Original article

Risk assessment of re-emerging *Plasmodium falciparum* on Ishigaki Island using a stochastic transmission model

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Abstract: On Ishigaki Island, *Plasmodium falciparum* and *Plasmodium vivax* epidemics occurred in 1945-1946 and were successfully suppressed. The epidemic re-emerged in 1949 because many settlers immigrated to the former endemic areas, but it terminated in 1961. The present study aimed at predicting an outbreak of a new epidemic based on the situation in which *P. falciparum* malaria patients stay on Ishigaki Island and also examined the re-emergence of the *P. falciparum* epidemic in 1951-1960 to determine the reliability of the model.

A stochastic transmission model of *P. falciparum* was constructed to detect a small number of infected persons. The seasonal fluctuation of the *Anopheles minimus* population obtained by observational data and meteorological data through statistical processing was introduced into the model.

Simulations were carried out to predict the risk of a new epidemic with scenarios in which the attribute of index patient, visiting season, and reduced inoculation rates of *An. minimus* were assumed. When an infected person visited the island in summer, a small number of patients with primary infections derived from the index patient appeared for all 1,000-iterations. On the other hand, when an infected person visited the island in winter, few or no patients with primary infections appeared for any of the 1,000-iterations because of the low mosquito density. In realistic conditions, the simulation results showed that there was little possibility of the occurrence of *P. falciparum* infection.

Keywords: *Plasmodium falciparum*, *Anopheles minimus*, Ishigaki Island, re-emergence, stochastic simulation

INTRODUCTION

Ishigaki Island belongs to the Yaeyama Archipelago located in southwestern Japan. It is the center of local government and economic activity in the Yaeyama Archipelago and is also known as a marine resort. Formerly a malaria endemic area, Ishigaki Island suffered a *Plasmodium falciparum* and *Plasmodium vivax* epidemic in 1945-1946, with a more than 50% prevalence on the island [1, 2]. Although suppressed successfully, the epidemic re-emerged in 1949 because many settlers immigrated to former endemic areas and finally terminated in 1961 [2]. Toma *et al.* [3, 4] showed the presence of *Anopheles minimus*, which is the unique vector of *P. falciparum* on Ishigaki Island [2]. It is feared that a *P. falciparum* epidemic may occur again as a consequence of global warming.

The purpose of the present study was to predict the

outbreak of an epidemic as a result of a *P. falciparum* malaria patient visiting Ishigaki Island and also to examine the re-emergence of the *P. falciparum* epidemic in 1951-1960. A stochastic transmission model of *P. falciparum* was constructed to detect a small number of infected persons, where the incubation period, recovery period, and period for the loss of infectivity were assumed to be governed by appropriate probability-distributions. A stochastic model can deal with infectious status at an individual level, in contrast to deterministic models dealing with a homogeneous mass of infected people.

Since *P. falciparum* induces more severe symptoms than other human malarias, many studies have been conducted on transmission models of *P. falciparum*. Dietz *et al.* [5] suggested a transmission model of *P. falciparum* using vectorial capacity [6] to produce quantitative results. Collett & Lye [7] developed the Dietz *et al.* model [5] to es-

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timate the effect of malaria control measures in Malaysia. Ishikawa *et al.* [8] developed a model from Collett & Lye [7] to estimate the effect of malaria control measures in Vanuatu. Nakazawa *et al.* [9] built a stochastic model of *P. falciparum* to estimate the effectiveness of preventative measures among villagers, and Gu *et al.* [10] carried out simulations of *P. falciparum* transmission using an individual-based model.

Assessment of the seasonal fluctuation of the *An. minimus* population on Ishigaki Island was obtained from observational data on the density of immature *An. minimus* [4] combined with meteorological data [11] through statistical processing. In addition, the inoculation rate of humans, which reflects vectorial capacity [6], was estimated by the collection of data on *An. minimus* by human bites [12] and the above seasonal fluctuations.

