprophylaxis had taken antimalarial self-medication. Latencies were longer in the tertian malaria group with regular chemoprophylaxis than in the group without chemoprophylaxis, but not all differences were statistically significant because of the small number of cases ($n = 40$).

Table 1 Demographic Data of Study Group

Characteristic	n *(%)*
Sex	
Male	184 (58)
Female	131 (42)
Nationality	
Swiss	222 (71)
Other European	33 (10)
African	47 (15)
Other	13 (4)
Duration of stay	
Short	101 (32)
Long (> 5 wk)	31 (10)
Repeated trips	51 (16)
Unknown	132 (42)
Species of transmission	
Plasmodium falciparum	227 (72)
Plasmodium vivax or *ovale*	51 (16)
Plasmodium malariae	10 (3)
Unspecified	27 (9)
Mosquito protection	
Regular	44 (14)
Partial	53 (17)
None	125 (40)
Unknown	93 (30)
Chemoprophylaxis	
Regular	93 (30)
Irregular	58 (18)
None	150 (48)
Unknown	14 (4)

Impact of Chemoprophylaxis on the European-Falciparum Group

The median onset of first symptoms after return was 4.5 days in the European patients with falciparum malaria without chemoprophylaxis versus 13 days in the group with regular chemoprophylaxis ($p = .004$). We calculated this latency only for 40% of the cases because the exact date of return from Kenya was often missing. The latency between the onset of symptoms and diagnosis could be calculated for 80% of the declared cases. It was significantly shorter in the group without chemoprophylaxis, with a median time of 3 days versus 8 days in the group with regular chemoprophylaxis ($p < .002$).

These results were confirmed with the analysis of the latency between return and diagnosis. In the European patients with falciparum malaria without chemoprophylaxis, the median time between return and diagnosis was 9 days versus 20 days in the group with regular chemoprophylaxis ($p < .0002$); 50% of the reported cases could be analyzed for this latency. Sixty-three percent ($n = 17$) of falciparum cases in the European group with regular chemoprophylaxis were diagnosed in the first month after return from Kenya, while patients were still taking their chemoprophylaxis.

The latencies appeared to be longer in the patients who had taken mefloquine, but the figures were too small to reach statistical significance. In our study population,

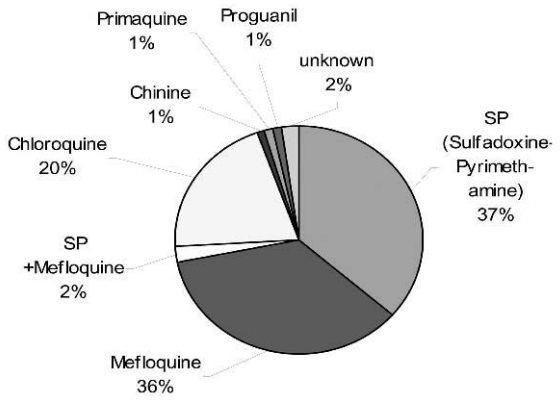

Figure 1 Chemoprophylactic drugs that were taken regularly ($n = 93$). Note: Four patients who took chloroquine plus proguanil have been included in the chloroquine group.

the longest delay of falciparum malaria symptom onset was 10 months after return to Switzerland; this patient had taken mefloquine regularly.

The analysis showed an earlier onset of symptoms among women with tertian malaria regardless of whether they had taken chemoprophylaxis. The median value of onset of symptoms after return was 175 days in men versus 77 days in women ($p = .026$). The number of analyzed cases was small (27). This difference was not found in the falciparum malaria group. There was no other impact of sex on the analyzed data.

