Epidemiology of *Plasmodium falciparum* Malaria and Risk Factors for Severe Disease in Hubei Province, China

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Abstract. This study aimed to describe the epidemiology of *Plasmodium falciparum* malaria and identify risk factors for severe disease in Hubei Province, China, using a case-based survey of retrospective data from 2013 to 2018. From 2013 to 2018, a total of 763 imported malaria cases were reported in Hubei Province; 69.2% (528/763) cases were caused by *P. falciparum* species. The proportion of malaria caused by *P. falciparum* increased from 66.7% in 2013 to 74.0% in 2018 ($\chi^2 = 21.378$, $P < 0.05$). *Plasmodium falciparum* malaria was reported in 77 counties of Hubei Province. The majority of imported *P. falciparum* cases originated from Africa (98.9%, 522/528); 9.7% (51/528) of patients infected with *P. falciparum* developed severe malaria. Three deaths (case fatality rate: 0.6%) were related to imported *P. falciparum* malaria. Risk factors for severe malaria were being female (odds ratio [OR] = 3.593, 95% CI: 1.003–12.874), age ≥ 50 years (OR = 2.674, 95% CI: 1.269–5.634), > 3 days between symptom onset and diagnosis (OR = 2.383, 95% CI: 1.210–4.693), and the first-visit medical institution at the township level or lower (OR = 2.568, 95% CI: 1.344–4.908). Malaria prevention should be undertaken among high-risk groups, infection with *P. falciparum* should be detected early to prevent severe disease and death, and healthcare providers in health facilities at the township level should be trained on early recognition of malaria.

INTRODUCTION

Malaria is one of the most common parasitic diseases in the world. According to the latest global estimates, in 2018, there were 228 million cases of malaria and 405,000 deaths.¹ Infection with *Plasmodium falciparum* species is the most common cause of severe malaria.² Importation of *P. falciparum* from endemic areas remains a challenge for malaria-free countries and countries working toward eliminating malaria. According to the WHO, 2–16% of imported *P. falciparum* infections caused severe malaria.³ With China working toward malaria elimination in 2020, no indigenous cases have been reported since 2017.⁴ However, the number of imported malaria cases in China has increased. Of 26,601 cases reported between 2011 and 2018, 93% were imported, with *P. falciparum* accounting for the majority of cases (58.3%, 15,501/26,601).^{5–7} From 2016 to 2018, the case fatality ratio of *P. falciparum* malaria was 5.05 per 1,000 cases (29 deaths in 5,745 *P. falciparum* imported cases).^{6–8}

The number of imported *P. falciparum* malaria cases has been rising in Hubei Province (from 28 in 2010 to 105 in 2014).⁹ *Plasmodium falciparum* malaria is challenging because of its potential of resulting in severe cases and death. Reducing severe cases and deaths caused by imported *falciparum* malaria is one of the important goals in Hubei Province. To better understand and address this challenge, we conducted a case-based epidemiological survey on each imported *P. falciparum* malaria case in Hubei Province and described their epidemiological profiles using data from the China Information System for Disease Control and Prevention (CISDCP) and Information System for Parasitic Disease Control and Prevention (ISPDPC) collected between 2013 and 2018. In addition, we identified risk factors associated with

severe malaria to help improve measures aimed at the prevention and management of *P. falciparum* malaria.

METHODS

Malaria case definition. All *P. falciparum* malaria cases were confirmed through microscopy, rapid diagnostic tests, or polymerase chain reaction. In this study, we excluded cases of mixed infections of *P. falciparum* with other species from *falciparum* malaria cases. Only *P. falciparum* infections were included in the analysis. The definition of imported malaria was based on the technical scheme of malaria elimination in China definition, where an imported case is defined as an individual with malaria who traveled to a malaria-endemic area outside China within the previous month of disease onset. “Severe” *P. falciparum* malaria was defined based on previously described criteria^{2,10}: 1) impaired level of consciousness, 2) prostration, 3) anemia (hemoglobin < 7 g/dL and packed cell volume $< 20\%$ in adults), 4) renal impairment (serum creatinine > 265 $\mu\text{mol/L}$), 5) pulmonary edema or acute respiratory distress syndrome, 6) hypoglycemia with blood glucose level < 2.2 mmol/L, 7) circulatory collapse or shock (systolic blood pressure < 80 mmHg in adults), 8) clinical jaundice, 9) hemoglobinuria, 10) acidosis (plasma bicarbonate < 15 mmol/L), and 11) hyperlactatemia (plasma lactate level > 5 mmol/L).

