Original Article

IMPORTED MALARIA IN A TERTIARY HOSPITAL IN BELGIUM: EPIDEMIOLOGICAL AND CLINICAL ANALYSIS

Yombi JC[1], Jonckheere S[1], Colin G[1], Van Gompel F[2], Bigare E[3], Belkhir L[1], Vandercam B[1]

[1]Department of Internal Medicine, Infectious Diseases and Tropical Medicine Unit, Cliniques Universitaires St Luc, Université Catholique de Louvain, Brussels, Belgium, [2]Department of Clinical Sciences, Institute of Tropical Medicine (ITMA), Antwerpen, Belgium, [3]Biostatistician, Cliniques Universitaires St Luc, Brussels, Belgium

Correspondence and offprint requests to: JC Yombi, E-mail: jean.yombi@uclouvain.be

ABSTRACT

Background and objective: There has been a marked increase in tourism, immigration, and business travel to malaria-endemic areas. Non-immune individuals (western travellers) or immigrants living for more than one year in non-endemic areas who visit friends and relatives (VFR) are particularly susceptible to developing severe malaria when travelling to areas with high levels of transmission. In this study, epidemiological, clinical and biological features of malaria in travellers returning from endemic areas were analysed. This may help clinicians unfamiliar with malaria not to overlook this disease in its early stage, and to initiate prompt treatment.

Patients and methods: we retrospectively analysed all cases of patients who presented with malaria in our institution between 2003 and 2008.

Results: Eighty patients were included. Most patients visited Africa (93.6%). Accordingly, *P. falciparum* was the main species identified (67/77 patients i.e. 87%). Sixty-five patients (65/78 i.e. 83.3%) had not taken any prophylaxis and 13 (16.7%) had taken it inadequately. Common clinical features were fever (80/80, 100%), influenza-like symptoms (16/80, 20.1%), respiratory symptoms (5/80, 6.3%), neurological symptoms (2/80, 2.5%) or digestive symptoms (15/80, 18.8%). Digestive symptoms were predominant in children < 16 y.o. (60% of these patients).

Conclusion: Imported malaria cases are mostly related to the lack of adequate use of chemoprophylaxis. *Plasmodium falciparum* is the main species responsible for imported cases of malaria in our institution. Clinical features vary, but fever is universally present at presentation. As such, all cases of fever upon return from a malaria-endemic area must be considered as malaria until proven otherwise, at least during the first three months after the return.

Key Words: Imported malaria, travellers, chemoprophylaxis, Plasmodium

INTRODUCTION

Four main Plasmodium species cause human malaria: *Plasmodium falciparum* (which is potentially fatal in non-immune travellers), *P. vivax, P. ovale*, and *P. malariae* (1). Recently, *P. knowlesi* was described in Southeast Asia (2). Ongoing transmission of malaria occurs in more than a hundred countries (3) including tropical countries with year-round transmission as well as some temperate countries where transmission occurs only during warmer seasons. Because of globalisation and increasing number of travels, non malaria-endemic countries are confronted with cases of malaria, with a risk of delayed or wrong diagnoses. It is a potential cause of death. Imported *P. falciparum* malaria occurs almost exclusively in people receiving no or inadequate chemoprophylaxis. Most imported cases of malaria occur in immigrants and their children who have returned to the country of their family's origin to visit friends and relatives (VFR travellers), and have overlooked chemoprophylaxis (4-6). This often occurs either for economic reasons or because of the mistaken belief that lifelong immunity to malaria is retained after immigration (1, 4-7). Expatriates and foreign visitors or migrants are also at high risk of developing malaria (8).

In this study, the epidemiological, clinical and biological features of malaria in travellers returning from endemic areas were analysed. We took the opportunity to review the most relevant reports in the literature as well. This might help clinicians who are not familiar with the disease not to overlook this diagnosis in its early stage, and to initiate prompt treatment.

PATIENTS AND METHODS

This is a retrospective study of all cases of malaria diagnosed in a teaching hospital of 1000 beds, between 2003-2008. The analysis was based on the electronic database of our RCM (Medical Discharge Summary), on the operating software for patient's medical records of our institution (Medical Explorer v3r0, Saint-Luc Hospital, 2008). We collected demographic features (age, gender, origin, travel area and length of stay, prophylaxis), clinical presentation (symptoms, time elapsed between return and onset of symptoms, time elapsed between onset of symptoms and diagnosis, signs of severe disease), laboratory findings (parasitaemia, plasmodium species, glycaemia, platelet count, INR, renal function, electrolytes).

