Jpn. J. Infect. Dis., 67, 27-32, 2014

**Original Article**

# Reducing the Delay in Initiation of Treatment Improved Clinical Outcomes in Patients with Imported Malaria

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(Received April 17, 2013. Accepted August 8, 2013)

**SUMMARY**: Although imported malaria poses a grave public health threat in Japan, diagnostic methods and disease management among patients and primary care providers has rarely been reported. Here, we retrospectively reviewed medical records of patients diagnosed with imported malaria in our hospital from 1991 to 2010. Thirty-four malaria cases were identified, corresponding to approximately 2% of the total number of cases in Japan. Falciparum malaria has become predominant in the last 2 decades, and compared with patients in the earlier decade (1991–2000), patients in the latter decade (2001–2010) showed significantly shorter delays in consulting medical facilities. The overall hospital delay also tended to be shorter in the latter decade, although delayed referral of patients by a week or more was still observed in more than one-third of the cases. The prevalence of risk factors for severe malaria among patients on the day of the referral visit was also lower in the latter decade. Further, the number of WHO-defined cases of severe malaria was smaller, and the length of the hospital stay was not prolonged during that decade. These findings indicated that a shorter delay in seeking medical treatment could reduce the risks of severe malaria.

## INTRODUCTION

Approximately 300 to 500 million new cases of malaria are reported annually, resulting in an estimated 1.5–2.7 million deaths (1–3). In Japan, approximately 100 travelers to malaria-endemic countries contract the disease every year (4–6). In addition, the number of cases of imported *Plasmodium falciparum* malaria, which is the most commonly associated with severe complications, has been increasing over the past decades in Japan (5–8). Falciparum malaria, if not diagnosed and treated quickly, represents a medical emergency because it is associated with a high risk of acute, severe complications and even death (9–16). The mortality rate of malaria is estimated to range from less than 1% to 4%; however, the rate could be as high as 20% depending on disease severity, despite progress in intensive care and antimalarial treatment (17–20).

The World Health Organization (WHO) established diagnostic criteria for severe malaria to identify individuals at risk of death and to specify clinical and laboratory parameters associated with an increased risk of contracting severe forms of the disease (21–23). Complications of severe malaria involve the nervous, respiratory, renal, and/or hematopoietic systems and include cerebral malaria, pulmonary edema, acute renal failure, severe anemia, acidosis, and hypoglycemia (24–27). Any of these complications can develop rapidly and cause death within hours or days. Using multivariate logistic regression analysis, Phillips et al. suggested 6 risk factors significantly associated with an increased risk of WHO-defined severe malaria: lack of history of previous malaria, parasitemia greater than 2%, platelet count, anemia, elevated white blood cell (WBC) count, and renal failure (26).

Given the increasing number of imported falciparum malaria cases in Japan, it is critical to recognize malaria as a potential cause of febrile illness in returning travelers and to initiate treatment before the development of severe complications. Unfortunately, a major obstacle for the control of imported malaria in Japan is the delay in diagnosis and appropriate treatment of falciparum malaria. Here, we retrospectively reviewed the medical records of patients diagnosed with imported malaria in our hospital from 1991 to 2010 to better understand how malaria is recognized and managed among patients and primary care providers.

## MATERIALS AND METHODS

The medical records of all patients diagnosed with imported malaria at Kyoto City Hospital from January 1991 to December 2010 were retrospectively reviewed. The study was approved by Kyoto City Hospital. Diagnosis was based on microscopic examination of thick and thin blood smears by laboratory technicians and specialists in tropical medicine. Thirty-four cases of imported malaria (17 falciparum and 17 non-falciparum cases) were identified, corresponding to approximately 2% of the total number of cases in Japan. Patients who were treated abroad and visited our hospital for follow-up after clearance of parasitemia were excluded, unless they showed positive blood smears in our examination.

Data were collected regarding patient nationality, age, gender, suspected region of contraction, purpose of

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visit, *Plasmodium* spp., history of previous malaria, and evidence of relapse or recrudescence. In addition, data was also collected regarding the period between the onset of symptoms and the first medical consultation and the period between the first medical consultation and transfer to our hospital.