Data collection. Data on individual *P. falciparum* cases reported at the county level in Hubei Province during 2013–2018 were obtained from the CISDCP and ISPDPC. Extracted patient characteristics included gender, age, nationality, purpose of travel, history of malaria infection, symptom onset before or after return to China, month of symptom onset, time from onset to diagnosis, and the administrative level of first-visit medical institution. Clinical information on severe malaria was obtained from attending clinicians after extraction of the medical records.

Statistical analysis. Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL). Categorical variables were reported as frequencies, whereas continuous variables were

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TABLE 1
Descriptive statistics of *P. falciparum* in Hubei Province, China, 2013–2018

Characteristic	2013	2014	2015	2016	2017	2018	Total
Total cases, <i>N</i>	129	140	120	151	96	127	763
<i>P. falciparum</i> (% of total cases)	86 (66.7)	105 (75.0)	91 (75.8)	103 (68.2)	49 (51.0)	94 (74.0)	528 (69.2)
Number of counties with imported <i>P. falciparum</i> cases	31	40	35	41	26	40	77*
Severe cases of <i>P. falciparum</i> (% of total <i>P. falciparum</i> cases)	11 (12.8)	9 (8.6)	10 (11.0)	10 (9.7)	4 (8.2)	7 (7.4)	51 (9.7)
Death number	1	1	0	0	1	0	3

P. falciparum = *Plasmodium falciparum*.

* County with imported *P. falciparum* cases for more than 1 year was counted only once.

reported as median and interquartile range (IQR). For categorical variables, the differences in characteristics between groups were tested using χ^2 test. Logistic regression analysis was used to identify risk factors associated with severe malaria, and to estimate associated odds ratios (ORs) and corresponding 95% CI. Only variables with *P*-values < 0.05 were considered to be statistically significant. ArcGIS version 10.0 (ESRI Inc., Redlands, CA) was used to present the geographical distribution of *P. falciparum* cases.

Ethical considerations. This study was reviewed and approved by the Ethics Review Committee of the Hubei Provincial CDC. As the study was based on a retrospective review of disease reported data, informed consent was waived.

RESULTS

Epidemiological profiles of *P. falciparum* cases. From 2013 to 2018, a total of 763 malaria cases were reported in Hubei Province. All the reported malaria cases were imported. *Plasmodium falciparum* was the most predominant species (69.2%, 528/763) of all reported malaria cases, with the highest peak occurring in 2014 (105 cases) and the smallest in 2017 (49

cases). The proportion of malaria cases caused by *P. falciparum* increased from 66.7% in 2013 to 74.0% in 2018 ($\chi^2 = 21.378$, $P < 0.05$). In 2018, a total of 127 imported malaria cases were reported, and 74.0% of them were identified as *P. falciparum* (Table 1). The number of counties with imported *P. falciparum* cases ranged from 31 to 41 per year; *P. falciparum* malaria cases were reported in 77 counties of Hubei (Figure 1). Of the patients with *P. falciparum* malaria, 9.7% (51/528) had severe malaria. The trend of proportion of patients with severe malaria from 2013 to 2018 was 12.8% (11/129), 8.6% (9/140), 11.0% (10/120), 9.7% (10/151), 8.2% (4/96), and 7.4% (7/127), respectively (Table 1). Three patients with *P. falciparum* malaria died (case fatality rate of 0.6%), and all of them were men who had returned from African countries. The times from onset of symptoms to diagnosis were 7, 8, and 4 days (Table 2).

Region of infection acquisition for imported *P. falciparum* cases. As shown in Figure 2, between 2013 and 2018, the 528 *P. falciparum* malaria cases imported into the Hubei Province were from 37 countries located in Africa, Asia, and South America. The largest number of imported cases was from Africa (98.9%, 522/528), mainly from Nigeria (13.1%, 69/528), Congo (Kinshasa) (12.3%, 65/528), Angola (12.1%, 64/528), Congo

FIGURE 1. Distribution of imported *Plasmodium falciparum* malaria cases at the county level in Hubei Province from 2013 to 2018. This figure appears in color at www.ajtmh.org.

TABLE 2
Demographic characteristics of patients who died because of *Plasmodium falciparum* malaria

Case number	Year	Age (years)	Gender	Nationality	Travel purpose	Origin country	Illness and diagnose		
							Month of onset	Time from onset to diagnosis (days)	The level of the first-visit health institution
1	2013	30	Male	Chinese	Labor	Congo (Kinshasa)	January	7	County hospital
2	2014	41	Male	Chinese	Business	Mozambique	March	8	County hospital
3	2017	28	Male	Chinese	Translator	Nigeria	October	4	Private clinics

(Brazzaville) (6.3%, 33/528), Liberia (5.7%, 30/528), and Ghana (5.3%, 28/528). Of the 51 patients who had severe malaria, 98.0% (50/51) had traveled to Africa.

