

## Preplanned Studies

**Plasmodium vivax in the Elimination Phase — China, 2013–2020**Li Zhang<sup>1</sup>; Boyu Yi<sup>1</sup>; Zhigui Xia<sup>1</sup>; Fang Huang<sup>1,†</sup>**Summary****What is already known about this topic?**

*Plasmodium vivax* (*P. vivax*) was the most widely distributed and major human malaria parasite in China, considered the last parasite to be eliminated.

**What is added by this report?**

The last domestic *P. vivax* case was reported in 2016, while hundreds of imported cases were reported annually from 2013–2020, predominantly from Southeast Asia.

**What are the implications for public health practice?**

In the post-elimination phase, adaptive and practical strategies focusing on imported *P. vivax* cases should be updated and adopted to prevent malaria resurgence.

*Plasmodium vivax* (*P. vivax*) is the most geographically distributed malaria parasite, and causes severe morbidity (1). Historically, *P. vivax* was the dominant parasite species in China for several decades (2). Since the National Action Plan for Malaria Elimination was launched in 2010 (3), domestic vivax malaria cases have steadily declined, while the proportion of imported vivax malaria cases has increased. To date, the epidemiological status and characteristics of *P. vivax* in the malaria elimination phase have not been adequately studied. The objective of this study was to analyze the epidemiological characteristics of *P. vivax* between 2013 and 2020 in China. The individual data of vivax malaria cases were collected to analyze the demographic characteristics, time distribution of cases and source infection countries of imported cases. The results revealed that the last domestic vivax malaria case was reported in Yunnan Province in 2016, and that hundreds of imported vivax cases were still reported every year, mainly from Southeast Asia. Men who worked outdoors were at high risk of *P. vivax* infection. This study suggests that *P. vivax* remains a key point of focus in the elimination or after elimination phase. Adaptive and updated strategies focusing on *P. vivax* should be considered.

Although *P. vivax* was endemic in China, the incidence of malaria had decreased to an estimated 2/100,000 in 2000, due to the widespread use of antimalarial drugs, unprecedented socioeconomic changes, and urbanization implemented nationwide since the 1980s (4). From 2004 to 2012, vivax malaria cases accounted for 76.9% of all reported malaria cases. Between 2001 and 2006 there was a resurgence of *P. vivax* malaria in central China, mainly caused by climate warming, which led to extending malaria transmission, with increasing vectorial capacity of *Anopheles sinensis* (*An. sinensis*) and low capacity of diagnosis leading to an accumulation of infectious sources (5). This resurgence was controlled by targeted mass drug administration (MDA) and case management (5). As most areas in central and southern China are susceptible areas where *An. sinensis* is prevalent, the imported *P. vivax* malaria may pose a high risk of malaria transmission re-establishment in these malaria-free localities during the transmission season (6).

Data on vivax malaria cases, including demographic information (age, sex, and occupation), diagnosis, case classification, interval between onset and diagnosis, and source infection of malaria from 31 provincial-level administrative divisions (PLADs), were collected via the Parasitic Diseases Information Reporting Management System (PDIRMS) during 2013–2020. Data from Hong Kong, Macao, and Taiwan were not included in the study. Demographic data were analyzed using Microsoft Excel 2010 and SAS (version 9.4, SAS Institute Inc, NC, USA). Differences between groups were evaluated by chi-squared test and Kruskal-Wallis test. Differences were considered statistically significant at  $P < 0.05$ .

From January 1, 2013 to December 31, 2020, a total of 23,114 malaria cases were recorded from 31 PLADs via PDIRMS, among them 4,817 vivax malaria cases were reported, including 138 domestic cases and 4,679 imported cases. Meanwhile, 120 malaria-associated deaths were reported during this period (Figure 1A). Yunnan Province reported the last domestic *P. vivax* case in 2016, which was also the last