The situation of the re-emergence of *P. falciparum* in the former Ohama Village in the 1951-1960 endemic area was simulated with 1,000-iterations. The simulation results followed the time-course of re-emergence and subsequent suppression of *P. falciparum* prevalence in the Yaeyama Archipelago.

To predict the risk of an epidemic when a *P. falciparum* malaria patient visits Ishigaki Island, several scenarios were prepared. When an infected person visited the island in summer, a small number of patients with primary infections that were derived from the index patient appeared for all 1,000-iteration simulations. On the other hand, when an infected person visited the island in winter, few or no patients with primary infections appeared for any of the 1,000-iteration simulations because of the low mosquito density. In realistic conditions, the simulation results showed that there was little possibility of an occurrence of *P. falciparum* infection.

MATERIALS AND METHODS

Study area

Belonging to the Yaeyama Archipelago, Ishigaki Island has an area of 222.63 km² [13] and is located at 24°20'–36°N, 124°04'–20°E, 411 km and 277 km from Naha (Okinawa) and Taipei (Taiwan), respectively [14]. The yearly average temperature and annual rainfall observed in 2007 were 24.8 °C and 2270.0 mm, respectively [11]. The daily temperature changes only slightly throughout the year. Previously, Toma *et al.* [3, 4] showed the presence of *An. minimus*, which is the unique vector of *P. falciparum* on Ishigaki Island [2].

The selected study area for the re-emergence of *P. falciparum* in the 1950s was the former Ohama Village in eastern Ishigaki Island, where malaria was endemic, and

Arakawa Town, a popular area for tourists in southern Ishigaki Island, was selected as a future invasion area of *P. falciparum*.

Tourists on Ishigaki Island

In recent years, many tourists visit Ishigaki Island in connection with its fame as a movie set, as a result of advertising, or on school trips. Tourists may play a key role as carriers in the invasion of *P. falciparum* to Ishigaki Island. The number of tourists visiting Ishigaki Island was reported to be about 767,000 in 2006, ranging between 50,000 (winter) and 80,000 (summer) a month [15]. The mean period of stay for tourists to the Yaeyama Archipelago in 2001 was estimated to be 2.8 days [16]. On the basis of the period of stay among tourists visiting Okinawa Prefecture in 2006 (mean 2.6 days) [17], the distribution of period of stay on Ishigaki Island was modified slightly from that for the whole of Okinawa Prefecture [18].

Re-emergence of *P. falciparum* in 1951-1960

The 1945-1946 *P. falciparum* and *P. vivax* epidemic in the Yaeyama Archipelago was successfully suppressed. However, it occurred again in 1949 because many settlers immigrated to the former endemic areas. The new epidemic terminated in 1961 [2, 19]. The occurrence of malaria patients in the Yaeyama Archipelago in the 1950s is shown in Fig. 1 [19]. The *P. falciparum* epidemic peaked earlier than the *P. vivax* epidemic.

Records show that 4,165 settlers immigrated to the Yaeyama Archipelago in 1949-1955 [20]. The change in the population of Ohama Village is based on the total number of settlers and demographic statistics in the 1950s [21], since no immigration data are available for Ohama Village in the 1950s.

Fig. 1 The number of malaria patients in Yaeyama Archipelago (1950-1960).

Dark and light bars indicate the number of patients of *P. falciparum* and *P. vivax*, respectively, while the line indicates the total number of malaria patients.

Vector density

Toma *et al.* [3, 4] observed the seasonal fluctuation of *An. minimus* in Nishihama Stream in the former Ohama Village, the study area for re-emergence in the 1950s. In 1957, a new vector control method, i.e., DDT residual spraying conducted drastically twice a year, was started. Consequently, no *Anopheles* mosquitoes were collected in 1961 mosquito surveys and malaria was eradicated in 1961 [2, 22]. The seasonal fluctuation of the *An. minimus* population in the 1950s was estimated by the generalized linear model in mathematical statistics through observation data on the density of immature *An. minimus* [4], collected data

Fig. 2 The observed and estimated temperature on Ishigaki Island.