The epidemiology of imported malaria and suspected contraction areas in a recent 20-year period were investigated. The 20-year period was divided into 2 decades, an earlier (1991–2000) and a latter (2001–2010) decade, and compared using the aforementioned parameters. Cases of relapse, recrudescence, and quarantine in domestic airports were excluded. In total, 27 Japanese patients with an initial infection of malaria, including 14 cases (5 falciparum and 9 non-falciparum) in the earlier decade and 13 cases (9 falciparum and 4 non-falciparum) in the latter decade, were selected for further analysis.

The delay in seeking medical treatment among patients was evaluated to determine how malaria was recognized and managed before referral to our hospital. This delay was analyzed from 2 perspectives: (i) the period between the onset of symptoms and the first medical consultation (patient delay) and (ii) the period between the first medical consultation and transfer to our hospital (hospital delay). The effect of the delay in malaria diagnosis on risks was then analyzed for severe malaria at the first referral level. In accordance with the study conducted by Phillips et al., 4 risk factors were selected that strongly correlated disease with severity (26).

Using laboratory data obtained at the time of patient referral, the prevalence of risk factors was calculated on the basis of a score of 1 or 0 obtained above or below a predetermined cutoff value used in our hospital: platelet count $<130{,}000/\mu L$, hemoglobin level $<13$ g/dL, WBC count $>8{,}500/\mu L$, and creatinine level $>1.1$ mg/dL. Information regarding the percentage of infected red blood cells was not adequately collected in past medical records; therefore, parasitemia was excluded from the analysis. Finally, patients were classified on the basis of the WHO criteria for severe malaria, and the length of their hospital stay was studied to evaluate clinical outcomes.

Collected data were analyzed using the statistical software IBM SPSS Statistics 20. The Fisher exact test was used to compare 2 independent binomial proportions, and non-parametric testing (Mann–Whitney *U*-test) was performed for non-normally distributed data.

## RESULTS

Thirty-four imported malaria cases were diagnosed in our hospital from 1991 to 2010, which included 17 cases of *P. falciparum* malaria, 15 cases of *Plasmodium vivax* malaria, and 2 cases of *Plasmodium ovale* malaria (Table 1). Twenty-seven patients were Japanese, and more than 85% were pleasure and business travelers to malaria-endemic countries. A total of 7 cases were of foreigners, including 6 of immigrants who developed malaria symptoms after returning to their home countries, which were malaria endemic.

Changes in the epidemiology of imported malaria and suspected contraction areas between 1991–2000 and 2001–2010 are shown in Fig. 1. A dramatic increase in falciparum malaria cases was observed, whereas the number of patients who contracted non-falciparum malaria was remarkably small in the latter decade (Fisher's exact test, $P < 0.01$). During the latter decade, the most frequent area of disease acquisition was Africa, with 8 cases corresponding to approximately 73% of the total falciparum malaria cases, whereas only 4 cases of falciparum malaria were contracted in Africa in the earlier decade. In contrast, the number of patients who contracted non-falciparum malaria in Asia decreased to 18% in the latter decade.

Malaria cases in the earlier decade showed a sig-

Table 1. Malaria cases diagnosed in our hospital from 1991 to 2010

| | | *P. falciparum* | *P. vivax* | *P. ovale* |
|---|---|---|---|---|
| Case | | 17 | 15 | 2 |
| Age (mean ± SD) | | 32.4 ± 12.0 | 32.4 ± 12.2 | 29.5 ± 2.1 |
| Gender (male:female) | | 14:3 | 13:2 | 2:0 |
| Japanese patient | | 12 | 13 | 2 |
| Foreign patient | | 5 | 2 | 0 |
| Nationality | | India, 1<br>Africa, 2<br>England, 1<br>Australia, 1 | Africa, 1<br>India, 1 | |
| Suspected contraction area | Africa | 12 | 3 | 2 |
| | Southeast Asia | 2 | 6 | 0 |
| | South Asia | 2 | 3 | 0 |
| | Others[1)] | 1 | 3 | 0 |
| Purpose of visit | Pleasure travel | 8 | 10 | 0 |
| | Business travel | 3 | 2 | 1 |
| | Volunteer work | 2 | 0 | 1 |
| | Homecoming | 4 | 3 | 0 |

Regions of acquisition are shown by species.
[1)]: Others included 2 cases of *P. vivax* acquired in South America and 2 cases (one case of *P. vivax* and one case of *P. falciparum*) in which the patients traveled to more than one area.

