ISSN 0915-5813

IASR

Vol. 39 No. 10 (No. 464) October 2018
Infectious Agents Surveillance Report
https://www.niid.go.jp/niid/en/iasr-e.html

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Tuberculosis and Infectious Diseases
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<THE TOPIC OF THIS MONTH>
Malaria, Japan, 2006-2017

Malaria is a protozoan infection transmitted by the bite of anopheline mosquitoes, and with more than 200 million infections and approximately 500,000 deaths annually, it is the world's most burdensome infectious disease. The causative agents for human malaria are four species of the genus *Plasmodium*, namely *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*, which cause falciparum malaria, vivax malaria, ovale malaria, and malarie malaria, respectively. Falciparum and vivax malaria account for more than 90% of notified cases, and the other two are uncommon. The major signs and symptoms of malaria are fever, splenomegaly, and anemia. In falciparum malaria, severe complications, such as cerebral malaria, acute renal failure, and acute respiratory distress syndrome, occur because of occlusion of blood capillaries in organs by sequestration of parasitized red blood cells.

Malaria is widely distributed, and 40% of the world's population live in the more than 100 countries that are considered endemic. There are no domestic infections of malaria in Japan, but travelers from malaria-free countries, including Japan, to malaria-endemic countries are increasing, and an estimated 30,000 imported malaria cases occur annually in the world.

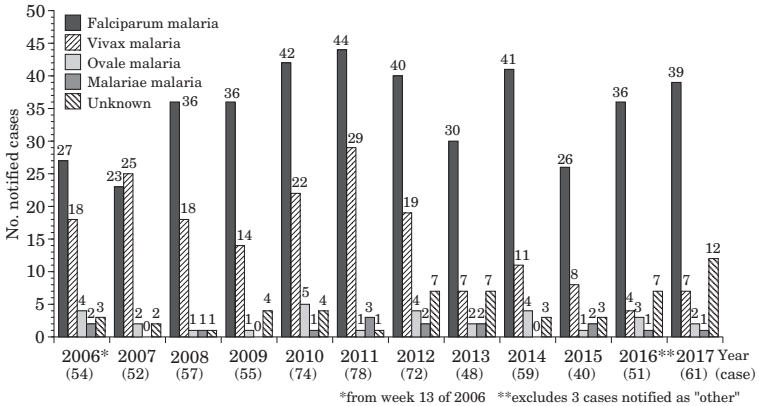
Malaria in Japan based on the National Epidemiological Surveillance of Infectious Diseases (NESID) system

Malaria represents a category IV notifiable infectious disease in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (the Infectious Diseases Control Law), and any physician who diagnoses malaria is required to notify a case (see https://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou11/01-04-33.html for the criteria of notification). This article summarizes 704 malaria cases notified from the 13th week of 2006 to the end of 2017. The annual notified number of cases was approximately 40 to 80 with an average of 59. All patients were suspected to have been infected overseas except for six patients whose suspected area of infection was unidentified. In terms of the causative *Plasmodium* species, the number of falciparum malaria was higher than the other three species since 2008, and this trend had become clearer in recent years (Fig. 1). As for gender, 539 cases were male (77%), and for age group, 215 cases were aged 20-29 years (31%) and 216 cases were aged 30-39 years (31%) (Fig. 2). However, these data may be associated with travel destination and the age distribution of travelers. There were 25 (3.6%) malaria cases in children under 15 years of age of which 15 were falciparum malaria, and 11 of those 15 cases were suspected to have been infected in Africa. Two cases were fatal at the time of notification; one was in the 40-49 and another in the 70-79 year age group, and both were falciparum malaria.

The suspected regions of infection were categorized into the major regions of Africa, Asia, Oceania, the Caribbean/Central/South America, and the Middle East, and the proportions of the causative *Plasmodium* species of the notified cases by these regions are shown in Figure 3 in p. 168. With 459 (65%) cases, the largest number of cases was attributed to Africa as the infection source of which 82% were falciparum malaria. In Asia, Oceania, and the Caribbean/Central/South America, vivax malaria accounted for approximately 70% [for the notification trends accounting for the number of travelers to the suspected areas of infection, see p. 170 of this issue (information in Japanese)].