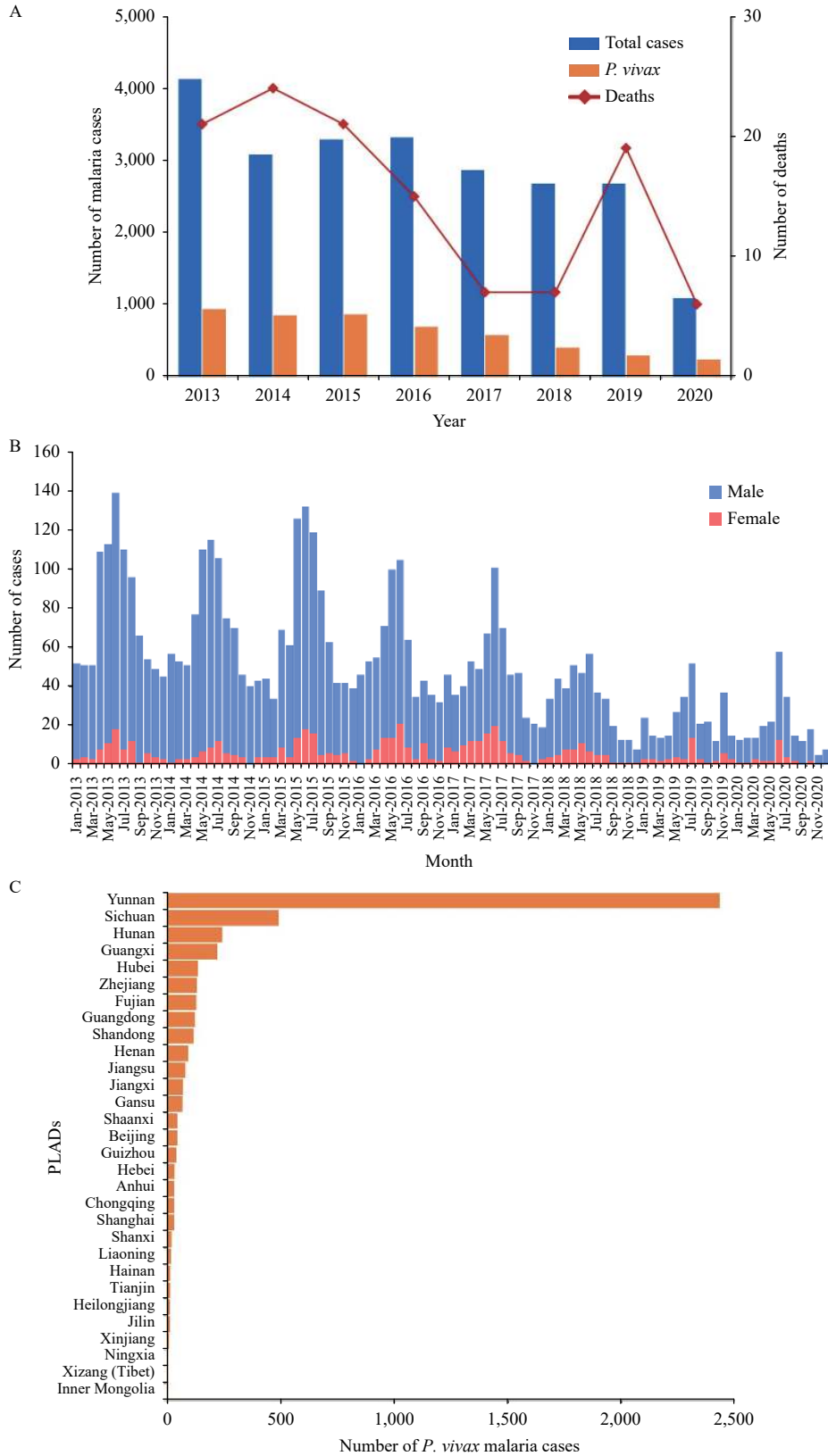


FIGURE 1. The PLADs of *P. vivax* malaria in China, 2013–2020. (A) Number of total malaria cases, vivax malaria cases, and deaths in China, 2013–2020. (B) Monthly distribution of imported and domestic vivax malaria cases based on sex, 2013–2020. (C) Provincial distribution of reported *P. vivax* in China, 2013–2020. Abbreviations: PLADs=provincial-level administrative divisions; *P. vivax*=*Plasmodium vivax*.

domestic malaria case in China. No domestic cases have been reported in the country since 2017. From 2013 to 2020, the proportion of *P. vivax* remained above 20%, except in 2018 and 2019. The number of vivax malaria cases gradually declined, from 935 in 2013 to 234 in 2020 (Figure 1A). The number of domestic *P. vivax* cases decreased from 68 in 2013 to 1 in 2016. In addition, among all the reported vivax malaria cases, 179 were recurrent cases, accounting for 3.7% of the total. The interval from last malaria infection to recurrence among different sources was significantly different ( $P < 0.01$ ).

