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REGULAR ARTICLE

Risk analysis of the re-emergence of *Plasmodium vivax* malaria in Japan using a stochastic transmission model

Tomoyuki Bitoh · Kaoru Fueda · Hiroshi Ohmae · Mamoru Watanabe · Hirofumi Ishikawa

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Abstract
Objectives This study analyzed the risk of infection with *Plasmodium vivax* in local residents through a stochastic simulation in which an infected tourist, local resident, or immigrants from an endemic area would visit Himi-shi, Toyama prefecture, which is a formerly endemic area in Japan.
Methods In Toyama, the habitats of *Anopheles sinensis*, which can transmit *P. vivax*, have been examined previously. We constructed a stochastic model of *P. vivax* transmission that can handle small numbers of infected persons and infected mosquitoes. The seasonal fluctuation in the numbers of captured *An. sinensis* was taken into account in the model.
Results Ten thousand trial simulations were carried out stochastically with a range of human blood indexes (HBI) of 1–10% for a range of months (June–September). The simulation results for a realistic assumption of a 1% HBI showed that the risk of infection for local residents was low (below 1%) except for the immigrants scenario.
Conclusions The risk of infection among local residents (second cycle) was estimated to be very low for all situations. Therefore, there is little possibility for *P. vivax* infection to become established in this area of Japan.

Keywords Re-emergence · *Plasmodium vivax* · Toyama · *Anopheles sinensis* · Stochastic simulation

T. Bitoh · K. Fueda · H. Ishikawa (✉)
Department of Human Ecology,
Graduate School of Environmental Science,
Okayama University, Okayama 700-8530, Japan
e-mail: ishikawa@ems.okayama-u.ac.jp

H. Ohmae
Department of Parasitology,
National Institute of Infectious Diseases,
Tokyo 162-8640, Japan

M. Watanabe
Department of Medical Entomology,
National Institute of Infectious Diseases,
Tokyo 162-8640, Japan

Introduction

This study analyzed the risk of infection with *Plasmodium vivax* for local residents through a stochastic simulation in which an infected tourist, local resident, or immigrants from an endemic area would visit Himi-shi, Toyama prefecture, a formely endemic area in Japan.

Before World War II, the inhabitants of the central part of the main island of Japan, especially Aichi, Toyama, Ishikawa, Fukui, and Shiga prefectures, suffered from *P. vivax* malaria [1]. After World War II, the prevalence of *P. vivax* was attributed to indigenous malaria and imported malaria derived from demobilized soldiers and citizens repatriated from overseas [2]. Recently, there have been no reports of malaria infection in Japan, except for imported malaria. About 61–109 patients with imported malaria, including 21–39 *P. vivax* patients, were reported in Japan between 2000 and 2006 [3].

The Toyama Institute of Health [4] has issued reports on the habitats of *Anopheles sinensis*—which is recognized as a *P. vivax* malaria vector—in Toyama prefecture, and there have also been observations for *Anopheles* mosquitoes in Shiga prefecture [5].

There have been several reports of the local transmission of *P. vivax* imported by a patient; for example, in Singapore [6]; far north Queensland, Australia [7]; Corsica, France [8]; and Michigan, United States [9].

Global warming may lead to increased numbers of malaria-vector mosquitoes and expansion of their habitats [10]. In South Korea, indigenous *P. vivax* malaria disappeared in the latter half of the 1970s, but *P. vivax* infection has been maintained since its re-emergence was first detected in 1993 [11–13]. The re-emergence of *P. vivax* was believed to originate from mosquitoes infected with *P. vivax* in North Korea, which subsequently moved to South Korea [14].