The light line indicates the observed temperature (1948-2007) and the dark line indicates the estimated temperature (2007-2016). The grey bold line indicates the estimated quadratic curve of the trend in temperature.

on human bites [12], and meteorological data [11], which would be reduced to 5-20% due to DDT residual spray after August 1957. The vector density correlated with water temperature, which in turn correlated with air temperature and rainfall [4].

To predict future temperature and rainfall changes which will reflect the global warming trend of recent years, the records on temperature and rainfall for the past 60 years (1948-2007) at Ishigaki Island were divided into seasonality, trend and noise components using standard methods in time series analysis. By the hypothesis testing, which detected an increase trend in temperature but not in rainfall, future temperature changes had trend and seasonality (Fig. 2), while future rainfall changes had only seasonality. The details were given by Ueki *et al.* [18]. The future density of *An. minimus* per person in 2008-2017 was estimated by the same way as the 1951-1960 period, except for the effect of DDT residual spraying.

The estimated densities of *An. minimus* per person in 1951-1960 and in 2008-2017 on Ishigaki Island are shown in Fig. 3 (a) and (b), respectively.

Mathematical model

Model Scheme

In the present study, a stochastic model was constructed for *P. falciparum* transmission. In this model, the human population was divided into five epidemiological classes: negative, preventive, incubation, positive, and protective. The preventive class was comprised of people receiving preventative treatment against malaria, while the protective class was comprised people under treatment for malaria. The injection of *P. falciparum* by infected vectors transferred an individual from the negative class to the incu-

Fig. 3 The estimated densities of *An. minimus* per person on Ishigaki Island.

(a) 1951-1960, (b) 2008-2017

bation class. After the incubation period, the individual showed parasitemia and suffered clinical symptoms such as fever. Repeated proliferation of parasites in erythrocytes brings on fever, and some parasites in erythrocytes differentiate into gametocytes. The positive class was subdivided into two subclasses: a positive and infectious subclass with gametocytes (PG) and a positive but not infectious subclass without gametocytes (PN). The appearance of gametocytes transferred an individual from the PN-subclass to the PG-subclass, while the disappearance of gametocytes transferred an individual from the PG-subclass to the PN-subclass. The protective class was also subdivided into two subclasses: a protective and infectious subclass (PrG) and a protective but not infectious subclass (PrN). The disappearance of asexual parasites by the effect of chemotherapeutic treatment transferred an individual from the PN and PG-subclasses to the PrN and PrG-subclasses, respectively, while the disappearance of gametocytes by the effect of chemotherapeutic treatment transferred an individual from the PrG-subclass to the PrN-subclass. Spontaneous recovery without treatment transferred an individual from the PN-subclass to the negative class. The interruption of medication transferred an individual from the PrG-subclass to the PN-subclass. An individual discharged from the hospital after complete recovery was transferred from the PrN-subclass to the negative class. After 1954, prevention by prophylactic treatment against malaria transferred an individual from the negative or incubation class to the preventive class, and the interruption of prevention transferred an individual from the preventive class to the negative class.

In the projected situation of a future invasion of *P. falciparum*, all patients will go to hospital and be diagnosed, so no spontaneous recovery without treatment was taken into account. An individual of the PN-subclass transferred not to the negative class but to the PG or PrN-subclasses. In addition, the interruption of medication and prevention were not considered. Since a patient was assumed to be in the hospital after diagnosis, he or she would no longer be

subject to mosquito bites.

Two model schemes for *P. falciparum* transmission on Ishigaki Island, one in the 1950s situation and the other in the future invasion situation, are shown in Fig. 4 (a) and (b), respectively.

Estimation of parameters in the model

In order to carry out stochastic simulations, it is necessary to include epidemiological parameters etc. to determine suitable probability-distributions with means and variances on the basis of field data.

