

Case Report: Two Cases of *Plasmodium falciparum* Malaria in the Netherlands without Recent Travel to a Malaria-Endemic Country

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Abstract. Recently, two patients of African origin were given a diagnosis of *Plasmodium falciparum* malaria without recent travel to a malaria-endemic country. This observation highlights the importance for clinicians to consider tropical malaria in patients with fever. Possible transmission routes of *P. falciparum* to these patients will be discussed. From a public health perspective, international collaboration is crucial when potential cases of European autochthonous *P. falciparum* malaria in Europe are reconsidered.

Plasmodium falciparum malaria is an important cause of morbidity and mortality worldwide.¹ It is not endemic to Europe, and reported cases in Europe are almost exclusively in travelers returning from malaria-endemic areas.² Imported infections with *P. falciparum* (*P. falciparum* malaria) account for most malaria-related morbidity and mortality in Europe.³ The Netherlands was declared malaria free by the World Health Organization in 1970.

The incubation period of *P. falciparum* malaria is 12–14 days, but longer incubation periods can occur in semi-immune persons and persons taking ineffective malaria prophylaxis, but is typically less than one month.^{4,5} Importantly, diagnosis of *P. falciparum* malaria may be missed or delayed in patients who have malaria years after leaving a malaria-endemic area or who do not report recent visits to malaria-endemic countries.⁶ However, early detection of apparently non-imported cases of *P. falciparum* malaria in Europe is of major public health importance because it enables effective response activities to prevent outbreaks. We describe two patients who had not been in malaria-endemic areas for years, but had *P. falciparum* malaria shortly after returning from countries in southern Europe. Informed consent was obtained from the patients for publication of this report.

CASE-PATIENT 1

A 23-year-old man from Liberia was seen at an emergency department in the Netherlands because of abdominal pain for three days and a fever of 40°C. Besides an episode of malaria in the past (before 2008), he had no medical history. His travel history indicated a visit to a malaria-endemic country, Liberia, in 2008. Nine days before admission to our hospital, he returned from a four-week holiday in Barcelona, Spain and Treviso, Italy, where he traveled by car. During his travel, he stayed with immigrants who recently returned from Africa, some of whom were sick and had fevers. The patient reported that in both places the living conditions were poor, and many

indoor insects, including mosquitoes, were present. No other risk factors for transmission of malaria (e.g., intravenous drug use, blood transfusion, surgical interventions, airport visit) were reported.

At a physical examination, he did not appear acutely ill. His blood pressure was 108/55 mm of Hg, his pulse rate was 84 beats/minute and his temperature was 40 °C. He had abdominal tenderness. There were no other abnormalities. Laboratory test results showed hemoglobin level of 8.3 mmol/L, a thrombocyte count of $56 \times 10^9/L$, a leukocyte count of $4.5 \times 10^9/cells/L$ and a normal differentiation pattern, a C-reactive protein level of 127 mg/L, and a lactate dehydrogenase level of 278 U/L. Surprisingly, examination of a peripheral blood smear showed *P. falciparum*-infected erythrocytes with a parasitemia index of 2.3%. A rapid immunographic test (Binax NOW Malaria Test; Binax, Portland, OR) result for *P. falciparum* was positive.

The patient was initially treated with intravenous quinine and improved after one day. After an initial increase of his parasitemia to 4.6% it decreased to < 0.1% after 3 days, after which he was treated with four tablets of atovaquone/proguanil a day for three days. He fully recovered and at follow-up visits at the outpatients department, no malaria parasites were seen on a thick blood smear. Although the patient denied making any recent visits to tropical areas, his blood count revealed 17×10^9 eosinophils/L and his feces contained *Schistosoma mansoni* eggs. He was then successfully treated with praziquantel.

CASE-PATIENT 2

A 34-year-old woman from Sierra Leone was seen at an emergency department in the Netherlands because of periodic spiking fever that lasted for two weeks. Her medical history was unremarkable, except for uterine fibroids and an episode of malaria several years ago. She used no medications. Besides the fever, she had abdominal pain and arthralgia since that time. She noticed that her symptoms felt like malaria, which she experienced in the past in her home country. Her travel history showed that her last visit to a malaria-endemic country, Sierra Leone, was in 2003. In recent years, her travel was limited to Belgium and France. On the first day she experienced symptoms, she had returned from a four-week stay in the Bourgogne area in central France, where

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she spent time in an apartment block with family and friends. According to the patient, several persons who recently returned from Africa to the apartment block, came down with malaria-like symptoms in the same period. The patient also reported a one-day visit to Charles de Gaulle International Airport. No other risk factors for the recent infection (e.g., intravenous drug use, blood transfusion, surgical interventions) were reported.