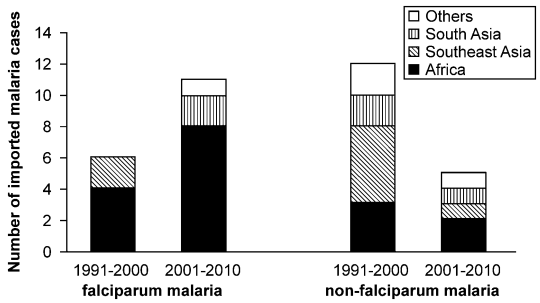


Fig. 1. Changes in the epidemiology of imported malaria and suspected contraction areas between 1991–2000 and 2001–2010. Overall, the predominant malaria species was *P. falciparum*, and the most frequent area of acquisition was Africa. The acquisition of falciparum malaria in Africa was dramatically increased in the most recent decade compared to the earlier one. In contrast, patients contracted non-falciparum malaria in Asia at a remarkably lower rate in the more recent decade (Fisher's exact test, $P < 0.01$).

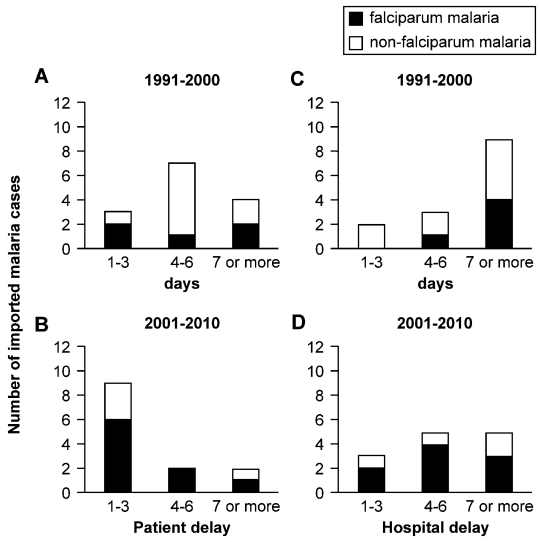


Fig. 2. Distribution of the patient delay in visiting the hospital and the hospital delay in diagnosing malaria. Delay was analyzed from 2 perspectives: (i) the period between the onset of symptoms to the first medical consultation (patient delay, 1991–2000 in [A] and 2001–2010 in [B]) and (ii) the period between the first medical consultation to the diagnosis of malaria (hospital delay, 1991–2000 in [C] and 2001–2010 in [D]). The horizontal axis represents the number of days from the onset of symptoms to the first medical consultation for the malaria patients. Longitudinal axis indicates the number of cases. The bar represents the total number of cases, and the black portion in each bar corresponds to the cases of falciparum malaria. Patient delay was significantly shorter in the more recent decade, and the hospital delay also tended to be shorter in the more recent decade.

nificantly longer patient delay period than those in the latter decade (Mann–Whitney *U*-test, $Z = 2.06$, $P < 0.05$) (Fig. 2). The mean and median patient delay periods were 6.1 days (95% confidence interval [CI], 3.3–9.0 days) and 5.0 days, respectively, (interquartile rage [IQR], 3.8–7.0 days) in the earlier decade and 3.4 days (95% CI, 2.1–4.7 days) and 2.0 days, respectively, (IQR, 2.0–5.0 days) in the latter decade. A comparison of the distribution of the patient delay between the 2 decades showed that, in the latter decade, there was a remarkable increase in the number of patients who

