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Analysis of Severe and Relapse Risks of Imported Malaria in Five Provinces of China

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Abstract. Although China has achieved malaria elimination certification, the risk of malaria transmission reintroduction due to imported malaria remains. We analyzed data on imported malaria cases collected from January 1, 2014 to December 31, 2021, using multivariable logistic regression analysis to identify the factors associated with severe and relapsing malaria. The odds of severe malaria were around 4-fold greater for patients who were initially diagnosed with a nonmalarial illness than for patients initially diagnosed with malaria. The risk of relapse from *Plasmodium vivax* or *Plasmodium ovale* varied depending on the regions of Africa where patients resided. Patients residing in western and southern Africa (compared with Central Africa) had a lower relative risk of relapse. In addition, treatment with primaquine provided protection against malaria relapse. Improving the timeliness of treatment of malaria patients could help reduce the severity of illness, and use of primaquine can mitigate the risk of relapse after treatment.

INTRODUCTION

Malaria is a vector-borne disease that has long existed in China, threatening public health efforts. China was certified malaria-free by the WHO and received its malaria elimination certification in 2021. This major achievement is an important milestone in Chinese public health history.[1] However, as of 2022, malaria was endemic in 85 countries worldwide with an estimated 249 million cases, contributing to 608,000 deaths.[2]

Despite malaria elimination certification, receptive conditions for malaria transmission remain, and there is a risk of local reintroduction of imported malaria into China.[3,4] Furthermore, deaths due to imported malaria continue to occur every year nationally; for example, between 2017 and 2019, there was an average of 2,734 cases of imported malaria and 11 deaths from imported malaria annually.[5–7] Even in 2020, during the COVID-19 pandemic with significantly decreased international travel, 1,085 cases of imported malaria and 6 deaths were reported nationwide.[8] Imported malaria has resulted in local transmission in some countries that have eliminated malaria, as seen with the resurgence of *Plasmodium vivax* malaria epidemics in India, South Korea, and China and the occurrence of imported secondary malaria cases in countries such as Greece, Italy, and Russia.[9,10] Between the 1930s and the 2000s, there were 75 resurgence events in at least 61 countries, which varied widely in scale and duration.[9] In 2023, for the first time in 20 years in the United States, the CDC reported five cases of locally transmitted *P. vivax* malaria.[11] Although China has achieved its national malaria elimination goal, the risk of malaria transmission reintroduction from imported malaria persists.

A robust surveillance and response system in a post-malaria elimination setting is key to preventing reestablishment of local transmission and reducing severe illness and death from all malaria parasites. *Plasmodium falciparum* is the main cause of imported malaria in China and the main contributor to serious illness and deaths.[12] Although there are few reports on imported *P. vivax* and *Plasmodium ovale* in China, their corresponding mosquito vectors are widely distributed, and relapsing patients entering society may become potential sources of infection. The challenges of early detection and timely treatment due to low parasite densities and the lack of effective diagnostic testing tools for detecting dormant forms in the liver that may recur weeks or years after the primary infection pose major challenges. All *P. vivax*, *P. ovale*, and *P. falciparum* parasites pose case management challenges and remain a threat to maintaining malaria freedom in China.

Therefore, this study focused on different malaria prevention and control aspects according to the characteristics of different protozoa, and five provinces in China (Anhui, Henan, Hubei, Zhejiang, and Guangxi Zhuang Autonomous Region) were selected to conduct the first systematic investigation into the risks of severe imported malaria and relapsing *P. vivax* and *P. ovale* malaria in China to provide an important reference for improving surveillance and response strategies post-malaria elimination.

MATERIALS AND METHODS

Study areas.

Historically, Anhui, Henan, Hubei, and neighboring provinces have had high incidences of malaria, and the risk of malaria retransmission is likely high.[13–15] Due to increased international exchange and trade, cases of imported malaria in Zhejiang Province have recently increased.[16] Guangxi has seen one of the largest numbers of imported malaria cases in the country in recent years.[17]

Data sources.