Most mathematical models of *P. vivax* transmission have adopted deterministic systems. De Zoysa et al. [15] examined the relapse of hypnozoites, and Ishikawa et al. [16] proposed a transmission model developed from the Dietz–Molineaux–Thomas model [17] to analyze prevalence in the Solomon Islands. Fujita et al. [18] investigated the relapse pattern of hypnozoites in South Korea. Ponçon et al. [19] assessed spatial variations in the risk of *P. falciparum* and *P. vivax* re-emergence in a formerly endemic region of southern France, adopting a probability distribution approach, and Nakagawa et al. [20] analyzed the risk of the re-emergence of *P. falciparum* on Ishigaki island, Japan, in the future, employing a stochastic model.

Our model of transmission for *P. vivax* handled infected mosquitoes and persons stochastically. The model took into account the seasonal fluctuation in the number of captured *An. sinensis*. Because the number of infected persons and also the number of mosquitoes would be small in the targeted area, unlike the numbers in an endemic area, stochastic simulations were regarded as adequate to estimate the risk of infection with *P. vivax* in the targeted area.

In the model we used the human blood index (HBI), a malariological parameter that expresses the proportion of human blood meals to blood-fed female mosquitoes. We designed scenarios with a 1-day-stay tourist, a local resident returning from abroad, or immigrants washed ashore who were infected with *P. vivax* visiting the targeted area during June–September, and the HBI of *An. sinensis* as set as 1–10%. The simulations showed that the risk of infection among local residents [second cycle (SC)] was estimated to be very low for all situations. Therefore, there was little possibility of the establishment of *P. vivax* infection among them.

Materials and methods

Study area

Seasonal fluctuation in the number of captured An. sinensis mosquitoes

In this study, Himi-shi, Toyama prefecture, was chosen as the study area. Himi-shi had a population of 54,945 in 2005 [21]. The Toyama Institute of Health [4] conducted capture surveillance of mosquitoes, using light-traps in stockyards at more than ten spots in Toyama prefecture between 1969 and 2004, in which the number of captured *An. sinensis* was reported. We used the 1994 data of *An. sinensis* in Himi-shi from the viewpoint of risk analysis, because the highest density was observed in 1994 during the period of surveillance 1980–1996. *An. sinensis* first appeared in the 2nd week of June, and the number captured increased from the 3rd week of July, reached a peak in the 4th week of July, and decreased thereafter. In the model we modified the number captured between the 4th week of July and the 2nd week of August using a straight line to avoid a sharp fluctuation because a drop of unknown cause was observed in the 1st week of August (Fig. 1).

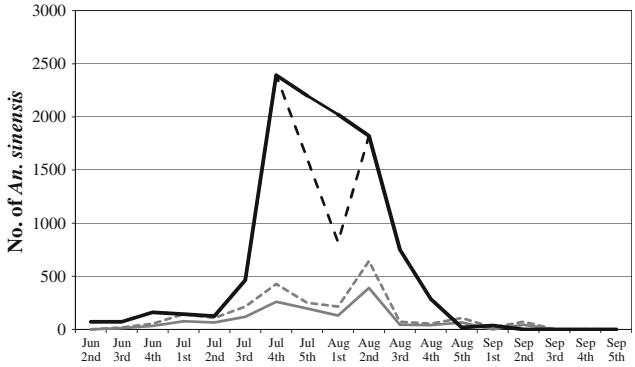

Fig. 1 Numbers of *Anopheles sinensis* captured using a light-trap in Himi-shi, Toyama. The *gray-solid*, *black-broken*, and *gray-broken lines* indicate 1993, 1994, and 1995 observations, respectively, and the *black-solid line* indicates modification of the 1994 observations

Frequency of mosquito bites

The mean frequency of bites by *An. sinensis* was assumed to be 0–3 per human per night in proportion to the number of captured *An. sinensis*, and the frequency was assumed to be governed by a Poisson distribution. The gonotrophic cycle was fixed at 3 days [22].

Period of sporozoite formation

The periods of sporozoite formation for *P. vivax* were estimated to be 16–17 and 9–10 days at 20 and 25°C, respectively [23]. In this study, the average period of sporozoite formation was assumed to depend on the temperature in Himi-shi, and the periods were assumed to be governed by a gamma distribution, with a mean of 9–17 days and a variance of 2^2 (range 7–19 days).