Travellers are either Western travellers, i.e. non-immune natives of western countries visiting tropical countries, or VFR travellers, i.e. immigrants living for more than one year in non-endemic areas who visit friends and relatives.

Destination or travel area: Africa has been divided into central Africa, western, eastern and southern Africa. Asia has been divided into India and Southeast Asia.

Length of Travel: We divided travel length into four categories: short (< 2 weeks), medium (2 to < 4 weeks), long (1 to 3 months) and travel for residential purposes (> 3 months).

Time elapsed between return and onset of symptoms: It has been divided into three categories: < 1 month (further divided into < 1 week and 1 to 4 weeks), 1-3 months, and > 3 months.

Malaria diagnosis: diagnosis is based on microscopic analysis of a blood smear.

Parasitaemia: We used 3 different categories (9): low (< 2% of infected erythrocytes), moderate (from 2 to 5%), and high (> 5%) proportion of infected red blood cells.

Symptoms: included fever, chills, other constitutional symptoms (general malaise, weight-loss, sweats, anorexia), influenza-like symptoms (diffuse myalgia, frontal headache, mild photophobia), abdominal presentation (with abdominal pain, nausea and vomiting, diarrhoea or constipation), neurological presentation (behaviour disorders, bradypsychia), and respiratory symptoms (dyspnoea, cough).

Severe malaria: In 2000, WHO published their revisited criteria of severe malaria (10).These include clinical features: temperature > 40°C, repeated fits, Glasgow Coma Scale score of less than 10, prostration and weakness, abnormal bleeding, hemoglobinuria, respiratory failure, acute pulmonary oedema or shock (10). They also consist of laboratory findings: high parasitaemia (> 5%), renal failure, metabolic acidosis, anaemia (< 5 g/dL), hypoglycaemia (< 40 mg/dL), lactate > 5 mmol/L, bilirubine > 3 mg/dL (10). Severe (or complicated) *P. falciparum* malaria was defined by the presence, at presentation or within the 3 following days, of at least one 2000 WHO criterion of complication (10).

STATISTICAL ANALYSES

In descriptive statistics, frequency was performed to describe each categorical data. The test applied for analysis of contingence tables was χ^2, and when this one was not valid, the exact Fisher test. For continuous variables, the following statistics were calculated: mean, median, standard deviation, minimum, maximum. To compare mean values, we used T-test and to compare median values we used Mann-Whitney-Wilcoxon test. For all analyses, p-values < 0.05 were considered significant.

RESULTS

Eighty (80) patients were included in this study. Demographic data are summarised in Table 1.

Travel area: Africa was the predominant travel area, with 93.6% of patients returning from this continent. Asia only accounted for 3.9% of travellers.

Length of Travel: Almost half of the patients (49.2%) were back from a residential stay. The others had mainly travelled either for 2 to 3 weeks (29.5% of the patients), or for 1 to 3 months (13.1%).

Type of prophylaxis: Sixty-five patients (83.3%) did not take any prophylaxis. The others (13/78, i.e. 16.7%) inadequately took the prescribed regimen. Among those, 2/78 patients (2.6%) were on chloroquine, 5/78 (6.4%) on mefloquine, 4/78 (5.1%) on a combination of chloroquine and proguanil, and a few remaining patients had taken a variety of other drugs (Figure 1).

Time elapsed between return and onset of symptoms: Sixty-five patients (90.1%) presented with first symptoms within three months of their return. This includes 33.8% of patients who were admitted within the week, and 43.7% from one to two weeks, though data was scarce (71 valid items) on this particular aspect of the medical history taken upon admission.

Time between symptoms onset and diagnosis: Median delay was 3.6 days (range from 0 to 15 days). Depending on

Table 1: Malaria Demography

	N	Valid Percent
Ethnicity		
Black	24	30.4%
White	56	69.6%
Age		
< 16 y.o.	10	85.0%
16 - 65 y.o.	68	2.5%
> 65 y.o.	2	12.5%
Travel Area		
Central Africa	35	44.9%
Western Africa	31	39.7%
Eastern Africa	7	9.0%
Southeast Asia	2	2.6%
Others*	3	3.8%

* India, Yemen, West Indies, y.o: year old.