Prevention

The transfer of an individual from the negative or incubation class to the preventive class under prophylactic treatment was assumed to be governed by a Bernoulli distribution with a low success rate of 0.005 because the prophylactic treatment resulted in failure [23], and the duration of prophylactic treatment was assumed to be governed by a Gamma distribution with a mean of 10.5 days and a variance of 3.5^2 .

Incubation period

Individuals injected with an infected vector showed clinical symptoms after 1 week at the earliest and most of them within a month [24]. The incubation period, that is, the appearance of parasites after infection, was assumed to be governed by a Gamma distribution with a mean of 10.52 days and a variance of 0.17^2 [25].

Period for loss of infectivity

The period for the loss of infectivity was assumed to be governed by a Gamma distribution with a mean of 19.5 days and a variance of 4.0^2 [26].

Recurrence

In the 1950s, the recurrence rate of *P. falciparum* in the PrN- PrG-subclasses was assumed to be governed by a Bernoulli distribution with a success rate of 0.08 [27].

Out of the hospital

The transfer of an individual from the PrN-subclass to the negative class in the 1950s was assumed to be governed by a Bernoulli distribution with a success rate of 0.05 due to

Fig. 4 Model schemes for *P. falciparum* transmission on Ishigaki Island.

(a) for the situation in the 1950s, (b) for the situation of a future invasion

a lack of field data. On the other hand, for the situation of a future invasion, an individual in the PrN-subclass was assumed to transfer to the negative class after 17 days-hospitalization.

Recovery period without treatment

The recovery period without treatment in the 1950s was assumed to be governed by a Gamma distribution with a mean of 250 days and a variance of 50^2 [28].

Recovery period under treatment

On Ishigaki Island in the 1950s, the drugs atebirin and plasmochin were used for malaria treatment. The recovery period with these drugs was assumed to be governed by an exponential distribution with a mean of 1.1 days and 3.5 days for asexual parasites and gametocytes, respectively.

In the situation of a future invasion of *P. falciparum*, it was assumed that a three-day course of Artemether-lumefantrine (AL), which is a type of Artemisinin-based combination therapy (ACT), will be adopted for malaria treatment [29]. The period for the loss of infectivity was assumed to be governed by a Gamma distribution with a mean of 19.5 days and a variance of 4.0^2 [26].

Efficacy of drugs

In the situation of a future invasion of *P. falciparum*, it was assumed that 96% of treated patients show an adequate clinical response [30]. The transition rate from both the PN and PrG-subclasses to the PrN-subclass was governed by a Bernoulli distribution with a success rate of 0.96.

Inoculation

The inoculation of *P. falciparum* by mosquitoes was assumed to be governed by a Bernoulli distribution with a success rate of $g(1-\exp(-CY))$ [5], where C , g , and Y stand for the vectorial capacity as described by Garrett-Jones [6], the susceptibility as a conditional probability of infection as described by Dietz *et al.* [5], and the ratio of the PG and PrG-subclasses. People in the PN and PG-subclasses were

assumed to have a risk of super-infection, and super-infection was governed by a Bernoulli distribution with the same success rate as above.

Other parameters

The rate of acquisition of infectivity (α) and susceptibility (g) cannot be determined by field or experimental data. A value satisfying the prevalence rate of 50% was chosen [1], and the number of infectious patients was equal to the number of noninfectious patients [31, 32]. A value of $\alpha=0.025$ was chosen, and $g=0.006$ as the minimum of χ^2 was recorded as 0.41. Here, χ^2 stands for the formula: $\chi^2 = (Y_1/Y_2 - 1)^2 + (X_1/X_2 - 1)^2$, with X_1 : negative class and incubation class, X_2 : Positive class, Y_1 : PN-subclass, and Y_2 : PG-subclass.

The estimated values and the types of distribution of these parameters are presented in Table 1.

Scenarios

Scenario in the situation of a future invasion

In the situation of a future invasion, two kinds of index case - resident and tourist - and two visiting season - high (July) and low (January) mosquito-density seasons - were presumed. The period for diagnosis was governed by a χ^2 distribution with degrees of freedom of 20 and 4.7, which stand for the mean period for diagnosis, within a month of index case's visiting, and thereafter, respectively [33]. The scenarios are summarized in Table 2.