Seasonal Fluctuation

The reported cases showed a bimodal peak for the falciparum cases, following the rainy seasons in October to November (discontinuous rainfalls) and March to June (daily rains). Most Swiss tourists traveled to Kenya from November to March and in July. The distribution of tertian malaria cases was spread more homogeneously throughout the year. Using the traveler numbers provided by the WTO and the General Consulate of Kenya in Zurich as the denominator and the diagnosed falciparum malaria cases as the numerator, we calculated yearly malaria rates of 4.0 to 11.6 in 10,000. Calculating the monthly figures we found seasonal fluctuations with rates up to 44.8 in 10,000 (Figure 5).

Duration of Stay

The analysis of durations of stay showed that the patients with repeated trips to Kenya failed to take chemoprophylaxis more often than did those with only one short or long stay ($p < .001$). They also did not apply mosquito protection more often ($p = .02$). Among the falciparum cases without chemoprophylaxis, the median time of onset of first symptoms after return to Switzerland was 2 days in the group with long stays versus 7 days in the group with short stays ($p = .006$). There was no difference between the groups with regular chemoprophylaxis. Regression analysis confirmed a negative influence of long stays on the onset of symptoms after return ($p < .02$) for the falciparum cases without chemoprophylaxis, and no effect ($p > .1$) for those with regular chemoprophylaxis.

There was a higher proportion of patients of African origin, particularly African children, in the group with repeated stays. The difference in the use of malaria prevention measures was found in both the African and European groups with repeated trips.

Nationality

The analysis of nationality groups showed that African patients reported intake of standby medication (antimalarial drugs or various antibiotics) in Kenya more often than did Europeans ($p < .001$). The latencies of first symptoms and diagnosis after return were significantly shorter ($p < .03$) in the African versus the European groups. These differences became nonsignificant when the results were corrected for species and chemoprophylaxis regimens.

Fatal Cases

In this group of fatal cases, six patients had taken no chemoprophylaxis, two patients had taken irregular chemoprophylaxis, and for two patients the information was missing. The median time between diagnosis and death was 8 days. There was no statistically significant difference in age between the patients with falciparum

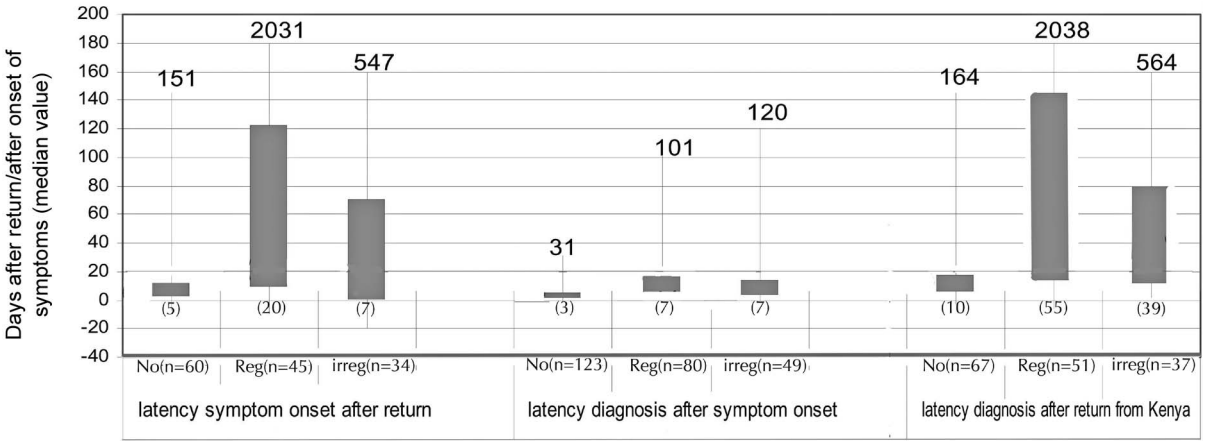

Figure 2 Comparison of latencies in cases with no, regular, and irregular chemoprophylaxis. The bar shows the distribution of cumulative cases within a certain time after return, symptoms, and diagnosis. The lower end of the bar represents the twenty-fifth percentile; the upper end represents the seventy-fifth percentile. Median values are in parentheses; maximal delays are written above each bar.

