

Patterns of Imported Malaria at the Academic Medical Center, Amsterdam, The Netherlands

Marije C. Baas, MD,* José C.F.M. Wetsteyn, MD, PhD,* and Tom van Gool, MD, PhD†

*Division of Internal Medicine, Department of Infectious Diseases, Tropical Medicine and AIDS, and †Division of Medical Microbiology, Parasitology Section, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

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Background. In the Netherlands, cases of imported malaria peaked in the late 1990s to around 500 (60% *Plasmodium falciparum*) annually. About 30% to 40% of all cases and 57% to 69% of the falciparum cases presented in the Academic Medical Center, Amsterdam. In 1991 to 1994, a shift in population groups to more semi-immune patients, mostly settled immigrants visiting friends and relatives (VFRs), was noticed, when compared to 1979 to 1988. This study shows the ongoing trend in 2000 to 2002.

Methods. All the patients diagnosed with malaria in the Academic Medical Center, Amsterdam, during 2000 to 2002 were analyzed. Nonimmune and semi-immune patients were analyzed separately.

Results. A total of 302 patients were diagnosed with malaria: 207 (69%) were male; mean age was 34.0 years (range 1–74 years). Of the 302 patients, 105 (35%) were nonimmune travelers and 197 (65%) were considered semi-immune. In 248 (82%) patients, *P falciparum* was found. In 28 (9.3%), 15 (5.0%), and 6 (2.0%) cases, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae* were diagnosed, respectively. Of the 248 falciparum cases, 233 (94%) were infected in sub-Saharan Africa; 90% of them had a parasitemia and <2 and 4% had a parasitemia exceeding 5% (maximum 43.7%). The majority of the falciparum cases (96%) were diagnosed within 30 days after return. The number of nonimmune patients with falciparum malaria decreased sharply from 42 in 2000 to 31 in 2001 to 13 in 2002, accounting for the decrease in all malaria cases, from 118 in 2000 to 82 in 2002. Fifty-four percent of vivax infections were acquired in Southeast Asia and 46% in Latin America and sub-Saharan Africa; 71% of the patients presented after 30 days (delayed primary attacks). All the *P ovale* infections were acquired in sub-Saharan Africa (73% delayed primary attacks).

Conclusions. During 2000 to 2002, the total number of patients with falciparum malaria was steadily decreasing due to a decrease in nonimmune patients. The number of semi-immune patients, mostly VFRs and visitors, remained stable. The increasing use of more convenient chemoprophylactic drugs, like atovaquone/proguanil, appears to improve compliance in those who can afford the drug.

Since November 1970, the Netherlands has been declared malaria-free by the World Health Organization. The last indigenous malaria case was notified in 1958.¹ From 1948 onward, the number of imported malaria cases has exceeded indigenous

cases.¹ Since 1972, the number of cases increased steadily, peaking in the late 1990s to about 500 cases annually.² Up to 1999, underreporting was estimated to be about 60%.³ In 1999, the way of notification of malaria was changed from doctor-based to laboratory-based. So, the total number of cases notified “increased” to 453 in 1999 and to 542 in 2000. However, from 2001 onward, a steady decrease is noted in the Netherlands.⁴

Trends in imported malaria are influenced by several factors: increase in number of travelers to

Corresponding Author: José C.F.M. Wetsteyn, MD, PhD, Clinic for Tropical and Travel Medicine, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands.

the tropics, more risky travel patterns and change in purpose of travel, more intense malaria transmission in certain destinations, and increasing drug resistance of the parasite. Imported malaria threatens not only nonimmune travelers but also settled immigrants in Western countries visiting friends and relatives (VFRs) and even more their children, born in a nonendemic country. In several European countries, an increase in the incidence of imported malaria in settled immigrants is noted.⁵⁻⁷ It is important to reach these travelers for pretravel advice because they do not take effective precautions as they believe that their risk is minimal. Their children need even more attention as they have no immunity at all.

In 1997, Wetsteyn and colleagues noticed that the number of semi-immune patients (VFRs or visitors from endemic areas) with malaria diagnosed in the Outpatient Department for Tropical Diseases in the Academic Medical Centre, Amsterdam, was increasing, whereas the number of nonimmune malaria patients was decreasing.⁸

The aim of this study was to assess whether the trend showing decreasing numbers of nonimmune cases of imported malaria continues. We analyzed the data of all (prospectively collected) malaria cases presenting in the Outpatient Department for Tropical Diseases in 2000 to 2002.