Daily survival rate of *An. sinensis*

The daily survival rate of *An. sinensis* was assumed to be governed by a Bernoulli distribution, with means of 71, 82, 87, and 79% in June, July, August, and September,

respectively; this assumption was based on surveillance in South Korea in 1999–2000 [24].

Epidemiological parameters

Relapse

Relapses occur frequently in *P. vivax* infection, and the relapse period varies widely [25, 26]. In this study, the relapse period was classified into two patterns: short and long relapse periods, of 1–4 months and more than 5 months, respectively [18]. The proportion of primary infections to relapses and the proportion of the short to long relapse patterns were assumed to be governed by a Bernoulli distribution, with means of 20:80 and 34:66, respectively [26], where the short and long relapse periods were assumed to be governed by an exponential distribution with a mean of 52 days and a variance of 52^2 and a log-normal distribution with a mean of 293 days and a variance of 59^2, respectively [18].

Incubation period of primary infection

The incubation period of the primary infection with *P. vivax* was estimated to be 8 days [25], so it was assumed to be governed by a gamma distribution with a mean of 8 days and a variance of 2^2.

Acquisition rate of infectivity and period for loss of infectivity

The period for loss of infectivity was assumed to be governed by a gamma distribution with a mean of 19 days and a variance of 8.3^2; these values were derived from a maximum likelihood estimation from the observation of the transition to loss of infectivity in patients with gametocytes when chloroquine was administered[27]. Gametocytes were detected in 615 (28.9%) of 2,125 *P. vivax*-infected persons in Thailand (1993–2003) [28]. The acquisition rate of infectivity per day was assumed to be governed by a Bernoulli distribution with a mean of 2.8% so as to assimilate the ratio of a PG-subclass in the positive class (for definition of "PG", see below "Model scheme") at 28.9%.

Diagnostic period

The diagnostic period was assumed to be governed by a gamma distribution with a mean of 20 days and a variance of 5^2.

Model scheme

A stochastic model was constructed for *P. vivax* transmission among humans and mosquitoes. The human population was divided into five epidemiological classes: negative, negative with hypnozoite (RE), incubation (PI), positive, and diagnosis. The positive class was subdivided into two subclasses: positive and infectious subclass with gametocytes (PG) and positive but not infectious subclass without gametocytes (PN). The mosquito population was divided into three epidemiological classes: negative, incubation, and positive.

Transfers among the epidemiological classes proceeded stochastically following the probability distributions. A local resident in the negative class who was bitten by vectors in the positive class was transferred to the RE- or PI-class. A resident would be transferred from the PI-class to the PN-subclass after the incubation period. A resident or an index patient in the PN- and PG-subclasses would be transferred between the PN- and PG-subclasses until diagnosis. An individual who was transferred from the PN- or PG-subclass to the diagnosis class would receive medical treatment, and afterwards he or she would be transferred to the negative class. A resident in the RE-class would be transferred to the positive class after relapse.

An. sinensis vectors that bite an individual in the PG-subclass were treated singly and stochastically in the model regarding daily survival, the period of sporozoite formation, and injection into residents. The model scheme for human-mosquito transmission of *P. vivax* is shown in Fig. 2, and the configuration of stochastic distributions in the model is summarized in Table 1. When the value of the probability distribution exceeds the range in Table 1, the stochastic process replaces it with the lower or upper limit of its range.