All imported malaria cases are reported by medical and health institutions in the study provinces through the National Notifiable Infectious Disease Reporting Information System (NIDRIS) and Information System for Parasitic Disease Control and Prevention. A total of 5,770 malaria cases were identified from January 1, 2014, to December 31, 2021, including

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340 severe and 80 relapse cases. Factors influencing disease severity and relapse were analyzed in all 5,770 patients.

Study variables.

The following data were extracted from the NIDRIS and Information System for Parasitic Disease Control and Prevention: demographic characteristics of imported cases (including age, gender, and domestic residence), epidemiological characteristics (including overseas residence [see Supplemental Table 1], reasons for traveling, infection history while living abroad, and case classification), and diagnosis and treatment records (including date of onset, date of treatment, initial diagnosis, date of diagnosis, and treatment medications).

Case definitions.

Imported malaria cases were defined as malaria infection in a person in which the presence of malarial parasites in the blood has been confirmed by a diagnostic test (microscopic examination and polymerase chain reaction [PCR]) and the infection has been determined to be acquired outside the country (in this study, outside of the study area) where it was diagnosed.[18]

Severe malaria cases were defined as confirmed cases with one or more of the following features: impaired consciousness or coma, severe anemia, renal impairment, pulmonary edema, acute respiratory distress syndrome, or other emergencies requiring intensive care unit admission.[19]

Relapsing malaria cases were defined as the clinical diagnosis and laboratory diagnosis of imported malaria cases are *P. vivax* of *P. ovale*. After several months or years of treatment, patients experience clinical symptoms of malaria again, and the species of malaria parasite diagnosed for the second infection is the same as that of the first infection.

STATISTICAL ANALYSES

We calculated the median and interquartile range (IQR) for continuous variables, as well as the number and frequency for categorical variables, and we performed χ^2 and Fisher's exact tests to compare the variables related to severe disease or relapse in each group. A P-value of <0.05 was considered indicative of a statistically significant difference, and the cases infected with *Plasmodium* species were divided into *P. falciparum* malaria and non-*P. falciparum* malaria groups to further analyze the association between severe cases and *Plasmodium* species. Confounding factors were screened based on the results of the χ^2 test-based analysis of epidemiological characteristics, and severe and relapsing malaria cases from Africa were matched at a ratio of 1:4 through propensity scores from the 5,770 cases. Single-factor and multifactor binary logistic regression models were used to analyze the two samples after 1:4 matching for risk factors associated with severe disease and relapse in Africa, respectively, and the results were reported as odds ratios (OR) with 95% CI. Factors that should be included in multivariate analysis should be factors that have a P-value <0.05 in univariate analysis, factors of interest, and factors that were previously known to be risk-associated factors in previous studies. Due to the collinearity between the duration (days) from symptom onset to the malaria diagnosis, which is the sum of the durations (days) from symptom onset to the first visit and the durations (days) from the first visit to the malaria diagnosis, we fitted two models: model 1 used separate time periods as variables for fitting (duration [days] from symptom onset to the first visit, duration [days] from the first visit to the malaria diagnosis), and model 2 used the entire time period as variable for fitting (duration [days] from symptom onset to the malaria diagnosis). All analyses were performed using R version 4.2.2 (The R Project for Statistical Computing).

RESULTS

Distribution of imported malaria cases.

A total of 5,770 imported malaria cases were reported in five provinces from 2014 to 2021, with a higher proportion of males (5,537, 96.0%) and people who go abroad for work (4,693, 81.3%). Patient ages ranged from 0 to 81 years (median, 41 years), and the most frequent three malaria *Plasmodium* species were *P. falciparum* (3,991, 69.2%), *P. ovale* (1,006, 17.4%), and *P. vivax* (417, 7.2%). The main source of imported cases was Africa, mainly West Africa (2,389, 41.4%), Central Africa (1,735, 30.1%), and Southern Africa (875, 15.2%) (Table 1). Among them were 340 severe and 80 relapsing cases. The median times (IQR) from symptom onset to the first visit, symptom onset to diagnosis, first consultation to malaria diagnosis, and symptom onset to diagnosis were 1 (<1–3), <1 (<1–2), <1 (<1–2), and 2 (1–5) days, respectively.