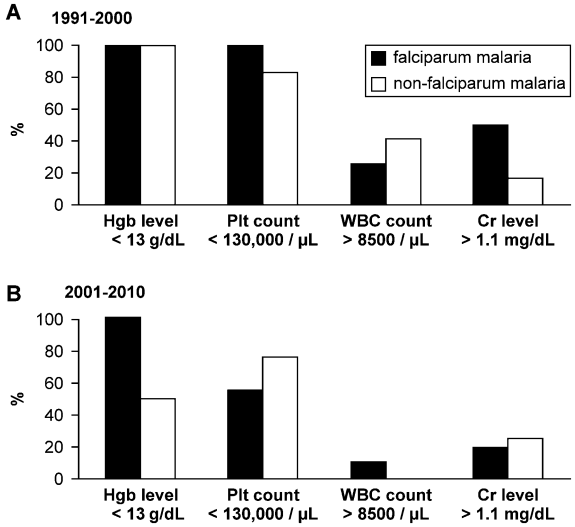


Fig. 3. Prevalence of selected 4 risk factors. Four risk factors that strongly correlate with disease severity: platelet (Plt) count, anemia, elevated white blood cell (WBC) count, and renal failure were evaluated (1991–2000 in [A] and 2001–2010 in [B]). The prevalence of these risk factors was calculated using one-zero scores, which were obtained by determining whether various values were above/below predetermined cutoffs: Plt count $< 130{,}000/\mu L$; hemoglobin (Hgb) level $< 13$ g/dL, WBC count $> 8{,}500/\mu L$; and creatinine (Cr) level $> 1.1$ mg/dL. Contrary to our expectations, the prevalence of the selected 4 risk factors was lower in the second half of the decade, although cases of falciparum malaria were predominant.

sought medical consultation within 3 days after becoming aware of malaria symptoms.

The hospital delay period also tended to be shorter during the latter decade, although the difference was not statistically significant (Mann–Whitney *U*-test, $Z = 1.68$, $P < 0.1$) (Fig. 2). During the earlier decade, the hospital delay averaged 8.8 days (95% CI, 5.9–11.7 days), and the median was 7.5 days (IQR, 5.8–11.8 days). The mean and median periods were 5.8 days (95% CI, 3.3–8.3 days) and 4.0 days, respectively, (IQR, 3.0–9.0 days) in the latter decade. More than 60% of the referral patients were transferred to our hospital after 1 week or more in the earlier decade, whereas more than one-third of the patients experienced an inter-hospital delay in the latter decade.

The impact of the delay in malaria diagnosis on patient risk for severe malaria at the first referral was subsequently analyzed. The prevalence of the 4 selected risk factors was lower both in falciparum and non-falciparum malaria cases in the latter decade (Fig. 3). However, in cases of falciparum malaria, the prevalence of all risk factors, except the platelet count, was lower in the latter decade.

The number of severe malaria cases and the length of hospital stay were compared to evaluate patient clinical outcomes. On the basis of the WHO criteria, 4 patients (with 1 death) were classified as having severe falciparum malaria in the earlier decade. In addition, only 1 case of severe malaria (vivax infection) occurred in the latter decade. Over the course of treatment, disseminated intravascular coagulation was detected in 4 patients, pulmonary edema and acute respiratory distress syndrome in 3 patients, renal failure in 3 patients, and cerebral malaria in 1 patient. Consequently, the length

of hospital stay was not prolonged in the latter decade (Mann–Whitney $U$-test, $Z = 0.73$, $P > 0.46$). The mean and median length of hospital stay from the date of admission were 11.3 days (95% CI, 8.4–14.2 days) and 9.5 days, respectively, (IQR, 8.0–14.3 days) in the earlier decade and 9.3 days (95% CI, 7.8–10.8 days) and 9.0 days, respectively, (IQR, 6.5–11.0 days) in the latter decade.

## DISCUSSION

Here, we analyzed the temporal sequence of events leading to the diagnosis and treatment of malaria by retrospectively reviewing the medical records of patients diagnosed with imported malaria in Kyoto City Hospital over a recent 20-year period. The total number of severe malaria cases did not increase between the 2 decades examined, although falciparum malaria did become more predominant. Our findings suggested that a shorter delay in seeking medical help may have reduced the risk of severe malaria, leading to early hospital discharge without complications.