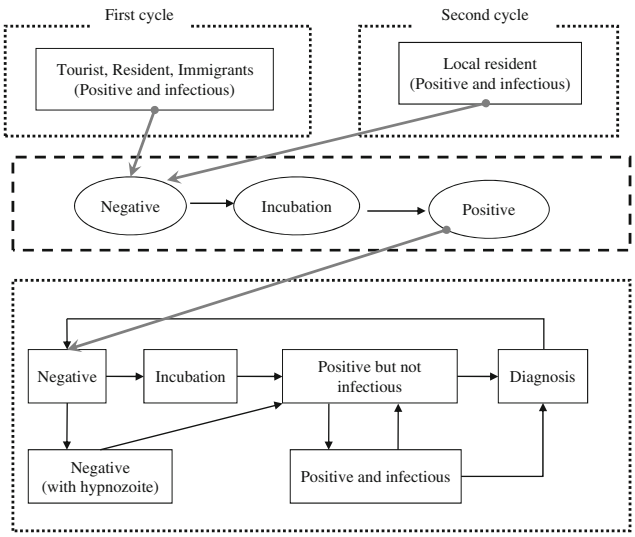

Fig. 2 Model schemes for *Plasmodium vivax* transmission of infection in the first and second cycles. *Dotted* and *dashed rectangles* indicate the profiles of human and vector stages, respectively. *Ovals* and *solid rectangles* indicate the profiles of vector classes and human classes, respectively

Table 1 Configuration of the stochastic distribution for invasion

Description	Type of distribution	Mean	Variance	Range
Assumed values				
Frequency of mosquito bites	Poisson	0–3 bites/human/night (depending on *Anopheles sinensis* density)	–	June–September
Diagnostic period	Gamma	20 (days)	5^2 (day^2)	15–25 (days)

Description	Type of distribution	Mean	Variance	Range (days)	References
Estimated values					
Period of sporozoite formation	Gamma	9–17 (days) (depending on temperature)	2^2 (day^2)	7–19	[23]
Daily survival rate of mosquitoes	Bernoulli	71–87 (%) (depending on season)	–	–	[24]
Ratio of primary infection	Bernoulli	Primary: 20 (%) (relapse: 80 (%))	–	–	[26]
Incubation period in primary infection	Gamma	8 (days)	2^2 (day^2)	6–10	[25]
Relapse pattern of hypnozoites	Bernoulli	Short: 34 (%) (long: 66 (%))	–	–	[18]
Relapse period (short)	Exponential	52 (days)	52^2 (day^2)	30–120	[18]
Relapse period (long)	Log-normal	293 (days)	59^2 (day^2)	120–510	[18]
Rate of gametocyte acquisition per day	Bernoulli	2.8 (%/days)	–	–	[28]
Loss of infectivity	Gamma	19 (days)	8.3^2 (day^2)	0–40	[27]

In the model, local residents were assumed to have no immunity to *P. vivax*. We used first cycle (FC) or SC according to the case where the infection of a local resident is caused by an index patient or the infection is caused by an infected resident.

Scenarios for invasions

We investigated three cases of *P. vivax* malaria patient(s) who would visit the targeted area during June–September; (1) a 1-day-stay tourist who exhibited gametocytemia during their stay, (2) a local resident returning from abroad who was infected with *P. vivax* and developed parasitemia after returning home, and (3) ten immigrants washed ashore who were infected with *P. vivax* and belonged to the positive class when landing and stayed in the area for 10 days. For cases (2) and (3), a patient was regarded as having gametocytes or not according to the probability distribution. We also investigated three HBI levels of *An. sinensis* assigned as 1, 5, and 10% (Table 2).

Table 2 Scenarios for invasions

Index case(s)				HBI (%)
Attribution	Number of patient(s)	The length of stay (day(s))	Visiting months	
Tourist	1	1	June–September	1
Resident	1	–		5
Immigrants	10	10		10

HBI human blood index

Results

Ten thousand trial simulations were executed for 1,000 days following the index case scenarios (Table 2) where the time step of a stochastic process was adopted as a day. The range of risk of infection with *P. vivax* among local residents during June–September with a 1% HBI was evaluated as 0.01–0.94, 0.01–0.34, and 0.11–1.61% for the index case(s) of a tourist, a resident returning from abroad, and immigrants, respectively. The risk of SC with *P. vivax* infection spreading among local residents for an assumption of a high HBI of 10% was estimated to be very low, at 0.52 and 0.34% at most, for a 1-day-stay tourist (1) and a local resident returning from abroad (2), respectively, while the risk of SC was estimated to be slightly higher, at 1.73% at most, for the immigrant index cases (3). The simulation results are summarized in Table 3.

