

Spread of *multidrug-resistant Plasmodium falciparum malaria* and predictors of treatment failures in Vietnam

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Research

Keywords: Plasmodium falciparum, severe malaria, early treatment failure, late treatment failure, Vietnam

Posted Date: December 13th, 2019

DOI: <https://doi.org/10.21203/rs.2.18720/v1>

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Abstract

Background Drug-resistant falciparum malaria is an increasing public health burden. We examined the magnitude of *Plasmodium falciparum* infection and the patterns and predictors of treatment failure in Vietnam.

Methods Medical records of all 443 patients with malaria infection admitted to the Hospital for Tropical Diseases between January 2015 and December 2018 were used to extract information on demographics, risk factors, symptoms, laboratory tests, treatment, and outcome.

Results More than half (59.8%, 95%CI 55.1%-64.4%) of patient acquired *P. falciparum* infection of whom 21.9% (95%CI 17.1%-27.4%) had severe malaria, while 10.2% (95%CI 6.8%-14.5%) and 19.2% (95%CI 14.7%-24.5%) developed early treatment failure (ETF) and late treatment failure (LTF) respectively. ETF was 6.8% among patients referred from Binh Phuoc province and Central Highland, 11.3% from other areas in Vietnam, and 6.9% from Africa. LTF was 16.2% among patients from Binh Phuoc province and Central Highland, 22.6% from other areas in Vietnam, and 27.6% from Africa. Most patients (98.5%) recovered completely. Having severe malaria was a predictor of ETF (AOR 4.42, 95%CI 1.85-10.61, P = 0.001). No predictor of LTF was identified.

Conclusion *P. falciparum* remains the prevalent malaria parasite. Despite low mortality rate, severe malaria is not rare and is a significant predictor of ETF. Parenteral artesunate and an oral partner drug should be concurrently used for severe malaria to reduce the risk for ETF. The study alerts the possibility of drug-resistant malaria in Africa and other areas in Vietnam which are known as nonendemic areas of antimalarial drug resistance. A more comprehensive study using molecular technique in these regions is required to completely understand the magnitude of drug-resistant malaria and to design appropriate control strategies.

Key words: *Plasmodium falciparum*; severe malaria; early treatment failure; late treatment failure; Vietnam

Background

Malaria is a mosquito-transmitted infection that affects 219 million people and causes 435 thousand deaths worldwide (1). Among the 5 *Plasmodium species* causing malaria in humans, *plasmodium falciparum* is responsible for the most severe forms of malaria (2). In Vietnam, *P. falciparum* is the most prevalent malaria parasite followed by *P.vivax* (3). Although the prevalence of malaria infection decreased in the last two decades, antimalarial drug resistance has been emerging in Vietnam (4, 5). Dihydroartemisinin (DHA) which is an artemisinin derivative has been used for treating malaria infection in Vietnam for more than 20 years (6). In line with the World Health Organization (WHO) recommendation (7), artemisinin-based combination therapy (ACT) including DHA and piperaquine (PPQ)

has been a mandatory first choice treatment of uncomplicated *P. falciparum* infection since 2007 (8). However, molecular markers *for artemisinin resistance have been detected* in Cambodia since 2009 and subsequently spread rapidly to other countries in the Greater Mekong Subregion (GMS) including Vietnam (9, 10). Moreover, resistance to PPQ has been confirmed recently (11). Diagnostic tests used to identify antimalarial drug resistance such as molecular assays are not always available, especially in low-resource countries (12). Therefore, monitoring response to treatment, mainly parasite clearance time and fever clearance time are recommended in the clinical management of patients with malaria and the surveillance of anti-malarial drug resistance (12). The resistance to DHA-PPQ combination therapy causes delayed parasite clearance time (13). The susceptibility of *P. falciparum* to DHA-PPQ combination therapy in southern Vietnam has declined rapidly with the increase in the proportion of patients with parasite clearance time of more than 72 hours (from 38% in 2012 to 57% in 2015) (5). To strengthen the current strategies to control the spread and impact of *drug-resistant P. falciparum* in Vietnam and other countries in the GMS, it is important to know the current burden of *P. falciparum* infection and the effectiveness of antimalarial drugs in Vietnam. The Hospital for Tropical Diseases (HTD) in Ho Chi Minh City is a tertiary hospital which receives patients with malaria from Central Highland and southern Vietnam including the Vietnam–Cambodia border area. We conducted our study at this hospital to examine the magnitude of *P. falciparum* infection, severe malaria and the response to antimalarial treatment including the pattern of and predictors for treatment failure.