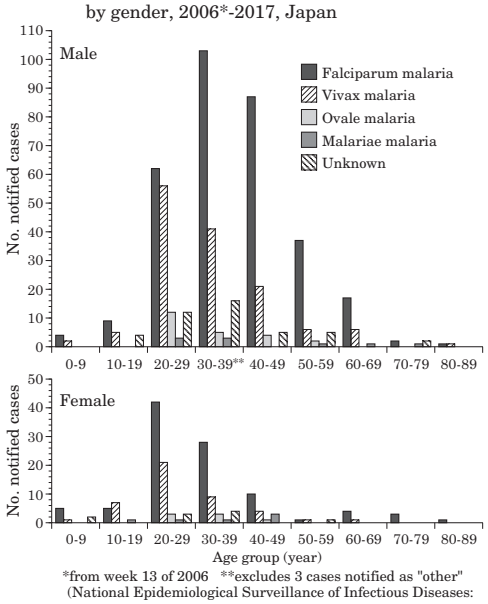
Suspected regions/areas/countries of infection were described by causative *Plasmodium* species (Table in p. 169 of this issue). For falciparum malaria, Africa accounted for 90%, of which 57%, 28%, and 12% were from Western,

Figure 1. Yearly number of notified malaria cases, 2006*-2017, Japan



*from week 13 of 2006 **excludes 3 cases notified as "other"
(National Epidemiological Surveillance of Infectious Diseases: as of July 11, 2018)

Figure 2. Age distribution of notified malaria cases by gender, 2006*-2017, Japan

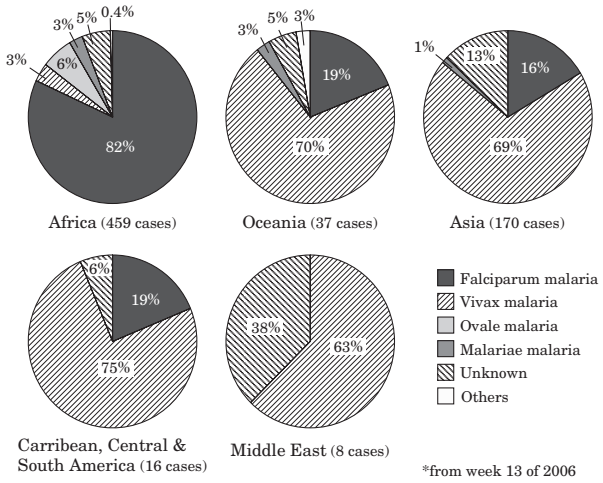


*from week 13 of 2006 **excludes 3 cases notified as "other"
(National Epidemiological Surveillance of Infectious Diseases: as of July 11, 2018)

(Continued on page 168′)

(THE TOPIC OF THIS MONTH-Continued)

Figure 3. Notified malaria cases by suspected region of infection, 2006*-2017, Japan



*from week 13 of 2006

**excludes the following: region unknown (6 cases) or had visited ≥2 regions (8 cases)

(National Epidemiological Surveillance of Infectious Diseases: as of July 11, 2018)

Eastern, and Middle Africa, respectively, followed by Asia (7%) and Oceania (2%). For vivax malaria, Asia accounted for 65%, of which 73% were from Southern Asia, 20% from South-eastern Asia, and 14% from Oceania. Ovale and malariae malaria cases were few; Africa accounted for 93% of ovale and 80% of malariae malaria.

New malaria

In addition to the four species of malaria protozoa mentioned above, *P. knowlesi* is frequently reported to cause malaria in humans in Borneo Island, Malaysia. This protozoan is not considered as a human parasite but rather a zoonotic simian parasite that infects Macaque monkeys. As a Japanese individual who had traveled to Malaysia was reported to be infected with *P. knowlesi* in 2012 (see IASR 34: 6-7, 2013), it is possible that this species may be included among those reported as an unidentified *Plasmodium* species.

Diagnosis of malaria

First, inquiring about travel history to endemic areas during the patient interview is important. Confirmatory diagnosis is achieved by verifying malaria parasites on Giemsa-stained thin blood smear under light microscopy. This method allows differential diagnosis for the four parasite species based on morphological characteristics and is still the gold standard. Although rapid diagnostic tests based on immunochromatography are performed in endemic areas, it is not classified as an approved test or drug and is used as a supplementary method for microscopic diagnosis in Japan. PCR methods to detect the parasite's genes are widely performed at the laboratory and can identify parasite species with high sensitivity.