According to the National Institute of Infectious Disease (NIID), Tokyo, the total number of imported malaria cases has decreased to 50–70 per year since a peak of 154 cases in 2000 (28). Although the number of malaria patients did not differ between the 2 decades examined in our study, local and national trends in contracting imported malaria were quite similar. The number of malaria patients from 1999 to 2010 in each suspected malaria-contraction area was reported on the NIID website. The website showed that the number of vivax malaria cases from Southeast Asian countries gradually decreased, whereas the number of falciparum malaria cases from African countries increased. We found the same trend in the present study.

A major clinical concern of imported malaria in Japan is the delay in medical consultation after patients become aware of malaria symptoms (7). Santos et al. reported that approximately half of malaria patients became aware of symptoms more than a week before diagnosis (19). Similarly, Miura et al. reported a mean and median duration of 4.7 and 3.0 days, respectively, between the onset of symptoms and medical consultation in Japanese patients from 1992 to 2001 (7). In addition, this duration was over 5 days in approximately one quarter of the patients who contracted falciparum malaria. In our study, the mean patient delay was over 6 days in the period from 1991 to 2000, which was slightly longer than that previously reported. It is noteworthy that some cases of delayed medical consultation were because of self-medication with analgesics or antipyretics after the onset of symptoms in our hospital during the latter decade. Therefore, the issue that remains is how to educate people who delay medical consultation regarding the potential seriousness of malaria and the need for prompt evaluation of fever during and after travel.

Dividing the 20-year time period into 2 decades revealed that the patient delay dramatically decreased in the latter decade, with approximately 70% of patients seeking medical support within 3 days after the onset of symptom. This shortened delay in seeking medical attention during the latter decade may be owing to increased accessibility to information on malaria management through websites and published traveler's guides over this time period. Guidelines for the prevention of malaria for Japanese overseas travelers were published by a group of malaria specialists under the auspices of the Japanese Society of Tropical Medicine but not until 2005. However, further studies are required to better understand when travelers obtain travel-related information on malaria, how they interpret their conditions using this information, i.e., their explanatory models, and how their experience varies because of this information.

Despite earlier hospital presentation, we found that delayed referral still occurred in the latter decade. Kain et al. reported that a diagnosis of malaria was missed by the physician at initial presentation in approximately 60% of the cases when the patient consulted a healthcare provider with no expertise in tropical medicine (17). Moreover, one-third of the patients with a history of fever consulted more than 3 physicians before malaria was suspected. In our study, a large number of patients were transferred to our hospital over 7 days after the first medical consultation in the earlier decade. Some patients were misdiagnosed with viral infections, such as flu, and others had been observed to be treating themselves with analgesics or antipyretics. The controversial issue here is that the inter-hospital delay often occurred even during the latter decade, which could have worsened the severity of malaria and subsequently led to higher mortality. Overall, a hospital delay over 7 days occurred in 4 of 5 WHO-defined severe malaria cases diagnosed in our hospital.

Typically, malaria causes a severe flu-like illness accompanied with a high fever, headache, and severe body and joint pain. Similar to a previous study, fever was recorded at presentation in more than 95% of patients, with chills and headache as the second most common symptom in our study (29). Patients, however, did not necessarily develop typical cyclical fever. Dizziness or vertigo, fatigue, arthralgia, myalgia, abdominal pain, nausea, vomiting, and diarrhea were also recorded in our cases. Most malaria patients had no specific physical findings and splenomegaly was rarely present at early disease stages (12). Laboratory data showed that thrombocytopenia was the most commonly observed abnormality in our study as previously reported (30–32). Hyperbilirubinemia, anemia, and elevated transaminase levels were also commonly observed abnormalities. However, it is difficult to distinguish malaria from non-malaria febrile illness solely on the basis of physical symptoms and laboratory data (17,32,33). Thus, a prompt diagnosis may be delayed because most patients with malaria have no specific physical and laboratory findings (34).