Methods

Design of the study

Medical records of all patients with malaria admitted to the HTD between January 2015 and December 2018 were retrieved for review. Information derived from medical records of patients with *P. falciparum* infection was extracted and included demographics (age, sex, job, and residential address), risk factors (blood transfusion, injecting drug use (IDU), travelling to malaria endemic areas domestically and internationally within 14 days before the onset of illness (14), current health conditions (pregnancy, end stage renal disease, cirrhosis, and HIV infection), malaria disease and treatment. It is noted that if patients have any risk factor for HIV infection, they will be consulted to undertake HIV testing in accordance with the HTD guideline. Information on malaria disease and treatment included admission time, number of days of illness at the time of admission, symptoms and signs (fever, anemia, splenomegaly, and hepatomegaly), laboratory tests (malaria microscopy, parasite counts, and aminotransaminases (AST and ALT)), antimalarial and other supportive treatments, response to treatment (*number of inpatient days*, fever clearance time, parasite clearance time, and early (ETF) and late treatment failure (LTF)) (15), outcomes (recovery and death), and having malaria previously. All laboratory tests including microscopy were performed at the HTD and in line with the national laboratory performance standards. According to the HTD policy, all cases were diagnosed using microscopy. Based on the course of the disease, *P. falciparum* infection was classified into different types of severe malaria in accordance with the WHO guideline for the treatment of malaria and included shock, acute kidney failure, impaired consciousness, jaundice, anemia, hemoglobiuria, acidosis, hyperparasitemia, prostration,

convulsion, hypoglycemia and bleeding (7). ETF and LTF were defined according to the WHO recommendation (15) and the distribution of these treatment failures was also examined. Given the updated guideline that recommends *increasing* the DHA-PPQ *dosage* in treating uncomplicated *P. falciparum* infection has been utilized in Vietnam since September 2016 (16, 17), the change in the magnitude of malaria and severe malaria before and after 2017 was also examined. The study protocol was approved by the HTD's Ethics Committee (approval number 65/QD-BVBND) and the Human Research Ethics Committee at UNSW Australia (approval number HC180340).

Statistical analysis

Data were managed and analyzed using SPSS version 22 (IBM). Continuous variables were presented as means \pm one standard deviation (SD), while categorical variables were presented as percentages. For comparison a calculation of 95% confidence interval (95%CI) for the prevalence rate of *P. falciparum* infection was performed based on the number of subjects with malaria infection and the point estimate of the prevalence of *P. falciparum* infection. Similar calculations were performed for the prevalence rates of severe malaria, ETF and LTF. Chi-square, chi-square for trend and Fisher's Exact tests were used to compare categorical data. Student's t-test was used to compare continuous data. Multinomial logistic regression models were developed to test predictors of ETF and LTF. Independent variables including age, living in or travelling to malaria endemic area 14 days prior to the onset of disease, severe malaria, and number of days of illness at the time of admission ≥ 7 were entered into the ETF model. Similarly, age, severe malaria, and patients with parasitemia 72 hours of treatment were entered into the LTF model. The significant level was set at $P \leq 0.05$.