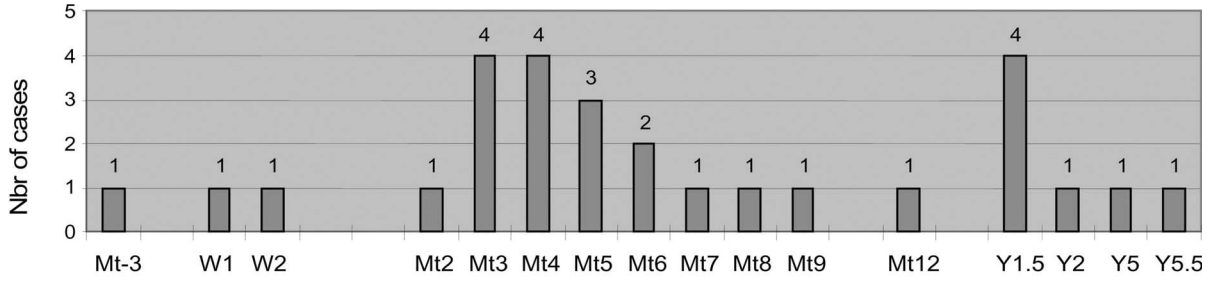

Figure 3 Latencies between diagnosis and return in the European group of tertian malaria. Mt-3 = 3 months after return; W = week; Y = year.

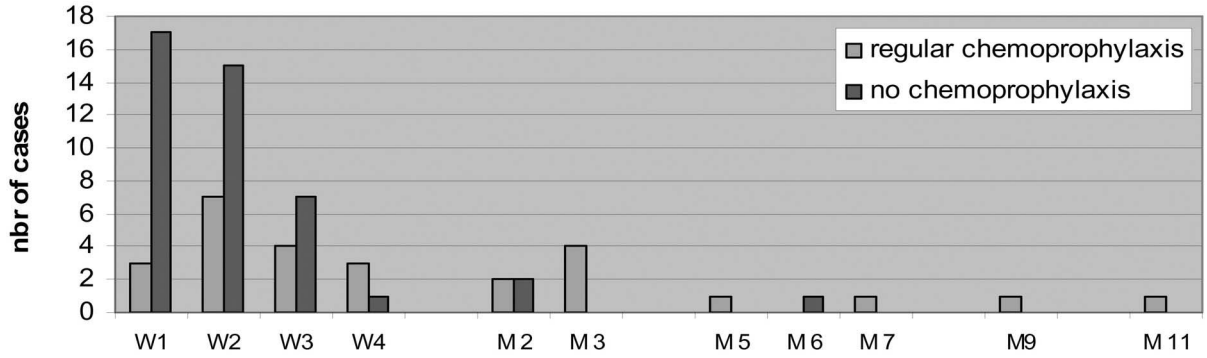

Figure 4 Latencies between diagnosis and return in the European group of falciparum malaria. M = month; W = week.

malaria who died (median age 48.5 yr) and those who survived (39 yr). The European patients with falciparum malaria who survived and had taken no chemoprophylaxis had a median age of 40 years.

Among the ten patients who died (all European), we did not find any significant difference in latencies (onset of symptoms after return, diagnosis after onset of symptoms and return) compared with the European patients with falciparum malaria who survived. The onset of symptoms was 6 days after return in both groups. The median latency between onset of symptoms and diagnosis was 5 days in the group of patients who died versus 4 days in the rest of the falciparum group ($n = 217$) ($p = .47$). This latency was 3 days in the European falciparum group without chemoprophylaxis ($n = 91$).

Multivariate Analysis

All models for "diagnosis after return" (DR) and "symptoms after return" (SR) showed an important and consistent influence of tertian malaria that lengthens the latencies. This is unlikely to be a chance finding ($p < .001$). There is no influence for "diagnosis after onset of symptoms" (DS).