Epidemiological characteristics of cases of severe and relapse malaria.

A total of 340 severe cases were reported in the five provinces from 2014 to 2021. The distribution-related differences

TABLE 1
Epidemiological characteristics of individuals with imported malaria in five provinces

Epidemiological Characteristics	Number	%
Age, years		
≤20	44	0.8
21–40	2,817	48.8
41–60	2,821	48.9
>60	88	1.5
Sex		
Male	5,537	96.0
Female	233	4.0
Domestic place of residence		
Anhui	743	12.9
Guangxi	1,643	28.5
Hebei	832	14.4
Henan	1,267	22.0
Zhejiang	1,285	22.3
Overseas residence		
East Africa	522	9.1
West Africa	2,389	41.4
Southern Africa	875	15.2
Northern Africa	12	0.2
Central Africa	1,735	30.1
Other	232	4.0
Plasmodium species		
P. vivax	417	7.2
P. falciparum	3,991	69.2
P. malariae	158	2.7
P. ovale	1,006	17.4
Mixed infection	38	0.7
Severe imported malaria		
Yes	340	5.9
No	5,430	94.1
Relapse of imported malaria		
Yes	81	1.4
No	5,689	98.6

between the severe and nonsevere groups were statistically significant in terms of age, gender, overseas residence, reasons for travel, and *Plasmodium* species ($P < 0.05$). The patient population who were aged >60 years (compared with other age groups), were female (compare with male), had lived in Southern Africa (compared with other overseas residence areas), had traveled for tourism (compared with other reasons for going abroad), and had been infected with *P. falciparum* malaria (compared with other *Plasmodium* species) had a higher rate of severe malaria (Table 2).

A total of 1,226 imported malaria cases from Africa (including 67 cases of relapsing malaria with *P. vivax* and *P. ovale*) were reported in the five provinces from 2014 to 2021. There were no statistically significant differences in distribution between the relapse group and the nonrelapse group in terms of age, gender, overseas residence, reasons for traveling, and species of *Plasmodium* infection ($P > 0.05$); the relapse rate was higher among those aged >40 years, among females, and among those living in Central Africa (Table 3).

To further analyze the association between severe cases and *Plasmodium* species, those infected with *Plasmodium* species were divided into *P. falciparum* malaria and non-*P. falciparum* malaria groups. The results showed that there were significant differences in distribution of the duration from symptom onset to first visit, from first visit to malaria diagnosis, and from symptom onset to malaria diagnosis between severe and nonsevere cases of *P. falciparum* malaria ($P < 0.05$). The proportion with >3 days in duration from symptom onset to malaria diagnosis for severe cases of *P. falciparum* malaria was 64.3%, but the proportion for nonsevere cases of *P. falciparum* malaria was just 28.7%. The difference in this proportion was not significant between severe cases (60.0%) and nonsevere cases (41.8%) of non-*P. falciparum* malaria. The proportion of patients with delayed diagnosis or treatment in severe cases was higher than that in nonsevere cases (*P. falciparum* malaria: OR = 4.352, 95% CI: 2.402–7.886, $P < 0.001$; non-*P. falciparum* malaria: OR = 1.673, 95% CI: 0.967–2.894, $P = 0.065$) (Table 4).

Analysis of risk factors for the severity and relapse of malaria.