Results

Demographic characteristics of study participants

There were 443 malaria infected patients admitted to our hospital between January 2015 and December 2018. Of these patients *P. falciparum* malaria accounted for 59.8% (265/443, 95%CI 55.1% - 64.4%). Among 265 *P. falciparum* infected patients, nearly half (44.5%, 118/265) of them acquired infection before 2017 and most of them (83.4%) were male with the mean age of 35.3 ± 13.1 years (Table 1). More than half (56.3%) of patients had jobs related to the forest or worked in malaria endemic areas, including mountain farmers (29.1%), forest workers (8.7%), forest ranger (1.9%), healthcare worker working in the forest (0.4%) and working in Cambodia and Africa (16.2%). There were 6.8% and 9.4% of study participants working in Cambodia and Africa respectively. Having previous blood transfusion was documented in 1 patient and each of IDU and pregnancy was noted in the other 2 patients. No one had HIV infection. Nearly half (44.9%, 119/265) of study participants lived in malaria endemic areas and 36.6% (97/265) travelled to endemic areas within 14 days prior to the onset of disease. The number of cases was peaked during the period between November and March annually (Figure 1).

Clinical manifestations of P. falciparum infected patients

Almost all patients (99.6%, 264/265) had fever on admission, while only 0.8% had anemia, 3% had splenomegaly, and 10.2% had hepatomegaly (Table 2). Fifty-eight patients (21.9%, 58/265, 95%CI 17.1% - 27.4%) had severe malaria of whom single manifestation accounted for 77.6% (45/58, 95%CI 64.7% - 87.5%). The most common manifestations included jaundice (24.1%, 14/58), impaired consciousness (20.7%, 12/58), and shock (8.6%, 5/58). A quarter (25.3%, 67/265) of patients had developed illness for more than seven days at the time of admission. One third of study participants had AST (31.3%, 83/265) and ALT (30.2%, 80/265) >40 U/L of whom the mean AST and ALT levels were 99.6 ± 98.8 U/L and 98.1 ± 60.2 U/L respectively.

Treatment, response to treatment, and outcome of *P. falciparum* infected patients

In addition to antimalarial treatment, 5.7% (15/265) of patients received red blood cell transfusion, 4.9% (13/265) received mechanical ventilation, and 3% (8/265) undertook hemodialysis (Table 3). Hospital acquired infection was developed in 11 (4.2%) patients.

Thirty-five (13.2%) and 40 (15.1%) patients had fever and parasitemia after 3 days of antimalarial treatment respectively. The mean fever clearance time was 2.4 ± 1.5 days and the mean parasite clearance time was 53 ± 30.8 hours. ETF and LTF were documented in 27 (10.2%, 95%CI 6.8% - 14.5%) and 51 (19.2%, 95%CI 14.7% - 24.5%) patients respectively. ETF accounted for 6.8% of patients coming from or travelling to Binh Phuoc and Central Highland, 11.3% from other areas in Vietnam, 15.4% from Cambodia and 6.9% from Africa. Similarly, the proportion of LTF was 16.2% among patients coming from or travelling to Binh Phuoc and Central Highland, 22.5% from other areas in Vietnam, 19.3% from Cambodia and 27.6% from Africa. The mean number of inpatient days was 5.7 ± 3.5 . There were 29 (10.9%) patients required ICU admission and the mean *ICU length of stay* was 2.9 ± 1.5 days. Most patients (98.5%, 261/265) recovered completely and 1.5% (4/265) of patients died.

Predictors for early and late treatment failures

Patients with severe malaria were significantly more likely to develop ETF ($P < 0.001$, OR 4.3, 95% CI 1.9-9.9) and less likely to develop LTF ($P = 0.044$, OR 0.44, 95% CI 0.19-0.99) compared with those who did not have severe malaria (Table 4). Gender, age, living in or travelling to malaria endemic areas 14 days prior to the onset of disease, number of days of illness > 7 days at the time of admission, acquiring malaria before 2017 and hyperparasitemia ($P > 0.05$) were not a predictor of ETF and LTF. Similarly, having parasitemia 72 hours of treatment and fever 3 days of treatment ($P > 0.05$) were not predictors of LTF.

Model for the prediction of early and late treatment failures

No predictor for ETF was identified other than having severe malaria (AOR 4.42, 95% CI 1.85-10.61, $P = 0.001$) (Table 5). No predictor for LTF was identified.