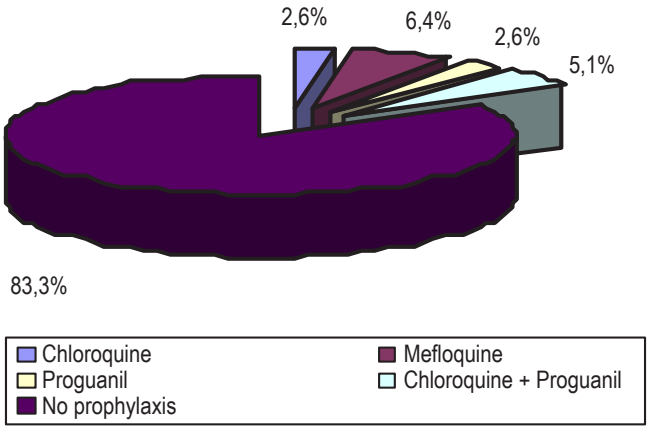

Figure 1: *Prophyloxis.*

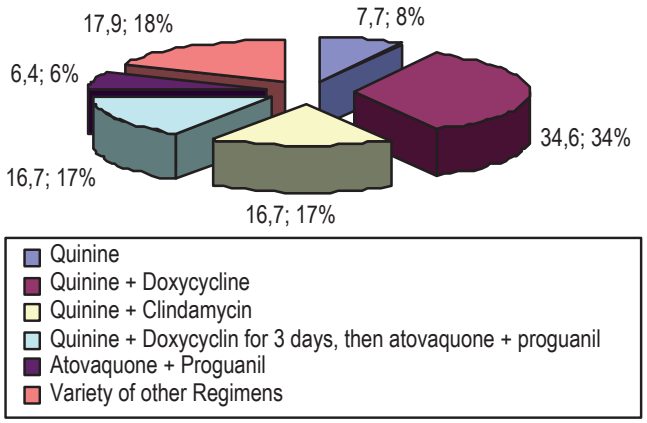

Figure 2: *Treatment Regimens.*

Plasmodium species, delays varied, from 3.1 days (0 to 14 days) for *P. falciparum*, to 9 days (4-15 days) for *P. vivax* (see Figure 2). Focusing on *P. faclciparum*, patients with complicated malaria presented with a median delay of 3.5 days (ranging 0-14 days), while uncomplicated malaria patients presented with a median delay of 2 days (0-10 days) ($p=0.045$). Patients admitted to the intensive-care unit (ICU) tended to be diagnosed after a longer duration of symptoms, with a median duration of 5.6 days (ranging from 3 to 8 days).

Plasmodium species: Sixty-six patients (85.7%) were exclusively infected with *P. falciparum*. *P. vivax* accounted for 6.5% (5/77) of cases and *P. ovale* for 5.2% (4/77) . Plasmodium species was not specified for 3 patients.

Symptoms: All (80/80) patients had fever and chills, and these were the only symptoms in 9/80 (11.3%) patients. These symptoms were associated with influenza-like symptoms in 16/80 (20.1%), to digestive symptoms in 15/80 (18.8%), to respiratory disorders in 5/80 (6.3%), and to neurological symptoms in 2/80 (2.5%) cases. The combination of fever, chills, influenza-like symptoms and digestive symptoms accounted for 8/80 (10%), whereas the combination of fever, chills, digestive and respiratory symptoms accounted for 4/80 (5%) cases. The association of fever, chills and digestive symptoms is common among children (60% of clinical presentation under the age of 16).

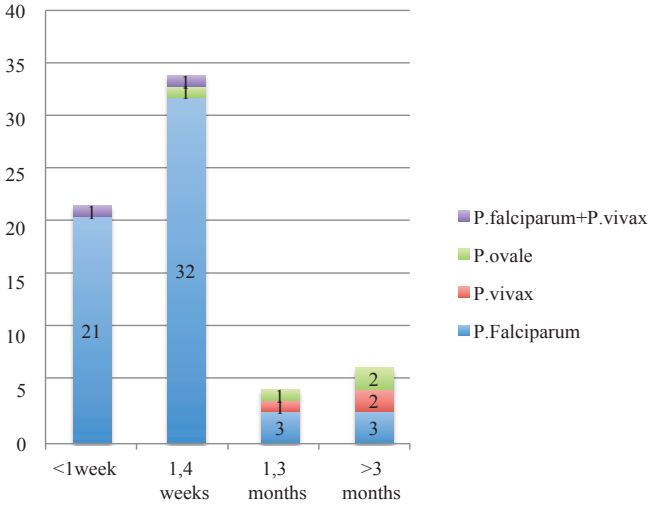

Figure 3: *Symptoms Onset/*Plasmodium *species.*

Parasitaemia: It was high in 21/78 (26.9%), moderate in 30/78 (38.5%) and low in 28/78 patients (35.9%).