Propensity scores were used to match the confounding factors of gender, age, domestic residence, reason for international travel, and *Plasmodium* species (Table 5). The matched results balanced the severe case data and the nonsevere case data in other aspects. The results of the single-variable binary logistic regression analysis found that time from first consultation to malaria diagnosis (OR = 1.11, 95% CI: 1.07–1.14) and time from symptom onset to malaria diagnosis (OR = 1.06, 95% CI: 1.04–1.08) and to first diagnosis results (OR = 4.26, 95% CI: 3.33–5.47) were independently and significantly associated with an increased risk of severe malaria.

The results of the multivariable binary logistic regression model 1 showed that time from symptom onset to first visit (OR = 1.04, 95% CI: 1.02–1.07) and time from first visit to malaria diagnosis (OR = 1.03, 95% CI: 1.00–1.06), as well as initial diagnosis (OR = 4.08, 95% CI: 3.09–5.38), were associated with the odds of increased risk of severe malaria ($P < 0.05$). The results of the multivariable binary logistic regression model 2 showed that the duration from symptom onset to malaria diagnosis (OR = 1.04, 95% CI: 1.02–1.06) and first diagnosis results (OR = 3.94, 95% CI: 3.05–5.09)

TABLE 2
Epidemiological distribution of severe imported malaria cases

Variable	Severe Group (n = 340, %)	Nonsevere Group (n = 5,430, %)	χ^2	P-Value
Age, years				
≤20	3 (6.8)	41 (93.2)	11.678	**0.009**
21–40	138 (4.9)	2,679 (95.1)		
41–60	190 (6.7)	2,631 (93.3)		
>60	9 (10.2)	79 (89.8)		
Gender				
Male	319 (5.8)	5,218 (94.2)	4.263	**0.039**
Female	21 (6.2)	212 (91.0)		
Overseas residence				
East Africa	27 (5.2)	495 (94.8)	23.542	**<0.001**
West Africa	141 (5.9)	2,248 (94.1)		
Southern Africa	79 (9.0)	796 (91.0)		
Northern Africa	1 (8.3)	11 (91.7)		
Central Africa	83 (4.8)	1,652 (95.2)		
Other*	7 (3.0)	225 (97.0)		
Reasons for international travel				
Work	263 (5.6)	4,430 (94.4)	13.638	**0.018**
Travel	5 (13.2)	33 (86.8)		
Official business	25 (10.2)	220 (89.8)		
Private business	38 (5.7)	632 (94.3)		
Visit friends	2 (6.3)	30 (93.8)		
Other†	6 (8.8)	62 (91.2)		
Plasmodium species				
P. vivax	8 (1.9)	409 (98.1)	66.791	**<0.001**
P. falciparum	300 (7.5)	3,691 (92.5)		
P. malariae	3 (1.9)	155 (98.1)		
P. ovale	18 (1.8)	988 (98.2)		
Mixed infection	1 (2.6)	37 (97.4)		

Bold display of P-value <0.05 in the table.
* "Other" includes Asia, Oceania, South America, and Europe.
† "Other" includes truck drivers, crew members, overseas students, and football players.

TABLE 3
Epidemiological distribution of cases with relapse of imported malaria

Variable	Relapse Group (n = 67, %)	Nonrelapse Group (n = 1,159, %)	χ^2	P-Value
Age, years				
≤40	29 (4.7)	588 (95.3)	1.406	0.236
>40	38 (6.2)	571 (93.8)		
Gender				
Male	65 (5.4)	1,135 (94.6)	0.255	0.614
Female	2 (7.7)	24 (92.3)		
Overseas residence				
East Africa	12 (5.5)	207 (94.5)	5.757	0.218
West Africa	23 (4.6)	472 (95.4)		
Southern Africa	3 (2.5)	115 (97.5)		
Northern Africa	0 (0.0)	4 (100.0)		
Central Africa	29 (7.4)	361 (94.5)		
Reason for international travel				
Work	60 (5.4)	1,050 (94.6)	4.118	0.359
Travel	0 (0.0)	1 (100.0)		
Official business	0 (0.0)	34 (100.0)		
Private business	6 (9.0)	61 (91.0)		
Visit friends	0 (0.0)	2 (100.0)		
Other*	1 (10.0)	9 (90.0)		
Plasmodium species				
P. vivax	16 (6.8)	218 (93.2)	1.055	0.304
P. ovale	51 (5.1)	941 (94.9)		