Treatment for malaria

Chloroquine has been used as a highly effective medicine. However, chloroquine-resistant parasites emerged and spread for falciparum malaria, and is no longer considered effective. Resistance to sulfadoxine/pyrimethamine mixture and to mefloquine has also been reported. The drug of choice for falciparum malaria is a derivative of artemisinin originally extracted from the Chinese herb. Introduction of this drug to endemic areas has dramatically reduced the number of malaria victims. However, emergence of parasites also resistant to this drug has been reported (see p. 173 of this issue). The World Health Organization recommends artemisinin-based combination therapy (ACT), which is the usage of a mixture of artemisinin-derivatives with another drug that has a different mode of action from artemisinin, to take advantage of the excellent anti-malaria effects without causing emergence of resistant parasites.

Chloroquine is still effective for malaria other than falciparum malaria, but resistant *P. vivax* is emerging in South-eastern Asia. For vivax and ovale malaria, primaquine that kills dormant parasites in the liver responsible for relapse must be used in addition to chloroquine.

Anti-malarial drugs licensed for treatment in Japan are oral quinine, mefloquine, atovaquone/proguanil mixture, and primaquine, and artemether/lumefantrine mixture has recently been added, which enables an ACT regime. The Research Group on Chemotherapy of Tropical Diseases has imported and stored other anti-malarial drugs, such as chloroquine, and has distributed them to several designated hospitals throughout the country (see http://www.nettai.org, and p. 171 of this issue).

Prevention and countermeasures

To prevent being infected with malaria, one may consider prophylactic treatment with mefloquine or atovaquone/proguanil mixture when traveling to an endemic area. Countermeasures for mosquito bites should be taken, for example, avoiding skin exposure at night when anopheline mosquitoes are active and the use of repellents with a high concentration of DEET.

Vaccine development

As a preventive measure against malaria, a malaria vaccine is anticipated. Many researchers in the world are working to develop a malaria vaccine, and are approaching realization towards this aim. However, there is no vaccine that has been approved at present (see pp. 174 & 175 of this issue).

Concluding remarks

Malaria is a rare imported infectious disease in Japan. If diagnosis or treatment is delayed in malaria patients, it may become fatal. Establishing a system within the Japanese clinical setting that can provide appropriate knowledge for prevention and timely diagnosis and treatment is desired. In addition, information concerning malaria-endemic areas is provided for travelers (http://www.forth.go.jp/), and malaria awareness is important not only for healthcare workers but also for travelers.

The statistics in this report are based on 1) the data concerning patients and laboratory findings obtained by the National Epidemiological Surveillance of Infectious Diseases undertaken in compliance with the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases, and 2) other data covering various aspects of infectious diseases. The prefectural and municipal health centers and public health institutes (PHIs), the Department of Environmental Health and Food Safety, the Ministry of Health, Labour and Welfare, and quarantine stations, have provided the above data.

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（特集つづき）（THE TOPIC OF THIS MONTH-Continued）

表. 原虫種ごとにみたマラリア患者の推定感染地域/国, 2006*〜2017年（原虫種不明・その他を除く計647例）

Table. Suspected region/area/country of infection of malaria cases by the type of causative *Plasmodium* species, 2006*-2017

Total of 647 cases (excludes cases where protozoa species was notified as “unknown” or “other”)