Inoculation rates in the situation of a future invasion

The inoculation rate could decrease with the spread of air conditioners and urbanization. Therefore, various inoculation rates (relative inoculation rate (RI)) reduced to 25%, 50%, and 100% compared with the level of *An. minimus* density in the 1950s were modelled.

Table 1 Estimated values and types of distribution for parameters.

(a)

Period	Type of distribution	Mean (days)	Variance	Range (days)
Incubation	Gamma	10.52	0.17^2	9-14
Recovery	Gamma	250	50^2	200-300
Loss of infectivity	Gamma	19.5	4^2	16-24
Prophylactic	Gamma	10.5	3.5^2	7-14
Recovery from parasitemia by atebirin and plasmochin	Exponential	1.1	-	-
Recovery from parasitemia with gametocytes by atebirin and plasmochin	Exponential	3.5	-	-

(b)

Rate	Type of distribution	Success rate
Prevention	Bernoulli	0.005
Recurrence (1950s)	Bernoulli	0.08
Out of the hospital	Bernoulli	0.05
Adequate clinical response	Bernoulli	0.96
Acquisition of infectivity	Bernoulli	0.025

(c)

Description (rate)	Symbol	Value
Susceptibility	g	0.006

Table 2 Scenarios for the situation of a future invasion.

Scenario	Relative inoculation rate (RI)	Index case		Number	Period for diagnosis Probability-distributions and mean (days)
		Attribution	Visiting season		
1	1 0.5 0.25	Resident	July	1	χ^2 -distribution 20 (First month) 4.7 (Second month)
2	1 0.5 0.25	Tourist	July	1	
3	1 0.5 0.25	Resident	January	1	
4	1 0.5 0.25	Tourist	January	1	

RESULTS

Stochastic simulation

The stochastic model of *P. falciparum* transmission was programmed by Intel Visual Fortran™ to work on any computer using the Microsoft Windows™ platform, where the random number generators in IMSL™ libraries were used. With regard to the method of simulation, the time step of the stochastic process was adopted as a day, and the results in this section were obtained through 1,000-iteration simulations.

Simulations

Simulation of the re-emergence of *P. falciparum* in 1951-1960

The situation of the re-emergence of *P. falciparum* in

Table 3 Assumption of the frequency and coverage of prophylactic and chemotherapeutic treatments.

Year	Frequency of treatment	Coverage of chemotherapeutic treatment (%)	Coverage of prophylactic treatment (%)
1951-1953	2	10	-
1954	3	30	0.5
1955-1960	3	70	0.5

the former Ohama Village of the previous endemic area in 1951-1960 was simulated stochastically using the model. In the simulation, the initial population in 1951 was assessed as 5,519 by demographic data from 1947 [34], and the population increased due to immigration (2.1.2). Five initial patients were introduced to the targeted village, but the exact number remained unexplained. For the situation in the 1950s on Ishigaki Island, it was assumed that prophyl-

Fig. 5 Simulations of re-emergence of *P. falciparum* in 1951-1960.

(a) The number of patients in 1951-1960 in 1,000-iteration simulations.

The black line indicates the profile of the mean numbers, and the dark gray and light gray zones indicate standard derivation range and the maximum-minimum range. (b) The average yearly incidence in 1951-1960 in 1000-iteration simulations.

Fig. 6 The profile of the number of *P. falciparum* patients in scenarios (Table 2) in 1,000-iteration simulations.