Discussion

In the model in the present study, we evaluated the risk of infection with *P. vivax* for local residents by applying a stochastic process to infected mosquitoes in addition to individuals.

Because the process of gametocyte production is uncertain, the acquisition rate of infectivity was decided by malariological surveillance [27, 28]. The distribution of the diagnostic period was taken from reports from Korea (1995) [29].

Table 3 Risk of *Plasmodium vivax* infection for local residents in 10,000-trial simulations

Infection	Risk ratio to more than one patient in the months shown (%)											
	Tourist				Resident				Immigrants			
	Jun	Jul	Aug	Sep	Jun	Jul	Aug	Sep	Jun	Jul	Aug	Sep
HBI 1%												
Primary infection	0.00	0.08	0.14	0.01	0.05	0.08	0.04	0.00	0.11	0.27	0.30	0.01
Short relapse	0.00	0.08	0.20	0.00	0.03	0.05	0.06	0.00	0.12	0.45	0.40	0.05
Long relapse	0.01	0.21	0.60	0.02	0.15	0.21	0.09	0.01	0.15	0.73	0.91	0.05
One patient	0.01	0.37	0.93	0.03	0.23	0.34	0.19	0.01	0.35	1.43	1.57	0.11
More than two patients[a]	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.03	0.02	0.04	0.00
	[1]	[1]	[2]	[1]	[1]	[1]	[1]	[1]	[2]	[2]	[2]	[1]
Total	0.01	0.37	0.94	0.03	0.23	0.34	0.19	0.01	0.38	1.45	1.61	0.11
95% CI	(0.00, 0.06)	(0.26, 0.51)	(0.76, 1.15)	(0.01, 0.09)	(0.15, 0.34)	(0.24, 0.47)	(0.12, 0.30)	(0.00, 0.06)	(0.27, 0.52)	(1.23, 1.70)	(1.38, 1.88)	(0.06, 0.20)
HBI 5%												
Primary infection	0.01	0.26	0.85	0.06	0.17	0.50	0.18	0.00	0.38	1.15	1.52	0.13
Short relapse	0.00	0.42	1.08	0.07	0.25	0.51	0.32	0.01	0.37	1.72	2.23	0.22
Long relapse	0.01	0.91	2.37	0.07	0.40	1.07	0.65	0.05	0.96	3.48	4.29	0.37
One patient	0.02	1.50	4.10	0.20	0.79	2.02	1.09	0.06	1.56	5.70	6.86	0.71
More than two patients[a]	0.00	0.09	0.20	0.00	0.03	0.06	0.06	0.00	0.15	0.57	0.92	0.01
	[1]	[2]	[2]	[1]	[2]	[2]	[2]	[1]	[3]	[2]	[6]	[2]
Total	0.02	1.59	4.30	0.20	0.82	2.08	1.15	0.06	1.71	6.27	7.78	0.72
95% CI	(0.00, 0.08)	(1.36, 1.85)	(3.91, 4.72)	(0.13, 0.31)	(0.66, 1.02)	(1.81, 2.38)	(0.95, 1.38)	(0.03, 0.13)	(1.47, 1.98)	(5.81, 6.76)	(7.27, 8.32)	(0.57, 0.91)
HBI 10%												
Primary infection	0.01	0.54	1.35	0.09	0.29	0.91	0.38	0.00	0.69	2.53	3.31	0.24
Short relapse	0.00	0.77	1.74	0.08	0.41	1.06	0.57	0.02	0.79	3.72	3.86	0.36
Long relapse	0.03	1.55	3.99	0.17	0.76	2.10	1.21	0.06	1.89	7.17	7.55	0.63
One patient	0.04	2.64	6.56	0.34	1.35	3.73	1.93	0.07	3.05	10.94	11.28	1.13
More than two patients[a]	0.00	0.22	0.52	0.00	0.11	0.34	0.23	0.01	0.29	1.98	2.74	0.10
	[1]	[2]	[2]	[1]	[2]	[2]	[2]	[2]	[3]	[11]	[8]	[3]
Total	0.04	2.86	7.08	0.34	1.46	4.07	2.16	0.08	3.34	12.92	14.02	1.23
95% CI	(0.01, 0.11)	(2.55, 3.21)	(6.59, 7.60)	(0.24, 0.47)	(1.23, 1.71)	(3.70, 4.48)	(1.89, 2.46)	(0.04, 0.16)	(3.00, 3.71)	(12.27, 13.59)	(13.35, 14.71)	(1.03, 1.47)