The monthly distribution of imported and domestic vivax malaria cases exhibited a seasonal trend (Figure 1B). The peak was in the period from May to August. Most *P. vivax* cases occurred in males (88.2%, 4,249/4,817) and in the 19–59 age group (91.8%, 4,421/4,817). The proportion of males among domestic cases (72.5%, 100/138) was lower than that among imported cases (88.7%, 4,149/4,679), which indicated that the majority of the population working abroad was male. Furthermore, most vivax malaria cases occurred among people working outdoors (43.0%, 1,307/4,817), who were at high risk of exposure to outdoor biting vectors including construction workers, farmers, open mine workers, drivers, field engineers, etc. Of the 4,817 reported malaria cases, 68.1% ( $n=3,281$ ) were diagnosed in a health facility of a city or county center for disease control and prevention (CDC)/hospital, while 19.4% were diagnosed in a township hospital (Table 1). Moreover, 89.8% were diagnosed and confirmed by PCR in the provincial malaria diagnosis reference laboratory. The median interval between the illness onset and the first visit to the doctor was different between domestic cases and imported cases ( $P < 0.05$ ), which were 3 days [interquartile range (IQR): 1–6] and 2 days (IQR: 0–4), respectively. The median interval between the first visit to the doctor and the final diagnosis was 0 days (IQR: 0–4).

Most imported vivax malaria cases were from Southeast Asia (63.8%, 2,986/4,679), followed by East Africa (16.1%, 753/4,679), Central Africa (6.5%, 304/4,679), West Africa (5.1%, 240/4,679), and South Asia (5.1%, 237/4,679) (Supplementary Table S1, available in <https://weekly.chinacdc.cn/>). Among these cases, the major source countries were Myanmar, Ethiopia, and Indonesia, accounting for 54.5%, 13.0%, and 5.2%, respectively. In addition, most vivax malaria cases were reported from Yunnan Province (52.7%), followed by Sichuan (10.3%), Henan

(5.0%), and Guangxi (4.6%) PLADs (Figure 1C).

## DISCUSSION

The results of this study showed that the number of vivax malaria cases in China declined significantly during 2013–2020 (Figure 1A and Table 1). The last domestic vivax case was reported in 2016 and hundreds of imported vivax cases have been recorded annually. China was certified malaria-free by the World Health Organization (WHO) in 2021 since there had been no domestic cases for more than three years. Malaria elimination in China has largely been achieved through China's "1-3-7" approach along with an adaptive malaria elimination strategy (6–7). *P. vivax* is more difficult to eliminate or control than *P. falciparum* and other species because it has dormant liver forms (hypnozoites) in its lifecycle (8). *P. vivax* patients may relapse due to the activation of hypnozoites and become a new source of transmission, even after the schizonts of *P. vivax* have been removed from the blood.

*P. vivax* remained the predominant species in China, and several interventions focused primarily on *P. vivax* elimination in the journey of malaria elimination phase, such as radical cure in the following spring, target MDA and adaptive case finding, and a focus-based surveillance system (4). The last domestic *P. vivax* case was reported in 2016, and since then there have been no reported domestic cases. However, hundreds of imported vivax malaria cases have been reported annually (Table 1), mainly due to the increasing number of Chinese workers or business people working abroad, especially from Southeast Asia and Africa, where malaria is highly endemic (Supplementary Table S1, available in <https://weekly.chinacdc.cn/>). In addition, the difference in sex ratio between domestic and imported cases indicated the population working abroad was predominantly male, especially those working outdoors, which was consistent with the previous study (6). The decrease in imported cases in 2020 was caused by the COVID-19 international travel restrictions (9). Additionally, a proportion of recurrent imported vivax malaria cases were identified in this study, which may be due to differences in radical treatment strategies, glucose-6-phosphate dehydrogenase (G6PD) deficiency rate, treatment adherence, and drug resistance in the infection source countries (10), suggesting that G6PD

TABLE 1. Demographic characteristics of the reported vivax malaria cases in China (2013–2020).