Discussion

A total of 433 patients with malaria admitted to the HTD between 2015 and 2018. Of these 433 patients more than half (59.8%, 95%CI 55.1% - 64.4%) acquired *P. falciparum* infection. This prevalence is lower than the rate of 98% (95%CI 97.5% - 98.5%) reported in 1990 (18) which is probably due to the effectiveness of ACTs (19). We found that most patients were male in labor age and more than half (56.3%) of them had jobs related to the forest or worked in areas which are known as malaria endemic areas in Vietnam, Cambodia and Africa (20, 21). Additionally, more than 80% of patients lived in or traveled to malaria endemic areas within 14 days before the onset of disease which is an established risk for malaria infection (14). These findings were not surprised since according to Vietnamese culture, *breadwinner* is perceived as the *man's* role in the *family*, and therefore more men tend to be exposed to malaria infection than women when they work in or travel to malaria endemic areas (22). At this stage, most malaria morbidities and mortalities occur in 21 out of 58 provinces, of which forested areas of provinces located in Central and Central-Southern Vietnam account for the highest malaria burden in Vietnam (23). In our study, *P. falciparum* infection was recorded throughout the year and peaked during the months from November to March of the following year. In Vietnam, Lunar New Year holiday which is the most important holiday usually occurs in the second half of this period. Based on our experience, to financially prepare for the holiday many people travel to malaria endemic areas to work in this period in response to the increase in the number of seasonal jobs in these areas.

Blood transfusion and IDU are considered as malaria risk factors (24, 25). We found only one patient who was suspected to have malaria infection from blood transfusion. Two other cases were injecting drug users who may have shared needles and syringes in the days before their illness developed. Pregnancy is the high risk for developing severe malaria (26). Fortunately, two pregnant patients in our study had uncomplicated malaria. HIV infection has been reported as an underlying disease that may delays parasite clearance time (27). We did not detect any HIV infection in our study.

According to the WHO definition of severe falciparum malaria (28) and the Vietnam Ministry of Health guidelines for the management of malaria infection (16), patients were classified into uncomplicated and severe malaria groups. In our study, severe malaria accounted for 21.9% (95%CI 17.1% - 27.4%) which is higher than the rate of 9.1% (277/3053, 95%CI 8.1% - 10.1%) reported in 1990 in Vietnam (18). Although our rate is comparable to the rate in Africa which is estimated to be between 10% and 70% based on a simulation-based study (29), our rate is higher than the rate of 6.6% (43/650, 95%CI 4.8% - 8.8%) from a study conducted in low and unstable malaria transmission settings of Colombia (30). This is probably because our hospital is a leading referral hospital that receives more severe cases. Our rate is also higher compared with the results of a study conducted on international travelers who were mostly exposed in sub-Saharan Africa (7.8%, 444/5689, 95%CI 7.1% - 8.5%) (31) because patients infected with all 4 *Plasmodium* species were recorded in this study.

Regarding the clinical symptoms, similar to previous reports (30, 32), fever was frequent (99.6%), while anemia was rare (0.8%) in our study. However, splenomegaly was reported to be a common symptom

among *P. falciparum* infected patients, while hepatomegaly was not mentioned in another study (32). We only detected splenomegaly in only 3% and hepatomegaly in up to 10.2% of study participants. Among 58 cases with severe malaria, the most common manifestations were impaired consciousness (20.7%), jaundice (24.1%) and mixed manifestations (22.4%). Other manifestations of severe malaria included anemia, renal failure, hyperparasitemia and shock. Our findings are in line with the other reports (18, 30). Mild elevations of transaminases are common in *Plasmodium* infection, particularly in *P. falciparum* infection because of hemolysis that affects the liver function (33). About 30% of patients in our study had transaminase higher than 40 U/L. Treatment delay of seven days or more is documented to be a risk for severe malaria with multi-organ failure (34). We noted that 25% of study population admitted to our hospital after seven days of illness and this included some patients receiving treatment from previous hospitals. In our study, more than one fifth of study participants receiving treatment from previous hospitals had been misdiagnosed as having dengue infection or septicemia. An inappropriate therapy provided in previous hospitals could aggravate patient's condition (35). This could explain why some patients admitted to the HTD late, after 7 days of disease and developed severe malaria. Therefore, clinicians must be more alerted to malaria infection when patients have a travel history to endemic areas (35). In addition, severe malaria should be suspected if patients have been under inappropriate treatment (36).