Methods

We analyzed the following data of all consecutive patients treated between January 1, 2000, and December 31, 2002: age, sex, country of origin, area of infection, time interval between return and diagnosis (in days), *Plasmodium* species, and parasitemia (in case of *P falciparum*).

Table 1 The number and percentage of the *Plasmodium* species in 302 patients diagnosed with malaria in the Academic Medical Center, Amsterdam, in 2000 to 2002

<i>Plasmodium</i> species	2000, n (%)	2001, n (%)	2002, n (%)	Total, n (%)
<i>Plasmodium falciparum</i>	97 (82)	82 (80)	69 (84)	248 (82)
<i>Plasmodium vivax</i>	11 (9)	11 (11)	6 (7)	28 (9)
<i>Plasmodium ovale</i>	7 (6)	5 (5)	3 (4)	15 (5)
<i>Plasmodium malariae</i>	1 (1)	2 (2)	3 (4)	6 (2)
Unclassifiable	2 (2)	2 (2)	1 (1)	5 (2)
Total	118	102	82	302

Patients born and bred in malarious areas, living in or visiting the Netherlands, were defined semi-immunes. Patients born and living in nonmalarious areas were considered nonimmune. Children born to immigrant parents in the Netherlands were included among the nonimmune patients.

The diagnosis was based on microscopic examination of a thick and thin blood smear; in case of *P falciparum*, the number of parasites were counted as trophozoites per 100 leukocytes in the thick smear or per 1,000 erythrocytes in the thin blood smear.

Results

Patients

During 2000 to 2002, 302 patients were diagnosed with malaria: 207 (69%) were male and 95 (31%) were female. The median age was 35.0 years (range 1-74 years). Of the 302 patients, 105 (35%) were nonimmune, including 10 children born to immigrant parents and 197 were semi-immune, mostly settled immigrants [171 (87%)] from endemic malarious areas, who had visited their country of birth. The remaining 26 patients were visitors and asylum seekers.

Travel Destination

A total of 260 (86%) people had traveled to sub-Saharan Africa, of whom 171 (66%) were settled immigrants. Twenty-two (7%) had visited Asia, 18 (6%) Central and South America, and in 2, the travel destination was unknown.

Plasmodium Species

In 248 (82%) patients, *P falciparum* was found. In 28 (9.3%), 15 (5.0%), and 6 (2.0%) cases, *P vivax*, *P ovale*, and *P malariae* were diagnosed, respectively. In 5 cases (1.7%), the *Plasmodium* species could not be classified (see Table 1).

Falciparum Malaria

Of the 248 patients with falciparum malaria, 233 (94%) were infected in sub-Saharan Africa, eight (3%) in Southeast Asia, and 5 (2%) in South America. In two patients, the travel destination was unknown.

Parasitemia

In 223 of 248 (90%) patients, the parasitemia was below 2%; 150 of 223 (60%) patients had parasitemia even below 0.1%; 14 (6%) had a parasitemia between 2 and 5%; and 10 (4%) had more than 5%. The maximum was 43.7%. In 1 patient, the parasitemia was not recorded. The case fatality rate was zero.

Interval

A total of 237 of 248 (96%) *P falciparum* infections were diagnosed within 30 days after return. Only 11 patients (4%) were diagnosed more than 30 days after their return from an endemic area. Of those 11 patients, six were considered to be semi-immune and five were nonimmune. All the 11 patients had low parasitemia (maximum 0.6%). The longest interval between return and diagnosis of *P falciparum* was observed after 85 days in the 3-year-old girl born to Ghanaian parents, who had not used chemoprophylaxis. Only a few trophozoites were found in the thick smear. It is unknown whether she had been treated with antimalarials or antibiotics before the diagnosis was made.

Vivax Malaria

Twenty-eight (9.3%) patients were infected with *P vivax*; 15 (54%) were infected in Southeast Asia, nine (32%) in Latin America, and four (14%) in sub-Saharan Africa. Twenty (71%) patients presented with symptoms after more than 30 days, with a maximum of 270 days, and they are considered to suffer from a delayed primary attack. Eight patients presented within 30 days; none of them had used chemoprophylaxis.

Ovale Malaria

Plasmodium ovale was found in 15 (5.0%) patients. All the infections were acquired in sub-Saharan Africa. The majority [11/15 (73%)] was diagnosed after 30 days, with a maximum of 215 days (delayed primary attacks). None of the four patients presenting within 30 days had taken chemoprophylaxis.

Malariae Malaria

Only six (2%) patients suffered from quartan malaria; three were nonimmune: four infections were acquired in sub-Saharan Africa, one in Southeast Asia, and one in South America. Four (66%) cases occurred after 30 days (range 31–121 days) after return.