CI confidence interval

[a] The figures in square brackets show the maximum number of patients in 10,000-trial simulations

An. sinensis has a marked preference for animal blood meals [30], but simulations were carried out employing three levels of HBI (1, 5, and 10%) from the viewpoint of risk analysis. The risk of infection among local residents also depends on the density of *An. sinensis*. The observations of mosquitoes in Himi-shi, Toyama, which were collected employing light-traps in a stockyard, revealed a low density (Fig. 1). The number of mosquitoes collected using light-traps in a stockyard was about 360-fold higher than the number of mosquitoes collected using dry ice-traps in the open air in the observation of *Anopheles* mosquitoes along the eastern shore of Lake Biwa, a formerly endemic area of *P. vivax* in Japan, on August 1, 2009 (unpublished work, M. Watanabe). The simulations were limited to low *An. sinensis* density.

The simulation results showed that August and July had higher risks of infection than other months for a visiting 1-day-stay tourist (1) and a local resident returning from abroad (2) as an index patient, respectively, and that both July and August would have almost the same level of risk of infection from immigrants (3); these simulation results were derived from the different assumptions on gametocytemia.

In Australia in 2002, a man with imported *P. vivax* malaria visiting a camping ground caused an outbreak, and 10 persons were infected with *P. vivax* due to the large number of *An. farauti*, which have a marked capacity to transmit malaria [31]; this finding is in contrast to the situation in Toyama, with a low density of *An. sinensis*, but there were no SC patients in that Australian outbreak [7]. In the present model, the risk of infection among local residents was estimated to be low (below 1%), and, in addition, there was only one patient involved in most cases of *P. vivax* infection, based on the scenario of a tourist (2) with the realistic assumption of a 1% HBI with regard to highly zoophilic *An. sinensis*. However, the risk would increase to about 4–7% if malaria vectors had a high HBI (5–10%), such as *An. culicifacies* [31], equivalent to the somewhat high-level nature of *P. vivax* transmission (Table 3).

Infected persons with *P. vivax* coming from endemic countries are sometimes asymptomatic or have no typical symptoms. Consequently, a delay in the diagnosis increases the possibility of expanding infections in the vicinity of the infected person [32, 33]. However, the model in the present study was limited to patients with symptoms, especially regarding the situation of immigrants.

In the United States, about 300 patients with imported *P. vivax* malaria were reported in 2003, more than 40% of whom were infected in Asia [34]. In Taiwan, about 40 patients with imported malaria, including 20 *P. vivax* patients, were reported every year during the period 1991–2000 [35], and in Japan, about 20–40 patients with imported *P. vivax* malaria were reported in 2001–2006 [3]. Although the density of *An. sinensis* has been reduced since 1997 [4], global warming may increase the numbers of *An. sinensis* and expand their habitats. Therefore, it is desirable to carry out surveillance for *An. sinensis* continuously.

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