DHA-PPQ combination has been widely used as a first-choice therapy for *P. falciparum* infection in many countries including Vietnam (44). However, the spread of artemisinin and partner drug resistance have caused high treatment failure rates to this combination (45) and subsequently threatens the success of malaria control and elimination (9). In Vietnam, before 2015 DHA-PPQ treatment dose depended on patient's age (46). However, many studies have showed that PPQ under-dosing (<48mg/kg) is an important factor for recrudescence parasitemia (44, 47). In order to optimize the effectiveness of DHA-PPQ, the WHO recommends treatment with 3 days of ATCs to cover at least two asexual life cycles of *P. falciparum* and DHA-PPQ weight-based dosing (7). In September 2016 the Vietnam Ministry of Health adopted the WHO guideline which has been widely used since 2017 (16). It is documented that the increased dose of DHA-PPQ reduces recrudescence parasitemia and sequentially decreases treatment failure (44). However, we did not find any difference in the proportion of ETF and LFT before and after 2017 in our study. The TRACII trial in 2015-2018 showed a substantial increase in the burden of DHA resistance (i.e. parasites carrying kelch13 Cys580Tyr mutations) and PPQ resistance (i.e. parasites carrying plasmepsin2/3 amplifications and crt mutations) in the GMS including Binh Phuoc- Vietnam compared to the TRACI trial in 2011-2013 (40). This increased burden of parasites carrying *mutations is probably responsible for the unchanged proportions of ETF and LTF before and after 2017 in our study even though the new treatment guideline has been utilized. To response to this increased burden of parasites carrying mutations, it has been suggested that the use of DHA-PPQ should be abandoned in the affected countries including Vietnam* (45).

A study on African children with uncomplicated falciparum malaria demonstrated the association between age less than 2 years and delayed parasite clearance (48). In addition, hyperparasitemia (>50.000/ul) was also reported as a predictor of delayed parasite clearance (48). We did not find any

association between both two treatment failure types and age and hyperparasitemia. However, we found that having severe malaria was a significant predictor of ETF ($P < 0.001$, OR 4.3, 95% CI 1.9-9.9) which has not been reported elsewhere. Similar to other countries, in Vietnam, treatment of severe malaria is at least 24 hours of parenteral artesunate single-therapy plus a three-day oral DHA-PPQ combination therapy when the patient can tolerate oral therapy (16). We wonder if the variation in time to receive DHA-PPQ combination therapy and the above-mentioned DHA-PPQ resistance may facilitate ETF among patients with severe malaria. In light of this, early initiation of combination therapy including parenteral artesunate and an oral partner drug for severe malaria may reduce the risk for ETF. It is important to re-evaluate the effectiveness of the current WHO recommended antimalarial therapy for both uncomplicated and severe malaria as well as to develop new intramuscular or parenteral antimalarial drugs in the context of antimalarial drug resistance in the GMS.

Our study had some limitations. First, this is a single center study, and thus we may have missed patients with falciparum infection receiving treatment at other hospitals but were not referred to the HTD. However, the HTD is the only major tertiary teaching hospital for infectious diseases including malaria in southern Vietnam and receives not only local patients, but also patients from the other countries. This would enhance the generalizability of the study findings. Our study interval included the period when the WHO's new treatment guideline has been adopted. This allowed us to examine the change in the pattern of treatment failure in response to the utilization of the new guideline. Second, we were unable to perform molecular tests to further examine the magnitude of parasites carrying *mutations* due to the nature of a retrospective study. Third, we were unable to examine the presence of *parasitemia* on *day 28* for all patients due to the same reason. *We may have missed some cases who had parasitemia on day 28 but did not exhibit any clinical symptom. Therefore, the burden of LTF that we have identified may be underestimated.*

Conclusions

P. falciparum remains the prevalent malaria parasite in Vietnam. Despite the low mortality rate, severe falciparum malaria is not rare and having severe malaria is a significant predictor of ETF. Parenteral artesunate and an oral partner drug should be concurrently used for severe malaria to reduce the risk for ETF. The study alerts the risk of the spread of *P. falciparum* that is resistant to both DHA and PPQ to other areas in Vietnam and Africa which are currently known as nonendemic areas of antimalarial drug resistance. A more comprehensive epidemiological survey using molecular technique in these regions is required to completely understand the magnitude of antimalarial drug resistance and to design appropriate control strategies.