Characteristics of patients with imported *falciparum* malaria in Hubei Province from 2013 to 2018. Characteristics of patients with imported *P. falciparum* malaria are shown in Table 3. Men were predominant in both non-severe (97.1%, 463/477) and severe cases (92.2%, 47/51). The median age of non-severe and severe cases was 40 (30–46) years and 40 (28–49) years, respectively. There was a significant difference in the proportion of patients aged ≥ 50 years between non-severe and severe cases ($\chi^2 = 5.179$, $P < 0.05$). There were no significant differences between non-severe and severe cases with regard to gender, nationality, and travel purpose, symptom onset before or after return to China, and month of symptom onset ($P > 0.05$).

The median time from onset to diagnosis was 3 days (IQR = 3–6 days) for non-severe cases and 5 days (IQR = 3–9 days) for severe cases; there was a significant difference in the proportion of cases with > 3 days from onset to diagnosis between non-severe and severe cases ($\chi^2 = 10.000$, $P < 0.05$). There was a difference in the history of malaria infection ($\chi^2 = 5.539$, $P < 0.05$), and the

proportion of first visits to medical institutions at a township level or lower ($\chi^2 = 12.212$, $P < 0.05$) (Table 3).

Risk factors for severe malaria. Being female (OR = 3.593, 95% CI: 1.003–12.874), age ≥ 50 years (OR = 2.674, 95% CI: 1.269–5.634), > 3 days between symptom onset and diagnosis (OR = 2.383, 95% CI: 1.210–4.693), and the first-visit medical institution at the township level or lower (OR = 2.568, 95% CI: 1.344–4.908) were identified as risk factors for severe malaria. However, no significant association was found between severe cases and nationality, purpose of travel, no history of malaria infection, symptom onset before return to China, and month of symptom onset in January and February ($P > 0.05$) (Table 4).

DISCUSSION

The present study has identified changes in epidemiological characteristics of *P. falciparum* malaria imported over the past 6 years into Hubei Province, China. *Plasmodium falciparum* was the most predominant species imported. This situation is similar to the distribution of *P. falciparum* in China.^{4,5,11} Men and middle-aged adults constituted most *P. falciparum* malaria cases during

FIGURE 2. Imported *Plasmodium falciparum* malaria country of acquisition in Hubei Province during 2013–2018. This figure appears in color at www.ajtmh.org.

TABLE 3
Characteristics of patients with imported *P. falciparum* malaria in Hubei Province from 2013 to 2018

Variable	All (n = 528)	Non-severe (n = 477)	Severe (n = 51)	χ^2	P-value
Gender, n (%)					
Male	510 (96.6)	463 (97.1)	47 (92.2)	2.045	0.153
Female	18 (3.4)	14 (2.9)	4 (7.8)		
Age (years)					
Median (IQR)	40 (30–47)	40 (30–46)	40 (28–49)		
Age-group (years), n (%)					
0–49	458 (86.7)	419 (87.8)	39 (76.5)	5.179	0.023
≥ 50	70 (13.3)	58 (12.2)	12 (23.5)		
Nationality, n (%)					
Chinese	515 (97.5)	465 (97.5)	50 (98.0)	0.000	1.000
Africa	13 (2.5)	12 (2.5)	1 (2.0)		
Travel purpose, n (%)					
Labor	479 (90.7)	434 (91.0)	45 (88.2)	0.152	0.697
Other*	49 (9.3)	43 (9.0)	6 (11.8)		
History of malaria infection, n (%)					
Yes	319 (60.4)	296 (62.1)	23 (45.1)	5.539	0.019
No	209 (39.6)	181 (37.9)	28 (54.9)		
Symptom onset, n (%)					
Before return to china	61 (11.6)	56 (11.7)	5 (9.8)	0.169	0.681
After return to china	467 (88.4)	421 (88.3)	46 (90.2)		
Months of symptom onset, n (%)					
1–2	115 (21.8)	104 (21.8)	11 (21.6)	0.001	0.969
3–12	413 (78.2)	373 (78.2)	40 (78.4)		
Time from onset to diagnosis					
Median (IQR)	4 (2–6)	3 (3–6)	5 (3–9)		
Group (days), n (%)					
0–3	256 (48.5)	242 (50.7)	14 (27.5)	10.000	0.002
> 3	272 (51.5)	235 (49.3)	37 (72.5)		
Administrative level of first-visit medical institution, n (%)					
Township level or lower	108 (20.5)	88 (18.4)	20 (39.2)	12.212	0.000
County level or higher	420 (79.5)	389 (81.6)	31 (60.8)		

IQR = interquartile range.