Severe malaria: patients with *P. falciparum* only displayed these criteria. The most significant WHO 2000 criterion for severe malaria in our series was high parasitaemia (13/29 of severe cases, i.e. 44.8%). Thirty-three patients had uncomplicated malaria. Main features of severe vs uncomplicated *P. falciparum* malaria are summarised in Table 2.

Treatment: Initial regimens were extremely variable. The most prescribed agents were quinine either as a single agent (7.7% of cases), or combined with doxycyclin (34.6%) or clindamycin (16.7%). Atovaquone combined to proguanil was found in 6.4% of cases. The remaining patients (17.9%), benefited from a variety of other regimens (arthemeter or a combination of any three of the above molecules).

Outcome: Patients with severe malaria were hospitalised for a significantly longer period than patients with uncomplicated malaria (median of 5 vs 4 days, $p<0.001$ see Table 2). Five patients were admitted to the ICU (see Table 3). Median length of stay in hospital was 26.8 days (ranging from 2 to 62 days), versus 5 days (ranging from 2 to 12) for patients with severe malaria not admitted to the ICU. The average number of WHO-criteria for ICU patients was 7 (ranging from 3 to 10) compared with 1.2 (ranging from 1 to 3) in patients with severe malaria not admitted to the ICU. None of the patients died.

Parasitaemia and Plasmodium species: All patients with parasitaemia >2% were infected with *P. falciparum,* as expected. Even with a parasitaemia lower than 2%, *P. falciparum* remains the main species, though the proportion of *P. vivax* and *ovale* is higher (8/28 patients altogether, i.e. 28.6%).

Plasmodium species and travel-area: P. falciparum is the main species encountered in Africa and South-East Asia (100%). *P. vivax* is mostly identified when travellers are back from India and in 16.7% of patients back from western Africa.

Prophylaxis and migrants: Sixty-five patients (83.3%) had not taken any prophylaxis and 13 (16.7%) had taken it inadequately. Among VFR travellers, 19/24 patients (i.e. 79.2%) did not take any prophylaxis, compared with 84.9% (45/53) of western travellers ($p=0.795$).

Table 2 Main Characteristics of Severe vs Uncomplicated P. falciparum Malaria Cases

Parameters	Severe P. faciparum malaria cases (n = 29)	Uncomplicated or non severe P. falciparum malaria cases (n = 33)	P-Value
	Median (Min - Max)	Median (Min-Max)	
Time elapsed between onset of symptom and diagnosis	3,5 (0-14)	2 (0-10)	0,045
Lenght of hospital stay (days)	5 (2-62)	4 (1-11)	< 0 ,001
Parasitaemia(% of infected RBC)	6 (0-30)	1 (0-5)	< 0,001
Platelet count at admission (/mL)	51000 (15000 -251000)	89000 (26000-357000)	NS
Platelet count nadir (/mL)	49000 (15000 -251000)	79000 (19000-357000)	0,018
	Mean (SD)	Mean (SD)	P-Value
Haemoglobin upon admission (g/dl)	12,4 (2,5)	13,2 (2,0)	NS
Haemoglobin nadir (g/dl)	10,48 (2,39)	12,02 (2,16)	0,010

Table 3 Features of Patients admitted to the ICU (WHO 2000 revisited criteria)

	P1	P2	P3	P4	P5
Repeated Fits (> 1/24h)					
Glasgow Coma Scale Score < or = 9	x				
Weakness / Prostration / Lethargy	x	x	x	x	
Abnormal Bleeding or DIC					
Respiratory failure (Pulmonary oedema or ARDS)	x	x	x		
Shock (Systolic BP < 80 mmHg)					x
Parasitaemia > 5%	x	x	x	x	
Macroscopic Haemoglobinuria	x		x	x	
Renal Dysfunction (Creatinine > 3 mmg/dL)	x	x	x	x	
Metabolic Acidosis (HCO3- < 15 mmol/L)	x	x		x	
Severe Anaemia (Hb < 7 g/dL)	x		x	x	
Hypoglycaemia					
Clinical Hyperbilirubinaemia	x	x	x	x	x
Lactate > 5 mmol/L	x		x		
Body temperature > 40°C				x	x

DISCUSSION

Epidemiology

Historically, malaria is the most common infection leading to hospitalisation and death in returning travellers (12-14). Each year, approximately 25 to 30 million international travellers from non-tropical regions visit countries where malaria is endemic, resulting in 30,000 cases of travel-associated malaria (15-16).