* "Other" includes truck drivers and crew members.

were associated with the odds of increased risk of severe malaria (P <0.05) (Table 5). Time from symptom onset to first visit, time from first consultation to malaria diagnosis, and time from symptom onset to diagnosis were associated with an increase in the risk of severe illness; both model 1 and model 2 indicated that misdiagnosis at the time of first diagnosis results increased the risk of severe disease (model 1: OR = 4.08, 95% CI: 3.09–5.38; model 2: OR = 3.94, 95% CI: 3.05–5.09) (Table 5).

The matching results balanced the confounding factors between relapse and non relapse malaria cases, reducing the impact of confounding factors. The results of single and multivariable binary logistic regression analyses found that overseas residence (adjusted OR = 0.02) and whether primaquine was received (adjusted OR = 0.57, 95% CI: 0.33–0.98) as independent variables were statistically significant (P <0.05). Adjusting the reference group (using Central Africa as a reference) showed that there was a significant difference in relapse risk between cases originating from western Africa and southern Africa (western Africa: OR = 0.43, 95% CI: 0.23–0.82; southern Africa: OR = 0.21, 95% CI: 0.06–0.77). Those from Central Africa had a relatively higher odds of relapse, whereas those from southern Africa had lower odds. In addition, having received primaquine was associated with a 43% reduction in the risk of relapse (Table 6).

DISCUSSION

This study found that increasing the times from symptom onset to first visit, first visit to malaria diagnosis, and symptom onset to malaria diagnosis increased the risk of severe illness to various degrees. Among them, the proportion of delayed diagnosis and treatment in severe malaria cases infected with *P. falciparum* malaria was higher than that in nonsevere cases, and the risk of severe malaria associated with an initial missed diagnosis was four times that of those with an initial correct diagnosis of malaria. During the period from symptom onset to malaria diagnosis, both medical

TABLE 4
Distribution of visit times for severe imported malaria cases

The Visit, Diagnosis and Treatment Status of Malaria Cases	Severe	Days			P-Value
		≤3 days	3–7 days	>7 days	
Days from symptom onset to first visit					
P. falciparum	Yes	236 (78.7)	40 (13.3)	24 (8.0)	**<0.001**
	No	3,172 (85.9)	376 (10.2)	143 (3.9)	
Non-*P. falciparum*	Yes	32 (80.0)	7 (17.5)	1 (2.5)	0.636
	No	1,364 (78.4)	271 (15.6)	104 (6.0)	
Days from first visit to malaria diagnosis					
P. falciparum	Yes	189 (63.0)	83 (27.7)	28 (9.3)	**<0.001**
	No	3,327 (90.1)	268 (7.3)	96 (2.6)	
Non-*P. falciparum*	Yes	27 (67.5)	9 (22.5)	4 (10.0)	0.057
	No	1,429 (82.2)	206 (11.8)	104 (6.0)	
Days from symptom onset to malaria diagnosis					
P. falciparum	Yes	107 (35.7)	129 (43.0)	64 (21.3)	**<0.001**
	No	2,630 (71.3)	765 (20.7)	296 (8.0)	
Non-*P. falciparum*	Yes	16 (40.0)	17 (42.5)	7 (17.5)	0.058
	No	1,012 (58.2)	477 (27.4)	250 (14.4)	

Bold display of P-value <0.05 in the table.