Item	2013		2014		2015		2016		2017	2018	2019	2020	P-value <sup>†</sup>
	IMP	IND	IMP	IND	IMP	IND	IMP	IND	IMP	IMP	IMP	IMP	
Total	867	68	798	45	836	24	685	1	573	397	289	234	
Sex													<0.001
Female	61	20	47	11	86	7	97	0	105	57	47	30	
Male	806	48	751	34	750	17	588	1	468	340	242	204	
Age group (years)													0.072
<5	3	0	6	3	9	0	9	1	10	4	1	2	
5–18	28	14	17	3	35	5	38	0	35	20	10	17	
19–59	832	47	766	37	776	18	615	0	510	353	263	204	
≥60	4	7	9	2	16	1	23	0	18	20	15	11	
Occupation													<0.001
Outdoors	NA	NA	NA	NA	80	1	233	0	379	272	190	152	
Indoors	NA	NA	NA	NA	13	0	34	0	34	39	33	13	
Unclear*	NA	NA	NA	NA	21	1	84	0	125	77	63	38	
Missing	NA	NA	NA	NA	722	22	334	1	35	7	3	31	
Diagnosis health facility													<0.001
Provincial-level CDC	38	3	21	0	1	0	7	0	5	2	1	0	
Provincial-level hospital	48	2	45	0	49	2	58	0	38	33	23	12	
City-level CDC	37	1	25	0	18	0	11	0	9	3	3	2	
City-level hospital	140	6	124	3	125	5	141	0	135	104	72	53	
County-level CDC	307	16	301	19	253	11	166	1	98	68	33	22	
County-level hospital	133	17	149	13	152	1	143	0	106	96	83	76	
Township hospital	90	20	73	8	197	5	153	0	170	89	68	62	
Village clinic	12	1	4	1	5	0	0	0	1	1	5	6	
Private clinic	61	2	56	1	36	0	6	0	11	1	1	1	
Missing	1	0	0	0	0	0	0	0	0	0	0	0	
PCR confirmation													<0.001
Yes	625	51	714	38	772	22	647	1	547	385	289	233	
No	242	17	84	7	64	2	38	0	26	12	0	1	

Abbreviations: NA=not available; IMP=imported cases; IND=domestic cases; PCR=polymerase chain reaction.

\* Unclear indicates that the risk exposure could not be estimated in populations such as children, retirees, students, unemployed persons, etc. Missing data were not included in the statistical analysis.

<sup>†</sup> P value was calculated by chi-squared test or Kruskal-Wallis test.

detection before treatment and supervised medication for imported vivax malaria cases are required.

China has been a malaria-free country, however *An. sinensis*, the major malaria vector in China, is prevalent in most parts of country (4,6). In the post-elimination phase, several challenges need to be considered to prevent re-transmission of vivax malaria through imported malaria cases. First, this study showed that the duration between disease outbreak and first doctor visit was slightly longer in areas with reported domestic cases, such as Yunnan Province, reflecting the residents' lack of knowledge, attitudes, and practices

regarding malaria treatment-seeking. Health education on malaria among the high-risk population is needed. Second, the capability for malaria diagnosis in health facilities was unbalanced at different levels. More training and refresher training should be conducted for case detection and diagnosis, especially in health facilities at the city or county levels. In addition, submicroscopic or asymptomatic patients with lower parasitemia were not diagnosed using RDT or microscopy, which is still a challenge in malaria elimination. Third, early detection and diagnosis with appropriate treatment and radical cure in the following

spring should be maintained for imported *P. vivax* patients to prevent relapse or recurrence. The radical cure rate was relatively higher in China, which might be caused by the spring radical treatment in the following year, although the dosage of 8-day primaquine in China was different compared with 14-day primaquine recommended by WHO. Fourth, the “1-3-7” approach was well implemented nationwide, and made an important contribution to achieving the national goal of elimination. However, the strategies and approaches should be updated or adapted, with a focus on imported cases, to prevent recurrence of malaria in the post-eradication phase.

The study was subject to some limitations. First, the source countries of 31 imported vivax cases were not available. Second, recurrent vivax cases were not analyzed in this study because no methods were available to distinguish recurrent vivax cases from new infections or recrudescence.

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SUPPLEMENTARY TABLE S1. Source of imported vivax malaria cases reported in China (2013–2020).