At a physical examination, she did not appear sick or anemic. Her blood pressure was 150/90 mm of Hg, her pulse rate was 85 beats/minute and her temperature was 36°C. Peripheral oxygen saturation was 98% at room temperature, and her respiratory frequency was normal. Abdominal examination showed uterine fibroids, which were known to be present, but no hepatosplenomegaly. Several small wounds, possibly caused by insect bites, were seen around her ankles.

At laboratory test examination, the most striking findings were an anemia with an hemoglobin level of 7.1 mmol/L (11.4 g/dL), thrombocytopenia (80×10^9 cells/L), and slight leukocytopenia (3.7×10^9 /L) and a normal differentiation. Lactate dehydrogenase (501 U/L) and C-reactive protein (109 mg/L) levels increased. A chest radiograph showed no abnormalities.

Despite absence of recent travel to malaria-endemic areas in her travel history, but given the patient's remark about her symptoms resembling malaria, microscopy of a thick blood smear and malaria antigen test (Binax NOW malaria test; Binax) were performed and showed an infection with *P. falciparum* with a parasitemia of 0.18% and gametocytes. She received a 3-day course of atovaquon/proguanil (4 tablets/day) and was sent home. She fully recovered and in follow-up visits at the outpatients department, no malaria parasites were seen on a thick blood smear.

We describe two residents of the Netherlands, both originating from Africa, who came to two hospitals in the Netherlands with *P. falciparum* infections. Thorough reviews of their travel histories did not show visits to a malaria-endemic area in recent years, but visits to different areas in Europe: Italy, Spain (patient 1), and France (patient 2). Other patients with

a *P. falciparum* infection without a designated source have been reported in Germany.⁷

These observations are important because of their relevance for public health and clinical practice. Regarding clinical practice, *P. falciparum* infections are rarely considered in the differential diagnosis of patients with fever returning from these parts of Europe. For clinicians in the Netherlands, malaria is a traveler's disease and often only considered when patients return from malaria-endemic (i.e., tropical) countries. A delay in the diagnosis and treatment of *P. falciparum* malaria can lead to increased morbidity and mortality.⁸ Therefore, a thorough review of the travel history is important in establishing the origin of the infection.

Discrepancies between reported and actual travel history may occur, giving rise to uncertainties and unexplained symptoms, such as signs of schistosomiasis despite absence of recent travel to tropical areas in the travel history reported by case-patient 1.⁹ There are no formal barriers against accessing emergency health care for anyone in the Netherlands. However, it is known from anecdotal evidence reported by clinicians that immigrants unjustly fear the existence of formal barriers, including payments and connections between immigrant regulations and health care and public health authorities. These barriers can potentially influence the reporting of their travel history, limiting thorough analysis of the transmission routes, including on-site entomologic investigations.

In accordance with the Public Health Act, both patients were reported to the Municipal Health Services and subsequently to the Dutch National Institute for Public Health and the Environment. Reporting of these patients in a short time interval without reported travel history to a malaria-endemic country was considered remarkable. European autochthonous malaria was considered as a diagnosis (Table 1). The Dutch National Institute for Public Health and the Environment informed the French, Spanish and Italian Public Health Authorities in France, Spain, and Italy through the European selective exchange Early Warning and Response System.

TABLE 1
Possible routes of *Plasmodium falciparum* transmission for the two case-patients described, the Netherlands

Possible cause	Arguments in favor	Arguments against	Interpretation
Travel to malaria-endemic countries	<i>Schistosoma</i> infection for case-patient 1	No history of recent travel to malaria-endemic countries	Possible for case-patient 1
Acquired in The Netherlands	2 case-patients notified within a short period, without travel history to a malaria-endemic country, and living nearby each other (10 km)	Presence of gametocytes for case-patient 2; low vector capacity; travel history/incubation time are not suggestive	Unlikely
Local transmission in southern Europe	Suggestive history/incubation time; friends sharing household and had complaints of malaria; reported presence of mosquitoes; insect bites present in case-patient 2	No known efficient vector present, but presence of vector cannot be ruled out without research at location of stay; rarely described and no other cases reported in 2012	Not ruled out, not clearly demonstrated
Airport malaria	Reported airport visit for case-patient 2	No airport/seaport visit for case-patient 1	Possible for case-patient 2
Luggage malaria	Both case-patients stayed with others returning from malaria-endemic countries; insects/insect bites observed	–	Possible for both case-patients
Blood transfusion/intravenous drug use	–	No history of blood transfusion or intravenous drug use	Unlikely
Late recrudescence	Both case-patients had had malaria in the past; both have lived in malaria-endemic countries (possible semi-immune status)	Very uncommon; rarely described for <i>P. falciparum</i>	Unlikely