In all models nationality and sex did not influence latency. For DR and DS there was evidence of a small effect of age. Unknown length of stay made important contributions lengthening DR and SR (p generally $< .01$ and $< .005$, respectively). Conversely, long duration of stay seemed to have a negative effect on the SR latency (p generally $< .03$). There was no evidence of an influence on DS.

Mosquito protection had little influence on any of the latencies.

Chemoprophylaxis increased all latencies ($p < .007$ for DR, $p < .03$ for SR, and $p < .003$ for DS).

Discussion

Species

The proportion of tertian malaria cases (16%) in this study was more than twice the proportion found in prospective studies analyzing imported malaria from East Africa.[2,3] One reason may be the longer latencies of onset of first symptoms after return in tertian malaria compared with those in falciparum malaria. The latencies were even longer in patients who had taken regular chemoprophylaxis. In studies without follow-up of more than 6 months, many of the tertian malaria cases would be missed as 75% of tertian malaria cases are diagnosed in the first 6 months after return (see Figure 3).

Chemoprophylaxis

In the 17 patients with falciparum malaria who had taken regular chemoprophylaxis, it could not be concluded whether there was a compliance problem or whether they

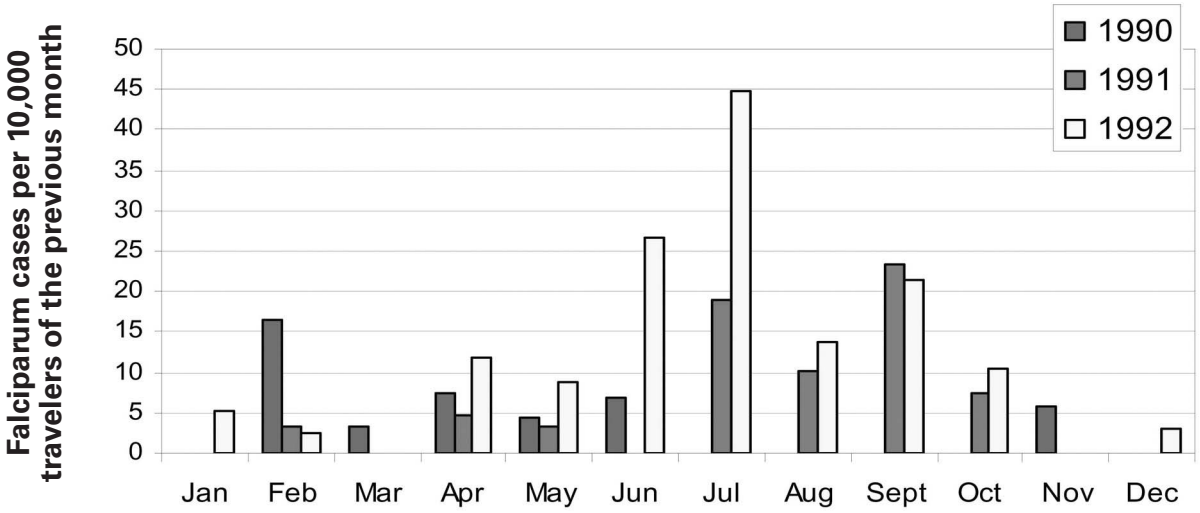

Figure 5 Seasonal fluctuation of the rate of falciparum malaria for 1990 to 1992.

had break-through infections. The drug concentration was not measured, and a systematic in vitro resistance testing was not performed. Our results appear to support the report on prophylaxis failure owing to probable mefloquine-resistant *Plasmodium falciparum* in East Africa.[9]

This study showed that intake of chemoprophylaxis had an important impact on all latencies for all *Plasmodium* species. The latencies between symptom onset and diagnosis after return were significantly prolonged after regular chemoprophylaxis. Similar observations were noted by Reyburn and colleagues and Grobusch and colleagues.[10,11]