Unclassifiable Malaria

In five patients (1.3%), the *Plasmodium* species could not be classified. In two patients, differentiation between *P ovale* and *P vivax* was not possible due to a very low number of parasites. Both patients had used chemoprophylaxis (mefloquine) and had a delayed primary attack after 73 and 200 days. The remaining three patients had not used chemoprophylaxis. They were diagnosed within 14 days after their return from Sri Lanka, Tanzania, and Mozambique. They were treated and followed-up

like *falciparum* malaria cases, and no relapses occurred.

Nonimmune Population

Of the 302 patients, 105 (35%) were nonimmune, including 10 children born to immigrant parents; in 71 of 105 (68%) patients, *P falciparum* was diagnosed; in 22 (21%), *P vivax*; in five (5%), *P ovale*; and in 3 (3%), *P malariae*. In four patients, the species could not be classified.

The total number of nonimmune patients decreased steadily: 50 in 2000, 41 in 2001, and 14 in 2002. The number of nonimmune patients with *falciparum* malaria decreased even more sharply: from 42 in 2000 to 31 in 2001 to 13 in 2002, a decrease of 26% (2000–2001) and 58% (2001–2002). This decrease accounted approximately for the decrease in all patients suffering from malaria. The number of semi-immune patients with malaria (immigrant VFRs or visitors) remained quite stable (2000, 68; 2001, 61; 2000, 68).

Discussion

Imported malaria remains a public health problem in industrial countries, as the result of increases in travel and immigration. The World Tourism Organization estimates that, each year, more than 650 million people are crossing international boundaries.⁹ In the United States, VFRs comprised approximately 40% of the US international air travelers in 2002; in the UK, VFRs made 40% of the 2 million visitors to Africa in 2000.¹⁰ In Europe, 10,000 cases of malaria are notified each year; the real number is probably thrice that much due to gross underreporting and marked heterogeneity in the type and availability of national data.¹¹ The principal importing countries were France, the UK, Germany, and Italy. During 2000 to 2002, a total of 1,470 cases were notified in the Netherlands; 302 (21%) of them were seen in our hospital, including 30% of all cases with *falciparum* malaria.

In Europe, *P falciparum* is the predominant species accounting for more than 50% of the imported cases. France has the highest proportion of cases due to *P falciparum*, exceeding over 80%.¹¹

In the Netherlands, *P falciparum* has always been the leading species, with 57% to 75% of the cases annually.⁴ In the Academic Medical Center, we are following-up prospectively all malaria cases since 1979. We have treated about 40% of all Dutch cases and 57% (1979–1988) and 69% (1991–1994) of all *falciparum* malaria cases notified in the Netherlands. Among the total number of malaria cases in our

hospital, between 69 and 84% are due to *P falciparum* (see Table 1).^{3,8} We must note that our hospital is situated in a part of Amsterdam with large immigrant (African) communities; only 39% are Dutch.

In our country, as in many European countries, immigrant communities account for an increasing proportion of malaria cases. In the study of Schlagenhaufl and colleagues, an average of 43% of the cases from the pooled data of five studies with a total number of 16,492 cases were in nonnationals, frequently settled immigrants, ranging from 33% in the UK to 86% in one region in France.^{5,12} The geographic origin of the immigrants plays a major role in the prevalence of the predominant species. Immigrants rarely use chemoprophylaxis or seek medical advice prior to travel as they mistakenly believe that they retain lifelong immunity.¹⁰ Most of them visit their friends and relatives every 2 to 3 years, often during summer holidays, a period corresponding to the rainy season, staying in rural areas, with little protection from mosquitoes. Although immunity does wane, when reexposure stops, some immunologic memory remains that partly explains the low to zero fatality rate. However, this is not the case in their children born in Europe.^{8,13} They have no immunologic memory and do not use chemoprophylaxis, but they share the risk profile as their parents.

In a former study, the shift to more semi-immune patients was described.⁸ In the present study, 9 years later, the trend proves to continue. In the years 2000 to 2002, the total number of malaria cases in our hospital decreased steadily owing to a decrease in nonimmune patients. The number of semi-immune patients (68, 61, and 68, mostly settled immigrants or visitors) remained stable.

Plasmodium falciparum remained the most important cause of imported malaria (82%). The majority (94%) was infected in sub-Saharan Africa; 96% of the cases were diagnosed within 30 days after return.