Abbreviations

95% confidence interval: 95%CI

Artemisinin-based combination therapy: ACT

Aminotransaminases AST and ALT

Dihydroartemisinin: DHA

Early treatment failure: ETF

Greater Mekong Subregion: GMS

Hospital for Tropical Diseases: HTD

Injecting drug use: IDU

Piperaquine: PPQ

World Health Organization: WHO

Declarations

Ethics approval and consent to participate: The study protocol was approved by the HTD's Ethics Committee (approval number 65/QD-BVBND) and the Human Research Ethics Committee at UNSW Australia (approval number HC180340).

Consent for publication: Not applicable

Availability of data and materials: The datasets used during the current study are available from the corresponding author on reasonable request

Acknowledgements: We thank Drs Cao Xuan Nam and Nguyen Thien Duc for cross-checking the validity of data.

Funding: Minh Cuong Duong is funded by the Australian Government through the Australian Alumni Grants Fund

Competing interests: No relevant disclosures

Authors' contributions: conceptualization: MCD, OKNP and PNH; data acquisition: OKNP, MCD, PTN, VVCN and PNH; formal analysis and writing original draft: MCD, OKNP and PNH; reviewing and editing: MCD, OKNP, PTN, VVCN and PNH.

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Tables

Table 1. Demographic characteristics of 265 *P. falciparum* infected patients receiving treatment at the Hospital for Tropical Diseases between 2015 and 2018

Characteristics	Summary statistics ^a
Male	83.4 (221)
Age (years)	
Mean \pm SD	35.3 \pm 13.1
Median (LQR - UQR)	33 (27 - 43.5)
Min - Max	2 - 85
Jobs	
Forest ranger	1.9 (5)
Mountain farmer	29.1 (77)
Forest worker	8.7 (23)
Healthcare worker working in the forest	0.4 (1)
Working in Cambodia	6.8 (18)
Working in Africa	9.4 (25)
Others*	43.7 (116)
Acquiring malaria before 2017	44.5 (118)
Concurrent health condition and lifestyle factors	
Blood transfusion	0.4 (1)
IDU	0.8 (2)
Pregnancy	0.8 (2)
Living in or travelling to malaria endemic areas 14 days prior to the onset of disease	
Living in endemic areas	
Travelling to endemic areas	44.9 (119)
Unknown	36.6 (97)
	18.5 (49)

^a%(N) for categorical variables and Mean \pm SD, Median (LQR, UQR) and Min - Max for continuous variables

*Others include office workers, teachers, and retailers

Table 2. Clinical patterns of *P.falciparum* infection among 265 infected patients receiving treatment at the Hospital for Tropical Diseases between 2015 and 2018

Characteristics	Summary statistics ^a
Signs and symptoms	
Fever on admission	99.6 (264)
Anemia	0.8 (2)
Splenomegaly	3 (8)
Hepatomegaly	10.2 (27)
Severe malaria	21.9 (58)
Manifestations of severe malaria (n = 58)	
Single manifestations	77.6 (45)
Shock	8.6 (5)
Acute kidney failure	6.9 (4)
Impaired consciousness*	20.7 (12)
Jaundice	24.1 (14)
Anemia	6.9 (4)
Hemoglobinuria	1.7 (1)
Acidosis	1.7 (1)
Hyperparasitemia	6.9 (4)
Prostration	0
Convulsions	0
Hypoglycemia	0
Bleeding	0
Mixed manifestations (i.e. patients had more than one severe manifestation)	22.4 (13)
Receiving treatment at previous hospital	31.7 (84)
Diagnosis at previous hospital (n = 84)	
Malaria	78.6 (66)
Others (i.e. dengue infection and septicemia)	21.4 (18)
Number of days of illness > 7 days at the time of admission (days)	25.3 (67)
Number of days of illness at the time of admission (days)	
Mean ± SD	6.6 ± 5.1
Median (LQR, UQR)	5 (3, 8)