The gray and black straight lines indicate the profile of the maximum numbers, the mean numbers, and the dark gray broken line indicates the profile of the minimum numbers in simulations. (a)-(c) and (d)-(f) show the situations based on scenarios 1 and 2 in Table 2, respectively, and (a,d), (b,e) and (c,f) show the relative inoculation rate (RI) of 1, 0.5, and 0.25, respectively. Figures for scenario 3 and 4 were omitted.

lactic and chemotherapeutic treatments against malaria (2.3.2) were conducted twice a month from 1951 to 1953 and three times a month after 1954 [19, 23]. The coverage rate of prophylactic and chemotherapeutic treatments was assumed from descriptions in Yaeyama Regional Public Health and Welfare Division [19] and Eshita [23], as shown in Table 3, due to the lack of old full records. The introduction of DDT residual spray [22] was also considered (2.2). The profiles of the number of patients and number of yearly incidences are shown in Fig. 5 (a) and (b), respectively.

The simulation showed that the number of patients increased from 1951 to 1954, reached at peak in 1954 with 150 patients as the mean and 480 patients as the maximum and decreased thereafter, no further patients being observed in 1957 in any of the trials.

Simulation of a future invasion of *P. falciparum* patients

Simulations with 1,000 trials for 1 year were carried out for a future invasion of a *P. falciparum* patient with gametocytes with various scenarios (Table 2). In the model, the initial population was assessed as 8,772 by demographic data from 2006 [21] and the movement of tourists was in-

troduced as 2.1.1. The profiles of the number of patients for 4 scenarios are shown in Fig. 6 (a)-(f). The number of patients among residents with primary infections that were derived from the index patient and the number of incidences among tourists are summarized in Tables 4 and 5, respectively. Tourists have little risk of infection and infected tourists seldom bring *P. falciparum* to any area other than Ishigaki Island, as shown by the fact that there were 2.98 infections on average and 11 infections maximum among tourists in the most serious situation of RI=1.0 in scenario 1 (Table 5). The probability that a *P. falciparum* epidemic will be terminated within 1, 3, and 6 months is shown in Table 6. In scenario 3 with RI=1.0 and scenario 4 with three levels of RI, however, simulations with 1,000-iterations showed that exceptional trials produced few patients with primary infections and that 1,000-iterations in the simulation for RI=0.5, 0.25 in scenario 3 produced no patients with primary infections. So these figures were omitted.

Table 4 The number of patients among residents with primary infections in 1000-iteration simulations.

Scenario	Relative inoculation rate (RI)	The number of patients with primary infections					
		Mean	Maximum	Third quartile	Median	First quartile	Minimum
1	1	24.96	70	34	22	11	0
	0.5	12.82	55	22	11	0	0
	0.25	5.69	22	11	0	0	0
2	1	14.99	62	22	11	7	0
	0.5	16.26	70	22	15	7.75	0
	0.25	12.09	56	20	11	0	0
3	1	0.19	11	0	0	0	0
	0.5	0	0	0	0	0	0
	0.25	0	0	0	0	0	0
4	1	0.82	20	0	0	0	0
	0.5	0.35	11	0	0	0	0
	0.25	0.24	11	0	0	0	0

Table 5 The incidence among tourists in 1000-iteration simulations.

Scenario	Relative inoculation rate (RI)	Incidence					
		Mean	Maximum	Third quartile	Median	First quartile	Minimum
1	1	2.98	11	4	3	2	0
	0.5	1.44	7	2	1	0	0
	0.25	0.65	4	1	0	0	0
2	1	1.73	9	3	1	1	0
	0.5	1.79	8	3	2	1	0
	0.25	1.3	7	2	1	0	0
3	1	0.02	1	0	0	0	0
	0.5	0	0	0	0	0	0
	0.25	0	0	0	0	0	0
4	1	0.09	2	0	0	0	0
	0.5	0.04	1	0	0	0	0
	0.25	0.02	1	0	0	0	0

Table 6 Proportions of extinction.