Another striking result was the significantly higher proportion of tertian malaria after regular chemoprophylaxis, especially after the use of mefloquine. This was interpreted as showing the efficiency of mefloquine against falciparum malaria. As Schwartz and colleagues have reported, mefloquine chemoprophylaxis appears to have less or even no impact on tertian malaria.[12,13] Hypnozoites in the liver cause relapses once the inhibiting drug level is low, even if a primary attack is suppressed by the drug. New drugs (eg, atovaquone-proguanil, tafenoquine) may have an impact on tertian malaria. The finding of shorter outbreak latencies for tertian malaria in women was puzzling but probably biased by the small case number as it was not confirmed by multivariate analysis. However, sex differences in hepatic metabolism or activation of the hypnozoites may exist.

Seasonal Fluctuations

The analysis of monthly malaria rates showed unexpected seasonal variations. They corresponded to the local malaria situation in Kenya.[14] Especially after heavier rainfalls (eg, in October and November), malaria cases can rise epidemically among the local population and travelers.[15] This is explained by higher transmission rates owing to larger mosquito populations.

It is interesting to compare figures of international travel to Kenya. They show that tourists from different nations travel to Kenya during different months.[16] Travel patterns tend to vary over the years too.[17] When comparing international data, seasonal differences in malaria risk need to be considered.

Duration of Stay

Most African and European malaria patients with repeated stays did not take any drugs for chemoprophylaxis. Consequently, their symptoms appeared earlier. At the same time, they belong to a special risk category with less counseling, possibly acquired semi-immunity, poorer travel conditions, and potentially higher exposure. There is an important percentage of children in the African group (34%) and in the group of people with repeated stays. Children of African immigrants who are born in Europe have no semi-immunity. If their families do not provide them with chemoprophylaxis and mosquito protection, they are at particularly high risk of getting malaria. More effort is needed to target this risk group in pretravel counseling.

The finding that the onset of first symptoms in patients after long stays is earlier than in those after short stays matches the general experience of other centers of tropical medicine. The greater risk of infection over a longer time in the first group and the minimum incubation period of 6 to 7 days does not fully explain this puzzling finding. Traveling itself might induce a clinical attack.[10]

Fatal Cases

The latencies of onset of symptoms and diagnosis were not longer in the patients with falciparum malaria

who died than in those who survived ($p > .1$, when comparing with the European falciparum group without regular chemoprophylaxis). Commonly a delay in diagnosis is incriminated as major cause of lethality in malaria. We found no evidence for this in our data. As there were two patients who had taken irregular chemoprophylaxis, it must be emphasized that irregular chemoprophylaxis does not prevent complications or even death.

In our small sample, the age factor was not statistically significant, although those who died were slightly older (48.5 vs 40 yr). A special virulence of the parasite and preexisting comorbidities of the patients are likely reasons for the fatal outcome of the disease.

Conclusions

Plasmodium species and chemoprophylaxis regimens have a considerable effect on outbreak latencies of malaria. The local malaria situation and development of data pertaining to tourists play an important role in the seasonal distribution of imported malaria and may vary considerably from year to year and from country to country of tourist origin. Malaria patients with African nationality and/or cases with repeated trips to Kenya had not usually taken any malaria prophylaxis. This is of major concern because a large proportion of children is found in these groups. Visiting friends and relatives originating from endemic countries should be reminded that their children are not immune.

All these confounding factors must be analyzed properly and need to be considered in their entirety to prevent errors in data interpretation, especially if data from different countries are compared. Extrapolation of results from one country to another needs to be made with caution in view of the many factors that influence the pattern of imported malaria cases. More detailed and homogeneous data are indispensable for a better understanding of the situation and to provide improved recommendations for prevention.

The obvious indications that chemoprophylaxis may not be effective against tertian malaria are of concern. Further studies are needed to investigate the effect of chemoprophylaxis drugs, especially the newly emerging ones, on tertian malaria. Factors causing a fatal course of falciparum malaria also need to be continuously monitored.

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Declaration of Interests

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