Preplanned Studies

Neglected Time Intervals Before "1-3-7" Approach About Imported Malaria Cases — China, 2014–2021

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Summary

What is already known about this topic?

China's "1-3-7" approach outlines specific targets to guide and monitor the processes of case reporting, investigation, and response. However, few studies have examined the time intervals preceding the initial step, and the timeline from the arrival of imported malaria cases in China to their diagnosis has been largely overlooked.

What is added by this report?

The study demonstrated that the median duration from arrival in China to the onset of symptoms for *P. ovale* was 78 days, with 71.59% of imported cases manifesting symptoms after more than one month. For *P. vivax*, the median interval was 42 days, with 55.91% exceeding one month. Additionally, the median time from symptom onset to malaria treatment in China between 2014 and 2021 was 2 days, with an interquartile range (IQR) of 1–4 days.

What are the implications for public health practice?

This study represents the initial effort to delineate the chronology of imported malaria cases, from their arrival in China to their subsequent treatment. The results underscore the importance of providing malaria health education to populations arriving from overseas. Furthermore, enhancing physician training is crucial for improving the diagnosis of malaria.

Malaria, caused by *Plasmodium* spp., remains a significant life-threatening infectious disease globally. The World Health Organization (WHO) reported 608,000 malaria-related deaths and approximately 249 million cases in 2022 (*1*). Although China received WHO certification for malaria elimination on June 30, 2021, the country continues to report thousands of imported cases annually, and *Anopheles* mosquitoes, vectors of the disease, persist in formerly endemic regions. Consequently, China must continuously strive to maintain its malaria-free status (*2*–*3*). Historically, research in China has focused on the time from the onset of fever symptoms to the diagnosis in patients with imported malaria prior to the implementation of the "1-3-7" strategy (*4*–*5*). This three-tiered approach involves: 1) reporting cases within one day; 2) conducting case investigations within three days; and 3) initiating focus investigation and action within seven days (*6*). Data from 2014 to 2021 across five provinces have been analyzed to map the timeline of imported malaria cases from their arrival in China to treatment. This study aims to underpin preventative strategies against the re-establishment of malaria and to enhance health education for overseas arrivals in China.

Data on imported malaria cases from January 2014 to December 2021 were collected from Henan, Anhui, Zhejiang, Hubei, and Guangxi using the National Notifiable Disease Reporting System (NNDRS) and the Parasitic Diseases Information Reporting Management System (PDIRMS). An imported malaria case was defined as a malaria infection acquired outside China, diagnosed in either Chinese or foreign residents within the country. The recorded data included variables such as age, gender, *Plasmodium* species, infection origin, severity, previous malaria infections, travel purpose, and relevant dates pertaining to the disease timeline — arrival in China, symptom onset, initial care-seeking, diagnosis, and treatment. Cases excluded from the study were those of indigenous malaria, imported secondary infections, relapses or recrudescence, and non-mosquito-borne transmissions, such as those acquired through blood transfusion or with incomplete information. The duration from the patient's arrival in China to treatment was segmented into the following intervals: 1) arrival to symptom onset, 2) symptom onset to initial care-seeking, 3) initial care-seeking to diagnosis, and 4) diagnosis to treatment. This study specifically focused on the timeline from symptom onset to treatment, as antimalarial drug administration followed China's National Guidelines per the Technical Regulations for

Application of Antimalarials (WS/T 485-2016) (7). Continuous variables following a normal distribution were analyzed using means and standard deviations (SD), while those not normally distributed were described using medians and interquartile ranges (IQR). Categorical variables were evaluated using the chi-squared test, and time intervals between the four primary malaria species were examined through the nonparametric Kruskal-Wallis *H* test. A *P*-value of <0.05 was considered statistically significant. Furthermore, multiple comparisons between the four main *Plasmodium* species groups (*P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale*) were assessed using the Bonferroni method with an adjusted significance level α set at 0.008 (0.05/6). Thus, *P*<0.008 was deemed statistically significant for these analyses. All analyses were performed using SPSS (version 21.0; SPSS, Inc., Chicago, US).