TABLE 5
Results of the binary logistic regression analysis of severe malaria cases

	Single Factor		Multifactor (model 1)		Multifactor (model 2)	
Factor	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
Onset to first visit (days)	1.03 (1.00–1.05)	**0.036**	1.04 (1.02–1.07)	**0.002**	–	–
First visit to malaria diagnosis (days)	1.11 (1.07–1.14)	**<0.001**	1.03 (1.00–1.06)	0.102	–	–
Symptom onset to malaria diagnosis (days)	1.06 (1.04–1.08)	**<0.001**	–	–	1.04 (1.02–1.06)	**<0.001**
Initial diagnosis						
Correct (reference)	Reference	–	Reference	–	Reference	–
Misdiagnosis	4.26 (3.33–5.47)	**<0.001**	4.08 (3.09–5.38)	**<0.001**	3.94 (3.05–5.09)	**<0.001**
Overseas residence						
East Africa (reference)	Reference	0.138	Reference	0.420	Reference	0.420
West Africa	1.07 (0.68–1.70)	0.761	1.27 (0.78–2.05)	0.341	1.26 (0.78–2.05)	0.342
Southern Africa	1.27 (0.77–2.07)	0.347	1.46 (0.87–2.44)	0.153	1.46 (0.87–2.44)	0.154
Northern Africa	0.81 (0.09–7.20)	0.848	0.77 (0.08–7.31)	0.819	0.77 (0.08–7.28)	0.816
Central Africa	0.78 (0.48–1.26)	0.311	1.06 (0.64–1.76)	0.819	1.06 (0.64–1.76)	0.817
Other*	0.86 (0.34–2.14)	0.741	0.80 (0.31–2.07)	0.643	0.80 (0.3–2.06)	0.637

Bold display of *P*-value <0.05 in the table.
* "Other" includes Asia, Oceania, South America, and Europe.

institutions and patients may experience delayed diagnosis and treatment. This is especially true after the elimination of malaria in China, due to insufficient diagnostic capabilities of medical institutions in some remote areas and the reduced awareness of malaria diagnosis and treatment among clinicians as well as among the general population.[20,21] These challenges can impede correct diagnosis and standardized treatment in a timely manner.

Two studies by Zhang et al.[22] and Lu et al.[23] found that the median time (IQR) from illness onset to diagnosis in imported malaria cases was 2 (<0–4) days, which was similar to the result of 2 (1–5) days obtained in this study. In this study, 16.7% of malaria patients in five provinces failed to seek medical treatment within 3 days, and 25.7% of patients were not correctly diagnosed with malaria at their first visit, higher than the proportions in a national study that showed 13% of patients with malaria who failed to seek medical treatment within 3 days and 15% of patients not correctly diagnosed with malaria at the first visit.[24] This may be because patient awareness of medical treatment of malaria increased in 2021 due to increased diagnostic training for health workers prior to certification elimination assessments to improve health workers' ability to correctly diagnose malaria or because different provinces were included in the study. However, the current challenge in diagnosing imported malaria may be that doctors lack knowledge about malaria and do not take into account travel history to areas where the disease is endemic, the patient's history of malaria chemoprophylaxis and other malaria prevention measures, and the fact that routine laboratory tests do not have high sensitivity for clinical malaria.[25] For patients originating from countries where malaria is not endemic, there was a considerable time delay in diagnosis of malaria and delays in seeking medical treatment, which may have accounted for a large proportion of the overall diagnosis delay.[26] In addition, studies have shown that imported malaria patients with a history of overseas malaria infections are more likely to seek medical treatment early, because patients with a prior malaria infection history are familiar with its symptoms and have an awareness to seek medical treatment more quickly than individuals without a prior malaria infection history.[23]

A study by Seringe et al.[27] concluded that the risk of *P. falciparum* malaria developing into severe disease increased with a delay in diagnosis. In four studies of severe cases of

TABLE 6
Results of the binary logistic regression analysis of cases of malaria relapse