Min - Max	1 - 30
AST > 40 U/L	31.3 (83)
Highest AST recorded (U/L) (n = 83)	
Mean \pm SD	99.6 \pm 98.8
Median (LQR, UQR)	67 (53, 116)
Min - Max	41 - 864
ALT > 40 U/L	30.2 (80)
Highest ALT recorded (U/L) (n = 80)	
Mean \pm SD	98.1 \pm 60.2
Median (LQR, UQR)	76.5 (52.5, 121.5)
Min - Max	43 - 308

^a%(N) for categorical variables and Mean \pm SD, Median (LQR, UQR) and Min - Max for continuous variables

* Glasgow coma score <11 in adults. There were 19 children patients in this study and none of them had impaired consciousness

Table 3. Treatment and outcome of 265 *P. falciparum* infected patients receiving treatment at the Hospital for Tropical Diseases between 2015 and 2018

Characteristics	Summary statistics ^a
<i>Mechanical ventilation</i>	4.9 (13)
<i>Hemodialysis</i>	3 (8)
<i>Red blood cell transfusion</i>	5.7 (15)
<i>Hospital acquired infection (HAI)</i>	4.2 (11)
Patients with fever 3 days of treatment	13.2 (35)
<i>Fever clearance times (days)</i>	
Mean \pm SD	2.4 \pm 1.5
Median (LQR, UQR)	2 (1, 3)
Min - Max	1 - 14
Patients with parasitemia 72 hours of treatment	15.1 (40)
<i>Parasite clearance times (hours)</i>	
Mean \pm SD	53 \pm 30.8
Median (LQR, UQR)	48 (30, 72)
Min - Max	1 - 228
<i>Early treatment failure</i>	10.2 (27)
<i>Distribution of early treatment failure</i>	
<i>Vietnam</i>	
Binh Phuoc and Central Highland (n = 148)	6.8 (10)
Other areas (n = 62)	11.3 (7)
Cambodia (n=26)	15.4 (4)
Africa (n = 29)	6.9 (2)
<i>Late treatment failure</i>	19.2 (51)
<i>Distribution of late treatment failure</i>	
<i>Vietnam</i>	
Binh Phuoc and Central Highland (n =148)	16.2 (24)
Other areas (n = 62)	22.6 (14)
Cambodia (n= 26)	19.2 (5)
Africa (n= 29)	27.6 (8)

<i>Number of inpatient days</i>	
Mean \pm SD	5.7 \pm 3.5
Median (LQR, UQR)	5 (4, 6)
Min - Max	1 - 28
ICU admission	10.9 (29)
<i>Response to treatment</i>	
<i>Recovery</i>	98.5 (261)
<i>Death</i>	1.5 (4)

^a%(N) for categorical variables and Mean \pm SD, Median (LQR, UQR) and Min - Max for continuous variables

Table 4. Unadjusted predictors tested for early and late treatment failures

	Early treatment failure*			OR (95%CI)	Late treatment failure*			
	Yes (n = 27)	No (n = 238)	P		Yes (n = 51)	No (n = 214)	P	OR (95%CI)
	88.9 (24)	82.8 (197)	0.5 ^a		90.2 (46)	81.8 (175)	0.1 ^c	
or travelling to malaria areas 14 days prior to the onset	29.6 (8)	46.6 (111)	0.054 ^b		41.2 (21)	45.8 (98)	0.4 ^b	
in endemic area	40.7 (11)	36.1 (86)			35.3 (18)	36.9 (79)		
to endemic area	29.6 (8)	17.2 (41)			23.5 (12)	17.3 (37)		
coming and not traveling to area								
no malaria before 2017	55.6 (15)	43.3 (103)	0.2 ^c		47.1 (24)	43.9 (94)	0.7 ^c	
more than 7 days of illness at the time of diagnosis	11.1 (3)	26.9 (64)	0.07 ^c		29.4 (15)	24.3 (52)	0.5 ^c	
no parasitemia	0	0.4 (1)	1 ^a		0	0.5 (1)	1 ^a	
no malaria	55.6 (15)	22.5 (43)	<0.001 ^c	4.3 (1.9 - 9.9)	15.7 (8)	29.9 (50)	0.044 ^c	0.44 (0.19 - 0.99)
	39.9 ± 12.9	34.8 ± 13.0	0.055 ^d		32.1 ± 12.3	36.1 ± 13.2	0.054 ^d	
no parasitemia 72 hours of diagnosis					25 (12)	13.5 (28)	0.047 ^c	2.14 (0.99 - 4.66)