From 2014 to 2021, a total of 4,614 malaria cases from five Chinese provincial-level administrative divisions (PLADs) were analyzed. The average age of the patients was 40.04±9.62 years, with males comprising 97.18% (4,484 cases) of the total. The most common malaria species identified were *P. falciparum*, followed by *P. ovale*, *P. vivax*, *P. malariae*, and *P. knowlesi*. A significant majority of the cases (96.66% or 4,460) were contracted in Africa, with the remaining 3.06% (141) originating from Asia. Migrant workers accounted for 87.31% (4,028 of 4,614) of the imported cases. Of the total cases, 253 were classified as severe malaria, while 4,361 were considered non-severe. Additionally, 74.36% (3,431) had a history of malaria infection abroad (Table 1).

TABLE 1. Epidemiological characteristics of 4,614 imported malaria cases in China, 2014–2021.

Characteristics	Number (%)
Age, years (mean±SD)	40.04±9.62
Sex, *n* (%)	
Male	4,484 (97.18)
Female	130 (2.82)
Plasmodium species	
Plasmodium falciparum	3,206 (69.49)
Plasmodium vivax	313 (6.78)
*Plasmodium ovale**	887 (19.22)
Plasmodium malariae	138 (2.99)
Plasmodium knowlesi	1 (0.02)
Mixed infections	69 (1.50)
Infection sites	
Africa	4,460 (96.66)
Asia	141 (3.06)
Others	13 (0.28)
Travel purpose	
Migrant work	4,028 (87.31)
Business	276 (5.98)
Official duties	206 (4.46)
Others	104 (2.25)
Severe malaria	
Yes	253 (5.48)
No	4,361 (94.52)
History of malaria infection	
Yes	3,431 (74.36)
No	1,183 (25.64)

Abbreviation: SD=standard deviation.
* contains the number of subtypes of ovale malaria.

In a study of 4,614 malaria patients, 214 (4.64%) exhibited symptoms before arriving in China, 3,313 (71.80%) developed symptoms within one month of arrival, 4,593 (99.54%) sought healthcare within that same timeframe, and 4,597 (99.63%) were diagnosed within a month. Among 3,206 *P. falciparum* patients, 2,842 (88.65%) presented symptoms within a month, 3,191 (99.53%) sought medical attention within a month, and 3,200 (99.81%) were diagnosed promptly within this period. For the 313 *P. vivax* patients, 120 (38.34%) showed symptoms within a month, 310 (99.04%) sought healthcare within a month, and two (0.64%) sought medical help after three months, with no cases delayed beyond six months. Among 138 *P. malariae* patients, 68 (49.28%) exhibited symptoms within a month, all sought healthcare within this period, and 98.55% were diagnosed within a month, with no diagnoses extending past three months. For 887 *P. ovale* patients, 236 (26.61%) showed symptoms within a month, 885 (99.77%) were diagnosed within a month, and seven (0.79%) were treated after a month (Figure 1).

As shown in Table 2, the median time interval from arrival in China to symptom onset was 9 days for all malaria species, with an IQR of 3 to 27 days. The median time from symptom onset to initial care-seeking was 1 day (IQR: 0–2 days). The median duration from initial care-seeking to diagnosis was 0 days (IQR: 0–2 days), and from symptom onset to treatment was 2 days (IQR: 1–4 days). Statistically significant differences were noted among the four main malaria species (*P*<0.001). Specifically, for the interval from arrival to symptom onset, the longest median and IQR were observed for *P. ovale* at 78 days (24–202