In Belgium the annual number of patients diagnosed with malaria varied from 314 (1991) to 191 (2008). Plasmodium species was known in 146 cases: *P. falciparum* was the main species and accounted for 75.3% of patients; 65 patients had been visiting Africa (89%) (17). In Belgium still, Bottieau et al., found, between 2000-2005, 408/511 cases (i.e. 79,84%) of imported malaria due to *P. falciparum*. Once again Sub-saharian Africa was the predominant travel destination (8).

Most cases of *P. falciparum* acquired in travellers are reported from Sub-Saharan Africa. It demonstrates: (1) the high risk of malaria transmission in this area, (2) that *P falciparum* is the predominant plasmodium species transmitted within this area, and (3) the occurrence of transmission in both rural and urban settings (18). All these figures are in keeping with those of our series.

Prophylaxis

Compliance to antimalarial chemoprophylaxis has consistently been shown to be poor. In several reports on travellers to malaria-areas, about 50% seek travel-health advice, and fewer adhere to insect protection measures or chemoprophylaxis (19-22). Around 60% of travellers to malaria-endemic countries take no prophylaxis, a further 15 to 20% do not take antimalarial drugs according to national recommendations and, of the remainder, more than half does not complete prophylaxis (23-25). Non-compliance varies with ethnicity. According to a British study, 78% of white British travellers took antimalarial prophylaxis compared with only 13·5% of travellers from ethnic minorities (23). Bottieau et al reported that malaria chemoprophylaxis was adequately taken by only 33% of western travellers and much less so by expatriates (10%) and VFR travellers (19%) (8).

This situation with VFR can partially be due to economic reasons or it might be due also to their trust into long-standing immunity (6, 12, 21, 26-27).

In our series, there is no difference between western and VFR travellers who did not take any chemoprophylaxis. This could be because of the kind migrants admitted to our institution, who tend to be of rather favoured social extraction (economically and schooling-wise).

Diagnosis – clinical features and laboratory studies

A clinical suspicion of malaria is the usual diagnostic tool among physicians. This method is the least expensive and most widely practised in malaria-endemic areas. However, the clinical presentation is nonspecific (28-30). Therefore malaria is often overdiagnosed in endemic areas, leading to inappropriate use of antimalarials, and neglect of other diagnoses (28, 31). The opposite is true in nonendemic countries, where malaria is often not considered as a potential cause of fever, because travel history has not been inquired into. This may lead to considerable delay in diagnosis and

therefore mortality risk, specifically in case of *P. falciparum* malaria, the predominant species by far (8).

Accuracy of malaria diagnosis can be greatly enhanced by combining clinical and parasite-based findings (28, 32). It is therefore very important not to rule out malaria after one blood smear. In non-falciparum malaria, exclusion of diagnosis requires 3 separate blood smears, performed and promptly read at 12-hour intervals over a 24 to 48 hours period (33-35). If a dipstick assay is used, it must be followed up with confirmatory blood smears, which allows determination of species and quantification of parasitaemia.

Methods other than microscopy exist for diagnosing malaria. Polymerase chain reaction (PCR) and malaria rapid-diagnostic tests (RDTs) are two such diagnostic tools. PCR is highly sensitive and can differentiate malaria species (36). However, the cost, time, training and laboratory infrastructure requirements make this an unrealistic tool for wide-spread use. Many RDTs are currently available and are being increasingly used in the field. Current RDTs identify *P. falciparum*-specific histidine-rich protein II (HRP2), parasite-specific lactate dehydrogenase (pLDH) or pan-specific aldolase. RDTs that detect HRP2 antigens pose further problems as the antigens can remain in the blood for up to 3 weeks following successful treatment, confounding diagnosis when patients present with multiple episodes of fever in a short time frame (36). However, it still is useful to confirm a recent episode of malaria,treated as such but not proven.