熱帯熱マラリア falciparum malaria（420）	アフリカ: Africa（376）	西アフリカ: Western Africa	213	ナイジェリア（61）、ガーナ（50）、ギニア（27）、ブルキナファソ（17）、シエラレオネ（12）、リベリア（8）、コートジボワール（6）、セネガル（6）、ベナン（6）、トーゴ（3）、ニジェール（3）、マリ（3）、ガンビア/ギニア（3）、ガーナ/セネガル（1）、ギニア/セネガル（1）、コートジボワール/ブルキナファソ（1）、シエラレオネ/リベリア（1）、ブルキナファソ/マリ（1）、ガーナ/トーゴ/ベナン（1）、ガーナ/セネガル/トーゴ/ブルキナファソ/ベナン（1）、不明（1）
		東アフリカ: Eastern Africa	106	ウガンダ（29）、ケニア（22）、モザンビーク（11）、タンザニア（8）、マラウイ（8）、ザンビア（6）、南スーダン（6）、マダガスカル（2）、ルワンダ（2）、エチオピア（1）、コモロ（1）、ブルンジ（1）、ウガンダ/ケニア（4）、ウガンダ/ケニア/タンザニア（2）、ウガンダ/タンザニア（1）、タンザニア/ルワンダ（1）、ウガンダ/タンザニア/マラウイ（1）
		中部アフリカ: Middle Africa	45	カメルーン（22）、コンゴ（11）、アンゴラ（3）、ガボン（3）、中央アフリカ（3）、チャド（2）、赤道ギニア（1）
		北アフリカ: Northern Africa	6	スーダン（6）
		２地域以上・詳細不明: ≥ two areas / unspecified	6	
	アジア: Asia（28）	東南アジア: South-eastern Asia	19	インドネシア（12）、タイ（3）、フィリピン（1）、ベトナム（1）、ミャンマー（1）、ラオス（1）
		南アジア: Southern Asia	8	パキスタン（4）、インド（3）、バングラデシュ（1）
		東アジア: Eastern Asia	1	中国（1）
	オセアニア: Oceania		7	パプアニューギニア（7）
	中米: Caribbean, Central America		2	セントルシア（1）、ハイチ（1）
	南米: South America		1	ベネズエラ（1）
	２地域以上・不明: ≥ two regions・unknown		6	
三日熱マラリア vivax malaria（182）	アジア: Asia（118）	南アジア: Southern Asia	86	インド（58）、パキスタン（26）、ネパール（1）、インド/バングラデシュ（1）
		東南アジア: South-eastern Asia	24	インドネシア（14）、カンボジア（2）、シンガポール（2）、タイ（2）、ミャンマー（2）、マレーシア（1）、東ティモール（1）、
		東アジア: Eastern Asia	4	韓国（3）、中国（1）
		２地域以上: ≥ two areas	4	
	オセアニア: Oceania		26	パプアニューギニア（23）、ソロモン諸島（2）、バヌアツ（1）
	アフリカ: Africa（16）	東アフリカ: Eastern Africa	7	ウガンダ（3）、エチオピア（1）、ケニア（1）、モザンビーク（1）、ルワンダ（1）
		西アフリカ: Western Africa	6	ナイジェリア（3）、ブルキナファソ（1）、マリ（1）、リベリア（1）
		北アフリカ: Northern Africa	2	スーダン（2）
		中部アフリカ: Middle Africa	1	コンゴ（1）
	南米: South America		11	ブラジル（6）、エクアドル（1）、ペルー（1）、仏領ギアナ（1）、チリ/ブラジル/ペルー（1）、不明（1）
	中東: Middle East		5	アフガニスタン（3）、アラブ首長国連邦（1）、イラク（1）
	中米: Caribbean, Central America		1	ホンジュラス（1）
	２地域以上・不明: ≥ two regions・unknown		5	
卵形マラリア ovale malaria（30）	アフリカ: Africa（28）	東アフリカ: Eastern Africa	15	ウガンダ（9）、ザンビア（4）、ケニア（2）
		西アフリカ: Western Africa	9	ガーナ（4）、コートジボワール（2）、シエラレオネ（1）、ナイジェリア（1）、ブルキナファソ（1）
		中部アフリカ: Middle Africa	3	カメルーン（3）
		北アフリカ: Northern Africa	1	スーダン（1）
	２地域以上・不明 : ≥ two regions・unknown		2	
四日熱マラリア malariae malaria（15）	アフリカ: Africa（12）	東アフリカ: Eastern Africa	6	ウガンダ（3）、マラウイ（1）、モザンビーク（1）、ケニア/南スーダン（1）
		中部アフリカ: Middle Africa	6	ガボン（2）、カメルーン（2）、アンゴラ（1）、中央アフリカ（1）
	アジア: Asia（2）	東南アジア: South-eastern Asia	1	ベトナム（1）
		東アジア: Eastern Asia	1	台湾（1）
	オセアニア: Oceania		1	パプアニューギニア（1）

（ ）: 届出数 *2006年は第13週からの届出数

（感染症発生動向調査：2018年7月11日現在報告数）

( ): Number of notified malaria cases *Number of notified malaria cases since the 13th week of 2006

(National Epidemiological Surveillance of Infectious Diseases: as of July 11, 2018)