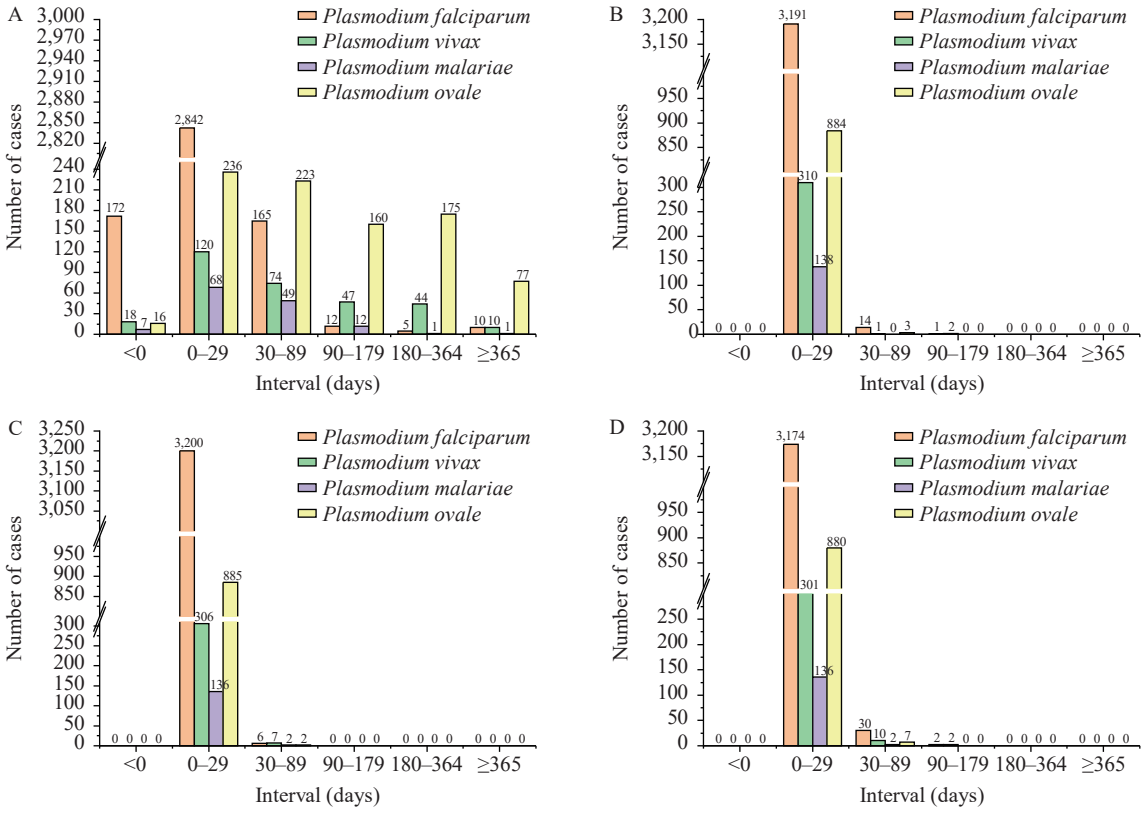

FIGURE 1. Number of patients for four malaria species from arrival in China to treatment. (A) Time from arrival in China to symptom onset; (B) time from symptom onset to initial care-seeking; (C) time from initial care-seeking to diagnosis; (D) time from symptom onset to treatment.

TABLE 2. Duration between arrival in China and initiation of treatment for imported malaria cases, 2014–2021.

Time intervals	*Plasmodium falciparum*		*Plasmodium vivax*		*Plasmodium ovale*		*Plasmodium malariae*		Total*		$H^{\dagger}$	*P*-value
	N	M (IQR)	*N*	M (IQR)	*N*	M (IQR)	*N*	M (IQR)	*N*	M (IQR)		
Interval between arrival in China and symptom onset	3,206	6 (2–11)	313	42§,*** (12–128)	887	78¶,**,*** (24–202)	138	24.5††,§§,¶¶,*** (11–49)	4,614	9 (3–27)	1,417.036	<0.001
Interval between symptom onset and initial care-seeking	3,206	1 (0–2)	313	1§,*** (0–3)	887	1 (0–3)	138	1.5††,*** (0–4)	4,614	1 (0–2)	24.324	<0.001
Interval between initial care-seeking and diagnosis	3,206	0 (0–1.75)	313	0§,*** (0–3)	887	0**,*** (0–1)	138	1††,¶¶,*** (0–4)	4,614	0 (0–2)	28.606	<0.001
Interval between symptom onset and treatment	3,206	2 (1–4)	313	3§,*** (1–7)	887	2¶,**,*** (1–5)	138	4††,¶¶,*** (2–8.75)	4,614	2 (1–4)	103.829	<0.001

Note: Unit: days.

Abbreviation: M=median; IQR=interquartile range.