Region	Country	2013	2014	2015	2016	2017	2018	2019	2020	Total
Asia		613	587	591	453	402	243	209	147	3,245
Southeast Asia		582	559	571	412	335	211	180	136	2,986
	Myanmar	478	418	502	358	297	190	171	134	2,548
	Indonesia	48	115	32	23	13	8	2	0	241
	Laos	35	16	22	26	13	4	2	1	119
	Cambodia	18	6	12	3	11	9	2	0	61
	Thailand	3	3	2	0	0	0	1	1	10
	Vietnam	0	1	1	1	1	0	2	0	6
	Malaysia	0	0	0	1	0	0	0	0	1
South Asia		29	27	18	39	65	31	23	5	237
	Pakistan	17	14	11	27	59	24	20	5	177
	India	12	12	7	12	4	7	3	0	57
	Bangladesh	0	0	0	0	1	0	0	0	1
	Bhutan	0	0	0	0	1	0	0	0	1
	Sri Lanka	0	1	0	0	0	0	0	0	1
East Asia		1	0	1	1	1	1	6	6	17
	Republic of Korea	0	0	0	0	1	1	6	6	14
	Democratic People's Republic of Korea	1	0	1	1	0	0	0	0	3
West Asia		1	1	1	1	1	0	0	0	5
	Palestine	0	1	0	0	1	0	0	0	2
	The United Arab Emirates	0	0	0	1	0	0	0	0	1
	Saudi Arabia	1	0	0	0	0	0	0	0	1
	Armenia	0	0	1	0	0	0	0	0	1
Africa		246	202	241	219	147	134	71	50	1,310
East Africa		79	123	144	132	94	100	47	34	753
	Ethiopia	42	106	117	117	79	85	40	22	608
	Sudan	21	13	15	0	5	2	3	2	61
	Uganda	0	1	3	6	1	3	1	6	21
	Tanzania	4	0	3	2	6	0	1	0	16
	Mozambique	6	1	1	2	0	2	0	1	13
	Djibouti	0	0	0	0	2	5	1	1	9
	Rwanda	0	0	0	1	0	2	1	2	6
	South Sudan	3	1	0	1	0	0	0	0	5
	Kenya	0	1	2	0	0	0	0	0	3
	Zambia	2	0	0	0	1	0	0	0	3
	Egypt	1	0	0	1	0	0	0	0	2
	Eritrea	0	0	1	0	0	1	0	0	2
	Malawi	0	0	1	1	0	0	0	0	2
	Madagascar	0	0	1	0	0	0	0	0	1
	Somalia	0	0	0	1	0	0	0	0	1

TABLE S1. (Continued)

Region	Country	2013	2014	2015	2016	2017	2018	2019	2020	Total
West Africa		113	35	23	19	20	16	10	4	240
	Ghana	91	7	5	7	5	2	2	0	119
	Nigeria	10	13	10	5	10	6	5	3	62
	Liberia	4	5	1	3	1	4	1	0	19
	Sierra Leone	2	3	4	1	1	1	1	1	14
	Cote d'Ivoire	0	1	1	3	1	2	1	0	9
	Togo	2	3	0	0	1	0	0	0	6
	Mali	3	0	0	0	1	1	0	0	5
	Benin	1	1	0	0	0	0	0	0	2
	Mauritania	0	1	1	0	0	0	0	0	2
	Niger	0	1	1	0	0	0	0	0	2
Central Africa		52	41	71	65	32	18	13	12	304
	Equatorial Guinea	16	16	21	21	7	2	4	1	88
	Angola	17	8	14	12	2	3	0	1	57
	Democratic Republic of Congo	5	4	10	16	8	6	1	7	57
	Cameroon	2	7	18	8	6	1	2	1	45
	Republic of Congo	4	3	4	7	4	3	4	0	29
	Gabon	5	1	2	0	0	1	1	1	11
	Burundi	0	0	1	0	5	1	1	0	8
	Chad	2	2	1	0	0	0	0	1	6
	The Central African Republic	1	0	0	1	0	1	0	0	3
South Africa		1	1	3	1	0	0	1	0	7
	South Africa	1	1	3	1	0	0	0	0	6
	Comoros	0	0	0	0	0	0	1	0	1
North Africa		1	1	0	0	1	0	0	0	3
	Libya	0	0	0	0	1	0	0	0	1
	Algeria	1	0	0	0	0	0	0	0	1
	Tunisia	0	1	0	0	0	0	0	0	1
Africa (other regions)		0	0	0	2	0	0	0	0	3
Oceania		5	8	2	11	17	10	8	8	69
	Papua New Guinea	4	8	2	9	15	10	8	8	64
	Solomon Islands	1	0	0	2	2	0	0	0	5
America		2	2	1	2	7	5	2	4	25
South America		2	2	1	2	7	4	2	4	24
	Guyana	1	2	1	1	5	1	0	3	14
	Venezuela	0	0	0	1	2	3	2	1	9
	Ecuador	1	0	0	0	0	0	0	0	1
Latin America	Nicaragua	0	0	0	0	0	1	0	0	1
Unknown sources		1	0	1	0	0	4	0	25	31
Total		867	798	836	685	573	396	290	234	4,679