During the past few years, outbreaks of *P. vivax* malaria have occurred in parts of southeastern Europe, but *P. falciparum* malaria outbreaks have not been reported.¹⁰ Historically, *P. vivax* in Europe has been transmitted predominantly by five *Anopheles* species.¹¹ However, these mosquito species have been shown to be incompetent for transmitting *P. falciparum* malaria.¹² The only two mosquito species in Europe known to be competent for transmitting *P. falciparum* are *Anopheles algeriensis* and *An. plumbeus*.¹³

Theoretically, with the presence of *P. falciparum*-competent mosquito species, local malaria transmission is possible when gametocyte-carrying persons that are infected in malaria-endemic areas reside in Europe.¹⁴ This hypothesis of local household transmission in France is supported by the fact that insect bite wounds on the lower extremities were reported by the second patient, whereas the indoor presence of mosquitoes, as well as other persons with malaria-like symptoms at the visiting location, were reported by both patients. However, no autochthonous transmission of *P. falciparum* has been reported in Italy, Spain, France, or any other country in Europe in 2012 (<http://data.euro.who.int/cisid/?TabID=303151>). Unfortunately, neither patient was willing to reveal their exact locations of stay, making any follow-up in France, Italy, or Spain impossible.

Local transmission in the Netherlands was also considered but seems unlikely. If one considers that the duration between infection and development of gametocytes was at least 14 days, symptoms developed in both patients within 1 and 9 days, respectively, after returning from travel, and gametocytes in blood smears in relation to reported recent travel of the patients, these three factors probably exclude infection acquired in the Netherlands. *Anopheles plumbeus* is endemic in the Netherlands. However, in the current circumstances, the vector capacity is considered to be low. There are no indications of autochthonous transmission.¹⁵

The latest reported cases of locally acquired tropical malaria in the Netherlands could be explained by airport malaria in patients staying near Schiphol Airport.^{16,17} This so-called airport malaria could be another possible route of transmission in our patients. Mosquitoes can hide in freight or passengers area of the planes, or can be transported in the wheel bays and released when the bays open during the approach for landing.^{18–21} Neither of the patients lived near an airport in the Netherlands, but airport malaria could have been a mode of infection for the second patient because she mentioned that she paid a one-day visit to Charles de Gaulle International Airport during her visit to France. Luggage malaria could also be a route of transmission because both patients visited friends who recently came from malaria-endemic countries. Mosquitoes could have been imported in their suitcases.

Plasmodium falciparum transmission by direct inoculation of infected blood is considered a route of transmission. However, neither of the two patients had received blood or undergone recent medical procedures before infection, reported use of intravenous drugs, or had scars at the physical examination.^{22–24}

Finally, late recrudescence or relapse has been described for different forms of malaria, mostly associated with *P. malariae*, *P. vivax*,^{25–29} or *P. ovale*.^{30,31} Interestingly, our patients were originally from malaria-endemic countries, but they reported that they had not returned to their countries of origin for four and nine years, respectively. Late recrudescence of

tropical malaria has been described in immunocompromised patients or pregnant women, although these findings are extremely uncommon.^{32–35}

Several cases have been attributed to infected *Anopheles* spp. mosquitoes traveling in luggage or at least associated with pre-existing partial immunity from repeated prior exposures.³³ Late recrudescence caused by pregnancy or immunosuppression in our patients was considered unlikely.

In conclusion, we report two *P. falciparum* malaria patients without reported recent travel to a malaria-endemic area. Physicians should be aware of the possibility of *P. falciparum* infections in patients who have been in contact with travelers who recently returned from malaria-endemic area (luggage, airport, local transmission). Rapid communication between physicians and public health authorities in Europe is needed to effectively respond to signs of possible autochthonous transmission.

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