* contains *P. knowlesi* and mixed infections; † means the four main malaria species were compared; § compares the *P. falciparum* group with the *P. vivax* group; ¶ compares the *P. falciparum* group with the *P. ovale* group; ** compares the *P. vivax* group with the *P. ovale* group; †† compares the *P. falciparum* group with the *P. malariae* group; §§ compares the *P. vivax* group with the *P. malariae* group; ¶¶ compares the *P. ovale* group with the *P. malariae* group; *** indicates statistically significant differences.

days), followed by *P. vivax* at 42 days (12–128 days), *P. malariae* at 24.5 days (11–49 days), and *P. falciparum* at 6 days (2–6 days) (P<0.008). For the interval from symptom onset to initial care-seeking, *P. vivax* was 1 day (0–3 days) and *P. malariae* was 1.5 days (0–4 days), which was longer than *P. falciparum* at 1 day (0–2 days) (P<0.008). For the interval from initial care-seeking to diagnosis, significant differences were observed among *P. falciparum* (0 day, IQR: 0–1.75 days) *vs.* *P. vivax* (0 day, IQR: 0–3 days), *P. ovale* (0 day, IQR: 0–1 day) *vs.* *P. vivax*, *P. falciparum vs.* *P. malariae* (1 day, IQR: 0–4 days), and *P. malariae vs.* *P. ovale* (P<0.008). Except for *P. vivax vs.* *P. malariae*, significant differences were recorded in

the intervals between symptom onset and treatment (P<0.008). The time intervals for *P. malariae* (4 days, IQR: 2–8.75 days) were longer than those for *P. falciparum* (2 days, IQR: 1–4 days) and *P. ovale* (2 days, IQR: 1–5 days).

DISCUSSION

The study revealed that the median duration from arrival in China to the onset of symptoms varied across *Plasmodium* species: 9 days for all species combined, 78 days for *P. ovale*, 42 days for *P. vivax*, 24.5 days for *P. malariae*, and 6 days for *P. falciparum*. Notably, the maximum duration reached 1,860 days for *P. ovale* and 1,225 days for *P. vivax*. Such extended periods may lead patients to overlook their history of international travel. The median duration from symptom onset to the first medical consultation was 1 day for all malaria cases. However, except for *P. malariae*, for which the median duration was also 1 day, the time from first healthcare-seeking to diagnosis was immediate (0 days) in this study. These findings slightly deviate from those reported in a previous study, which observed median durations of 3 days from fever onset to healthcare-seeking and 2 days from healthcare-seeking to diagnosis (*4*). The discrepancy might be due to the relatively low number of malaria cases (90 cases) included from Shanxi Province, potentially affecting the outcomes. *P. falciparum* cases demonstrated a shorter duration between symptom onset and treatment initiation than the other three *Plasmodium* species, with *P. malariae* showing the longest duration (4 days). This variation could be attributed to interactions among *P. malariae* and *P. ovale* with co-infections of *P. falciparum* and *P. vivax* in regions where these last two species predominate, leading to frequent underdiagnosis of the former species (*8*). Additional studies have indicated median intervals between onset and diagnosis of 4 days (IQR: 2–7 days) in Henan Province during 2010–2017. In Yunnan Province, where there is significant mobility of the migrant population along the China-Myanmar border, the duration was longer, averaging 5.1 days (*9*–*10*).

The primary limitations of this study are twofold. First, the inclusion of a limited number of PLADs may not adequately represent the time intervals between entry into China and subsequent treatment. Second, the time intervals between the onset of illness and treatment could have been influenced by the coronavirus disease 2019 (COVID-19) period.

In summary, *P. falciparum* is characterized by a shorter interval between arrival in China and symptom onset, as well as between symptom onset and treatment initiation, compared to the other three *Plasmodium* species. *P. ovale* and *P. vivax* typically have extended periods from arrival to symptom onset, though the duration from symptom onset to treatment commencement is brief. Conversely, *P. malariae* demonstrates a shorter timeline from arrival to symptom onset, with a prolonged period from symptom onset to treatment. It is crucial to provide malaria health education to overseas populations arriving in China, particularly from Africa and Southeast Asia, and to enhance diagnostic vigilance among physicians to increase the rate of timely diagnosis and prevent severe cases of malaria and fatalities.

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