* Other, including business and study.

the study period. This study indicated that travel to malaria-endemic countries for work-related purposes might be the most important cause associated with imported malaria cases in Hubei. The main source of imported *P. falciparum* malaria in Hubei was Africa, where *P. falciparum* is highly endemic. Previous studies have indicated that the incidence of malaria was high among Chinese workers who had worked in African countries.^{12–16} Overseas workers generally lack immunity to *P. falciparum* species which is endemic in the new work area.¹⁷ In addition, workers tend to have insufficient knowledge and awareness regarding the risk of malaria infection.¹⁸ Thus, these workers should receive pretravel health advice as a matter of priority. Moreover, appropriate preventive measures, such as use of antimalaria chemoprophylaxis and personal protection measures against mosquito bites, should be enforced.

No indigenous cases of *P. falciparum* malaria have been reported since 1963 in Hubei Province. The first imported *P. falciparum* case was reported in 1999.¹⁹ During 2013–2018, imported *P. falciparum* malaria cases were reported in 77 counties of Hubei. In addition, the threat of *P. falciparum* drug resistance remains a problem for malaria treatment.^{20,21} Global warming can cause latitudinal and altitudinal shifts in vector distributions, thereby changing the risk of malaria.²² Imported *P. falciparum* malaria will continue to pose a challenge for eliminating malaria. Therefore, intensifying proactive surveillance systems and ensuring that the risk of transmission of *P. falciparum* is detected early are paramount to malaria elimination.^{4,23}

Our analyses have indicated that four factors were associated with severe cases of *P. falciparum* malaria. The correlation

between female gender and severe malaria found in this current study has not been reported in previous studies.^{24–26} The reasons for this result were likely due to the small sample size. Age ≥ 50 years was a risk factor for severe malaria among imported *P. falciparum* cases. Previous studies have indicated that older age is a risk factor for severe imported *P. falciparum* malaria.^{26–28} This finding should prompt clinicians to advise travelers aged ≥ 50 years on malaria prevention, and highlights the need for early diagnosis and treatment for patients with early symptoms of malaria. Time delay of > 3 days between onset and diagnosis was associated with an increased risk of severe malaria in this study. Seringe et al.²⁹ have reported that a time lapse of 4–12 days between the onset of symptoms and diagnosis of malaria was a risk factor for severe malaria. Some studies have also indicated that delays in diagnosis contribute to severe malaria.^{30,31} Early diagnosis is crucial for malaria control and treatment.

The first-visit medical institution at the township level or lower is likely to contribute to high numbers of severe malaria cases. This finding might be due to either lack of perceived risk and skills, or insufficient training provided by medical institutions at township and lower levels. Ding et al.³² have reported that the capacity for malaria diagnosis at institutions at township or lower levels was insufficient. Regular training and supervision of malaria diagnosis-related skills at institutions at township levels or lower should be emphasized in Hubei Province.

Lai et al.¹⁴ found higher case mortality rates in imported *P. falciparum* cases during January and February, a period that includes the Chinese New Year celebrations. Delayed

TABLE 4

Factors associated with the risk of severity in *Plasmodium falciparum* malaria cases from 2013 to 2018

Variable	Odds ratio (95% CI)	P-value
Gender, female	3.593 (1.003, 12.874)	0.049
Aged ≥ 50 years	2.674 (1.269, 5.634)	0.010
Nationality, Chinese	2.082 (0.202, 21.448)	0.538
Travel purpose, labor	0.740 (0.250, 2.190)	0.587
No history of malaria infection	1.633 (0.888, 3.003)	0.115
Symptom onset before return to china	0.696 (0.256, 1.891)	0.477
Month of symptom onset in January and February	1.106 (0.596, 2.053)	0.750
Time from onset to diagnosis > 3 days	2.383 (1.210, 4.693)	0.012
First-visit medical institution at the township level or lower	2.568 (1.344, 4.908)	0.004

presentation to medical services and fewer medical staff on duty during the holiday might contribute to delayed diagnosis that results in a more severe malaria course. However, in our study, there was no significant association between risk of severe malaria and symptom onset in January and February.

Inability to assess factors such as educational level, parasite genetics, access to appropriate treatment, and antimalarial drug resistance, which are related to clinical outcomes of *P. falciparum* malaria, is considered a major limitation in this study. Future research should examine the contribution of these factors to the epidemiological profile of imported malaria cases in Hubei Province, China.

In conclusion, *P. falciparum* was the predominant imported plasmodium species. Imported *P. falciparum* malaria cases were reported in 77 counties of Hubei. Severe disease accounted for 9.7% of all *P. falciparum* cases. Risk factors for severe malaria were female gender, age ≥ 50 years, > 3 days between symptom onset and diagnosis, and the first-visit medical institution at the township level or lower. This research can further enrich knowledge and help provide valuable reference for the effective management of these cases in the future.

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