								4.61)
with fever 3 days of treatment					14.6 (6)	15.8 (29)	0.9 ^c	

* %(N) for categorical variables and Mean ± SD for continuous variables

^a Fisher's Exact test

^b Chi-square for trend test

^c Chi-square test

^d Student's t test

Table 5. Multinomial logistic regression analysis for predictors of early and late treatment failures

Factors	Early treatment failure		Late treatment failure	
	P	Adjusted OR (95%CI)	P	Adjusted OR (95%CI)
Age (years)	0.25	1.02 (0.99 - 1.05)	0.11	0.98 (0.95 - 1.01)
History of or travelling to malaria endemic areas 14 days prior to onset of disease	0.24	0.49 (0.15 - 1.60)		
History of malaria	0.001	4.42 (1.85 - 10.61)	0.094	0.49 (0.21 - 1.13)
Duration of days of illness at the time of admission > 7 days	0.09	3.02 (0.84 - 10.80)		
Patients with parasitemia 72 hours of treatment			0.11	1.93 (0.87 - 4.30)

Figures

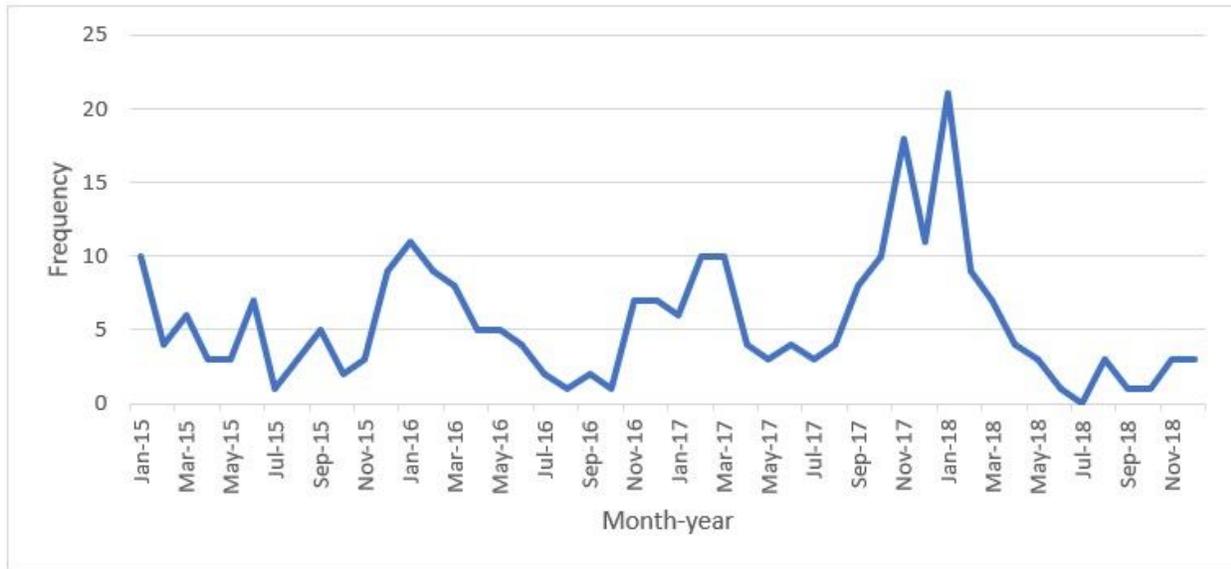


Figure 1

Frequency distribution of *P. falciparum* infected cases between January 2015 and December 2018