	Single Factor		Multifactor	
Factor	OR (95% CI)	*P*-Value	OR (95% CI)	*P*-Value
Age, years				
≤40	Reference	–	Reference	–
>40	1.18 (0.69–2.03)	0.547	1.21 (0.69–2.12)	0.499
Sex				
Male	Reference	–	Reference	–
Female	1.62 (0.31–8.53)	0.570	1.49 (0.27–8.26)	0.650
Overseas residence				
Central Africa	Reference	**0.027**	Reference	**0.019**
East Africa	0.56 (0.26–1.21)	0.141	0.52 (0.24–1.16)	0.110
West Africa	0.44 (0.24–0.82)	**0.010**	0.43 (0.23–0.82)	**0.010**
Southern Africa	0.25 (0.07–0.89)	**0.033**	0.21 (0.06–0.77)	**0.019**
Whether to take primaquine*				
No	Reference	–	Reference	–
Yes	0.57 (0.33–0.98)	**0.043**	0.57 (0.33–0.98)	**0.043**
History of malaria infection abroad				
No	Reference	–	Reference	–
Yes	1.39 (0.62–3.10)	0.429	1.51 (0.64–3.58)	0.345

Bold display of *P*-value <0.05 in the table.
* "Yes" indicates that 15 mg primaquine base was taken daily for 14 days.

P. falciparum malaria, the median reported delay in medical treatment (IQR) was >4 (5–7) days.[28–32] Our study concluded that the risk of developing severe disease for all malaria cases increased with a delay in diagnosis. And the strength of the association between severe disease and a delay in seeking treatment was greater among *P. falciparum* malaria cases than among cases infected with other *Plasmodium* parasites.

The risk of severe malaria could be attributed not only to delayed diagnosis and treatment but also to patients' health conditions. Young adults aged 21–40 years had the lowest proportion of severe cases; elderly patients older than 60 years had the highest proportion of severe cases (Table 2). The patient's own health status also affects to some extent whether severe malaria will occur. Different clinical symptoms may be caused by differences in the malaria immune status of the host.[33] However, since this study did not collect data on patients' underlying diseases and health conditions, detailed research could not be conducted.

These study results are consistent with those of previous studies on delays in diagnosis and treatment of malaria. *Plasmodium falciparum* malaria remains an overwhelming problem in Africa, where approximately 90% of global cases and deaths occur.[2] Therefore, malaria research in Africa has focused primarily on *P. falciparum*. Although *P. falciparum* transmission has continued to decline in recent years, the neglected *P. ovale* parasites continue to circulate. This shows that the transmission pattern of non-*P. falciparum* parasites does not necessarily follow the transmission pattern of *P. falciparum*, and malaria elimination must inhibit the transmission of the entire parasite species.[34]