Treatment

In our institution, Quinine is the drug most commonly used to treat malaria, either alone or in combination with either doxycycline, clindamycine or atovaquone, as per national or international guidelines (37-39). Uncomplicated *P. falciparum* malaria can be treated orally with quinine, atovaquone plus proguanil (Malarone®) or co-artemether (Riamet®). Quinine is highly effective but poorly tolerated in prolonged courses and is thus supplemented with additional treatment, usually with oral doxycycline, which allows shortening the quinine intake to 3-5 days instead of a full 7 days (37-39). Patients treated for *P. falciparum* malaria are usually admitted to hospital for at least 24 hours, since patients can deteriorate suddenly, especially early in the course of treatment. Ambulatory treatment could be considered, as a Belgian study demonstrated that it is possible and safe in treatment-naïve malaria with parasitaemia < 1%, who do not vomit, do not exhibit any criteria of severe malaria and are treated with oral atovaquone-proguanil (40).

Severe *P. falciparum* malaria, or infections complicated with a relatively high parasite count and vomiting are usually treated with intravenous therapy until the patient is well enough to continue with oral treatment (38). Treatment of choice for severe or complicated malaria currently is an infusion of intravenous quinine (35, 41-43). This may exacerbate hypoglycaemia that can occur in malaria; patients treated with intravenous quinine therefore require careful monitoring. Artesunate, a water-soluble artemisinin derivate extracted from the plant Artemesia annua (quinghao/huang hua hao), is considered safe and highly effective (44-45). Resistance to artesunate at the Cambodia–Thailand border has been reported, but artesunate resistance has not yet been considered a problem in most malaria–endemic regions (45-46). On basis of 6 randomized controlled trials comparing artesunate and quinine, a recent Cochrane review recommends artesunate as first-line treatment in adults with severe malaria in such areas (47). Similar recommendations were issued by the World Health Organization (WHO) in 2006 (39). The European surveillance network, TropNetEurope, and the Advisory Committee on Malaria Prevention in UK Travellers advocate artesunate as first-line treatment for severe *P. falciparum* malaria in travellers as well (38, 48). Unfortunately, intravenous artesunate is unlicensed in the EU (49-51).

Patients with severe or complicated malaria should be managed in a high-dependency or intensive care environment (38, 51). They may require haemodynamic support and management of acute respiratory distress syndrome, disseminated intravascular coagulation, renal impairment/failure, seizures, and severe infections including gram-negative bacteraemia/septicaemia. In our series, five patients were treated in the ICU. Criteria of admission were high parasitaemia (> 5%) with/or organ failure upon admission. In a 5-years prospective study of selective ambulatory management of imported *P. falciparum* malaria (40), all patients with high parasitaemia (> 5%) upon diagnosis developed organ failure after admission. In the same study, non-survivors presented with a substantially high average number of WHO criteria of severity (mean of 5) compared with survivors (mean of 1, 7). There was a strong correlation between mortality and the number of complications upon diagnosis (40). In our series the average number of WHO 2000 criteria of severity was 7 for patients admitted to the ICU versus 1.2 in non-ICU patients.

Outcome

Malaria is a potentially fatal but readily treatable condition. Inadequate or no chemoprophylaxis, inability of travellers and then health-care providers to recognise the importance of fever in returned travellers, and delayed initiation of treatment all contribute to the burden of severe imported malaria, especially with *P. falciparum*. When malaria cases are due to *P. falciparum*, overall fatality rate varies from 0.6 to 3.8% (52-54). Non-immune patients are more likely to have serious complications (6.3% vs 3.7% of non-immune vs immune patients) and are subsequently more likely to die (5/55 (i.e. 9·1%) non-immune patients who developed serious complications died compared with none of the immune patients) (23-24). In Belgium the fatality rate due to *P. falciparum* varies between 1.2 and 1.3% (8, 40). Recently Bruneel et al in a large cohort of 400 malaria in adults admitted to an ICU found an overall mortality of 10.5%. By multivariate analysis, three variables at ICU admission were independently associated with hospital death: older age, Glasgow Coma Scale score, and higher parasitaemia (per 5% increment) (55). In our study none of the 80 patients died.

CONCLUSION

Malaria cases are mostly related to the lack of an adequate use of chemoprophylaxis. *Plasmodium falciparum* is the main species responsible for imported cases of malaria in our institution. Clinical features vary, but fever is universally present at presentation. Therefore all cases of fever upon a return

from a malaria-endemic area must be considered as malaria until proven otherwise, at least during the first three months after the return.

CONFLICT OF INTEREST: None.

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