During 1979 to 1988, the ratio of nonimmune to semi-immune patients with falciparum malaria was 85:15; in the period 1991 to 1994, this ratio was 51:49. In 2000, 2001, and 2002, the ratios were 44:56, 38:62, and 19:81, respectively (see Table 2). The most remarkable decrease in falciparum malaria (58%) occurred between 2001 and 2002; the decrease in all cases was less impressive, 16%, a trend also observed in the UK (5%) and Germany (17%).^{14,15}

Plasmodium vivax was, with 9.3%, the second most frequent *Plasmodium* species. This is much lower than the overall percentage in our country, ie, 17.6% during 1994 to 2002.⁴ Within Europe, Germany heads the list, with 24.3% (1999–2003), followed by Spain (15.5%) and the UK (12%), reflecting the travel destinations and populations from these countries.¹⁶

The majority of the vivax and ovale malarias are delayed primary attacks: 71% of *P vivax* malaria and 73% of *P ovale* malaria occurred after more than 30 days after return. These attacks cannot be prevented by appropriate chemoprophylaxis, unless the antimalarial drug has antihypnozoite activity. Only primaquine and, perhaps in the near future, tafenoquine have this effect.

With the increasing use of atovaquone/proguanil as chemoprophylaxis, it is possible that more *P vivax* infections will be seen within 30 days, as the efficacy of this drug combination for *P vivax* is less (84%) than that for *P falciparum* (96%).¹⁷

The reason for the sharp decline in Dutch patients with imported malaria is not clear. The number of travelers has not decreased, and the travel destination might have changed, but exact Dutch travel data are lacking. Maybe Dutch travelers have become more compliant. The increasing use of more convenient chemoprophylactic drugs, like atovaquone/proguanil (see Figure 1), could have improved compliance in those who can afford the drug, providing better protection against falciparum malaria. In conclusion, during 2000 to

Table 2 Total malaria and falciparum malaria patients treated in the Academic Medical Center (AMC), Amsterdam, in five time periods and the numbers of nonimmune/semi-immune patients among them

Time period	Total malaria cases in AMC (% of n notified in the Netherlands)	<i>Plasmodium falciparum</i> in AMC (% of total AMC)	<i>P falciparum</i> nonimmune/semi-immune (%)
1979–1988 ²	Not known	427	361/66 (85/15)
October 1991–1994 ⁸	286 (42)	197* (69), annual mean: 88	100/95† (51/49)
2000	118 (22)	97 (82)	42/53† (44/56)
2001	102 (19)	82 (80)	31/51 (38/62)
2002	82 (21)	69 (84)	13/56 (19/81)

*Including one mixed infection.

†In two patients, the origin was not recorded.

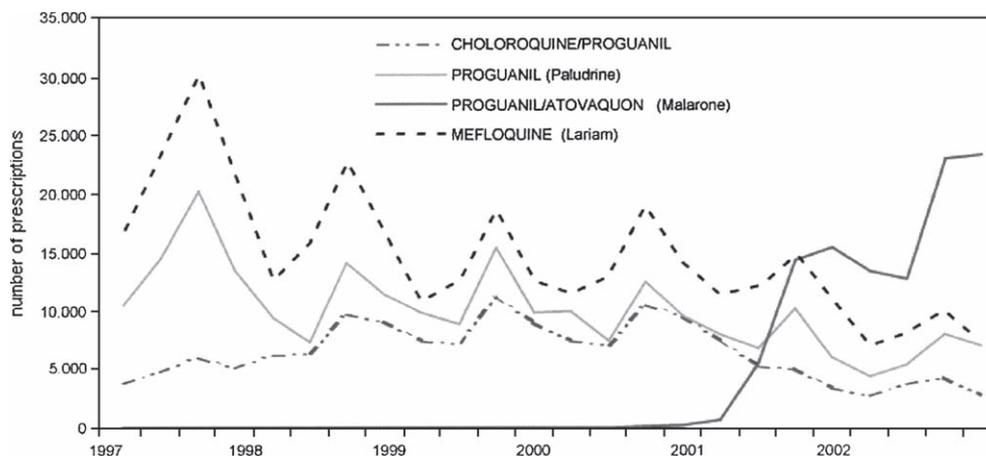


Figure 1 The number of prescriptions for malaria chemoprophylaxis in the Netherlands during 1997 to 2002, provided by the Foundation of Pharmaceutical Statistics.¹⁸

2002, the total number of patients with imported malaria had decreased due to a decreasing number of nonimmune patients. The number of semi-immune patients, mostly VFRs, remained stable. The trend, described in 1991 to 1994, appeared to continue.

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Declaration of Interests

The authors state that they have no conflicts of interest.

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