In China, the transmission vector and ecological conditions have not fundamentally changed.[3,4] *Anopheles sinensis* is currently the most important vector for malaria transmission in China, especially in high-latitude areas where it has become the dominant species or the only vector for malaria transmission. *Anopheles sinensis* mosquitoes breed mostly in sunny, relatively clear, and warm waters such as in rice paddies and reed ponds.[35,36] With the decreasing availability of blood sources such as cattle, pigs, and other domestic animals and poultry, the chances of humans being bitten will gradually increase, and the mosquito's biting behavior can increase the chances of malaria transmission.[37] Additionally, *A. sinensis* is not susceptible to *P. falciparum* infection but is susceptible to *P. vivax*.[38,39] The incidence rate of *P. vivax* malaria is higher than that of *P. falciparum* malaria because *P. vivax* has an adaptive mosquito vector in China.[40] This study has found that differences in the geographical origins of patients affected the risk of relapse. Central Africa had the highest risk of *P. vivax* and *P. ovale* malaria relapse, while southern Africa had the lowest. This may be related to geographical differences in strains of *P. vivax* and *P. ovale*. It has long been recognized that the incubation period of *P. vivax* varies with strain and geographical latitude, and the intensity and seasonality of *P. vivax* transmission also vary greatly in different regions.[41] These findings suggest that the epidemiology of *P. vivax* infection is affected by intrinsic differences between *Plasmodium* subpopulations, and the hemisphere and latitude are strong drivers of the epidemiology of malaria. Strain-specific observations show that relapse of infections with temperate strains is slower and less frequent than that of tropical strains.[42] This is consistent with the vast majority of relapsed patients in this study who traveled to Central, eastern, and western Africa, because their geographical locations are on the equator. Studies have shown that in areas where *P. vivax* malaria is endemic, the proportion and number of relapses of *P. vivax* malaria may decrease with age through the acquisition of immunity. But the population of all ages in areas where the disease was not endemic have almost no immunity.[40]. No significant association was found between age and relapse in this study, warranting additional research. Previous studies on the geographical distribution of *P. ovale* have shown that the distribution of *P. ovale* is limited to tropical Africa and islands in the western Pacific, with very few distributions in other areas. The distribution of *P. ovale* is affected by climatic conditions. The prevalence of *P. ovale* in West Africa decreases regularly from south to north with decreasing rainfall.[43] Because there have been few studies on *P. ovale* in the past, the global disease burden caused by *P. ovale* may have been largely underestimated.[34,44–46] In this study, cases of *P. ovale* malaria were not uncommon among the relapsed population, and future studies should focus on the distribution and transmission of *P. ovale* malaria.

This study showed that patients receiving primaquine when first infected with malaria had a 43% lower risk of relapse than those not receiving primaquine. Primaquine treats *P. ovale* infections the same way it treats *P. vivax* infections and is the only available drug to prevent malaria relapse. Primaquine has a unique and effective impact on the prevention and treatment of malaria. According to the WHO's malaria treatment guidelines, primaquine is effective in preventing early relapse caused by *P. vivax* and *P. ovale* and can improve the killing effect of blood schizonts in chloroquine-resistant *P. vivax* malaria. This is the only approved drug available to treat relapsing malaria in China.[47–49] Most (79–96%) relapsing malaria cases are infected with *P. vivax*, with the remainder infected with *P. ovale.*[50] Previous studies have shown that the risk of relapse of *P. vivax* malaria in patients who did not take primaquine treatment ranges from 5% to 80% or higher, and the pattern and probability of its relapse vary according to geographical origin.[47] Another study showed that patients with *P. vivax* malaria who were treated radically with primaquine for 14 days had an 80% lower risk of first relapse than patients who did not receive treatment.[51] The degree of relapse prevention in this study was not as good as that in the abovementioned studies, which may be due to the differing compliance of patients with medication. Although the duration of treatment with this medication is short, a survey showed that less than 70% of people complete short-term primaquine treatment, mainly because its treatment regimen is complicated, treatment adherence is still difficult, and its efficacy is occasionally poor.[52]

The results of this study suggest that clinicians should consider history of travel to areas of endemicity and history of malaria chemoprophylaxis in diagnosing patients suspected of malaria. In addition, people traveling to areas with high malaria prevalence should be educated regarding malaria risks and preventive practices. Patients infected with *P. vivax* and *P. ovale* should be treated with primaquine to reduce the probability of relapse.

Given that there will be continual sources of imported malaria infections, plus the widespread distribution and high density of *Anopheles* mosquitoes, preventing and controlling

local retransmission caused by imported malaria will remain a challenge in maintaining malaria elimination in China.

This study has some limitations, since studies based on systematic records of retrospective cases cannot obtain reliable and complete data. Data bias, as well as updates of surveillance systems and questionnaires, makes the collection of core data from cases before updates incomplete. In addition, data such as health status of patients, drug prevention that patients received abroad, and patient compliance during treatment are difficult to obtain. Due to sample problems, there are very few relevant cases for some variables, making it difficult to conduct analysis and further research.

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