Malaria should be suspected more strongly, until proven otherwise, in patients with fever who have traveled to or through malaria-endemic regions. Leder et al. calculated the relative risks of presenting with malaria by region using data collected through the GeoSentinel database, a global sentinel surveillance network established through the International Society for Travel Medicine and the Centers for Disease Control and Prevention (34). They reported that the greatest relative risks occurred in travelers to sub-Saharan Africa,

followed by travelers to Oceania. Compared with the relative risk in other non-endemic areas, the relative risk was 208 in sub-Saharan Africa and 77 in Oceania. Other studies attempted to estimate the malaria risk for travelers using malaria surveillance data. These studies also showed that the risk of malaria in travelers who were not taking chemoprophylaxis was highest in sub-Saharan Africa and Oceania, intermediate in the Indian subcontinent, and lowest in Asia and Central and South America (18,35–38). Thus, it is important to obtain travel histories of febrile patients and include malaria in the differential diagnosis for those who have recently travelled to regions with higher relative risks.

The importance of obtaining travel histories from febrile patients is an issue not only for business and pleasure travelers but also for Japanese people living in endemic countries and foreign immigrants from these countries. The subjects in our study were African and Indian immigrants who developed malaria after returning from their home countries. Thus, what remains challenging is to increase awareness among community physicians of the fact that malaria can be imported to Japan not only by travelers but also by Japanese patients living in endemic regions and foreign immigrants from endemic regions. The evaluation of such cases should always include a comprehensive life history.

Typically, the period between malaria exposure and the onset of symptoms is 1–4 weeks. Approximately, 85% of non-immune patients develop malaria symptoms within 30 days of departing from a malaria-endemic area (14,17). However, clinical presentation can vary depending on the malaria-causing species. The average incubation period is 9–14 days for *P. falciparum* and 12–17 days for *P. vivax* (39). In our study, the number of patients with vivax malaria was greater in the first half of the decade. Prolonged incubation periods of vivax malaria could lead to the development of less severe clinical signs and symptoms, which possibly caused a longer patient delay in the earlier decade. However, the delay in the first medical consultation in the earlier decade could not be explained by a predominance of vivax malaria. The patient delay showed a similar distribution pattern for falciparum and non-falciparum malaria infections. In both falciparum and non-falciparum malaria cases, the median patient delay was 4–6 days and 1–3 days in the earlier and latter decade, respectively (Fig. 2).

The incubation period may be prolonged up to 2–3 months in patients taking antimalarial prophylaxis. This observation indicates that malaria must be included in the differential diagnosis among patients who have returned from an endemic area within the past 3 months and present with unexplained fever or clinical deterioration. If the patient has received a prophylactic medication, the symptoms are often mild, if present at all. In addition, the plasmodium count in the peripheral blood may be low, causing a possible delay in malaria detection.

Since the approval of mefloquine hydrochloride as an oral prophylactic medication against malaria in Japan in 2001, a number of medical institutions have established outpatient travel medicine clinics. They have also begun providing information regarding the current epidemiological trends of malaria in tourist destination countries and regions. In addition, medications for prophylactic use against malaria have been prescribed in increasing numbers, and numerous health consultations have been provided to travelers after returning to Japan. Similarly, our hospital has adopted the practice of prescribing mefloquine as a prophylactic medication against malaria since 2003. Initially, mefloquine was prescribed to approximately 5 patients per year, but since 2006, prophylactic mefloquine administration has continuously been practiced, with the number of patients receiving prophylactic treatment increasing to approximately 10–15 per year.

Unfortunately, we could not collect precise data on preventive administration in most study cases using their medical records. The lack of information on the administration of antimalarial medication in most cases makes it increasingly important to inquire about the patients' travel history (40) and the time and duration of their chemoprophylaxis for malaria.

**Acknowledgments** The authors are grateful for the tremendous support in preparing this article given by the staff of Department of Infectious Diseases. The authors also thank the laboratory technicians and medical records room staff for their support.

An earlier version of this manuscript was presented as a plenary at the 61th annual meeting of the Japanese Association for Infectious Disease in October 2012.

**Conflict of interest** None to declare.

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