Scenario	Relative inoculation rate (RI)	Proportion of extinction (%)		
		Within 1 month	Within 3 months	Within 6 months
1	1	25.6	99.2	100
	0.5	49.8	99.9	100
	0.25	71.3	100	-
2	1	57.6	99.9	100
	0.5	61.3	99.9	100
	0.25	70.9	100	-
3	1	94.8	100	-
	0.5	96.0	100	-
	0.25	94.9	100	-
4	1	97.5	100	-
	0.5	99.2	100	-
	0.25	99.7	100	-

DISCUSSION

The epidemics of *P. falciparum* and *P. vivax* that occurred on Ishigaki Island in 1945-1946 were successfully suppressed. However, the epidemic occurred again in 1949 because many settlers immigrated to the former endemic areas. Malaria control programs beginning in 1947 were mostly ineffective in suppressing the epidemic. The eradication programs were revised in 1947 and again in 1957 [2, 23], and the epidemics of *P. falciparum* and *P. vivax* were terminated in 1961 [19]. A mathematical model of *P. falciparum* transmission was constructed and simulations were carried out following scenarios (3.2.1) to review the re-emergence of *P. falciparum* in the 1950s on Ishigaki Island. Moreover, the risk of re-emergence of *P. falciparum* when a *P. falciparum* malaria patient visits Ishigaki Island was predicted through model simulations following further scenarios (2.4), because the continuing presence of *An. minimus* on Ishigaki Island has been reported by Toma *et al.* [3, 4].

The phenomenon of inoculations of *P. falciparum* into individuals by mosquitoes was assumed to be governed by a Bernoulli distribution with a success rate following the formula: $g(1 - \exp(-CY))$ (2.3.2), the basis of which was introduced by Dietz *et al.* [5]. All of the epidemiological and entomological parameters in the model, except for the rate of acquisition of infectivity (α) and susceptibility (g), were estimated on the basis of malariological surveys. Because the process of gametocyte production has not as yet been ascertained [35], it is difficult to determine the rate of acquisition of infectivity as an accurate value. In addition, susceptibility cannot be determined by experimental methods or field surveys. The rate of acquisition of infectivity and susceptibility were chosen to satisfy the conditions that the number of infectious patients would be equal to half the number of infectious patients [31, 32] and that the preva-

lence rate would be 50% [1].

The simulation examining the re-emergence of *P. falciparum* in 1951-1960 (Fig. 5, (a)) showed that the number of patients increased gradually and reached a peak in 1954, and that the epidemic terminated in 1960 because of the effects of enhanced malaria control from 1954 (Table 3) and DDT residual spray from 1957 [2], factors that were brought into the assumptions of the scenario. The profile of the incidence obtained by the simulation (Fig. 5) was compared to that in the Yaeyama Archipelago in the 1950s (Fig. 1). Although there are still few details known about the situation in the 1950s in the former Ohama Village, the simulation results followed the time-course of re-emergence and the subsequent suppression of *P. falciparum*, which led to the transmission model being regarded as sufficiently reliable.

The inoculation rate was reduced by the improvement of public health, urbanization, and the spread of air conditioners [36]. Therefore, scenarios were arranged with reduced inoculation rates of 25% and 50% (RI=0.25 and 0.5) compared with the level of *An. minimus* density in the 1950s (RI=1.0). The supposition that RI=0.25 was better reflected the present conditions on Ishigaki Island.

In all scenarios, the diagnosis period was set at 20 days as the mean within the first month after the index case visits Ishigaki Island and 4.7 days thereafter. Christen [33] and Chalumeau *et al.* [37] reported that a mean of 4.7 days was required to diagnose *P. falciparum* in Europe, a non-endemic region. On the other hand, Chalumeau *et al.* [37] reported that it took a maximum of 19 days to diagnose *P. falciparum*. Since an epidemic of *P. falciparum* has not occurred for about 40 years on Ishigaki Island, it could take several days to reach a diagnosis of *P. falciparum* correctly at the beginning of the outbreak from the viewpoint of the risk assessment for *P. falciparum*.

From the viewpoint of risk assessment of an epidemic, the present study compared the two seasons when an infected person visited the island, that is, scenarios 1 and 2 (July, summer) and scenarios 3 and 4 (January, winter). In scenarios 1 and 2, a mean of 5-24 patients with primary infections derived from the index patient appeared for all 1,000-iterations, while in scenarios 3 and 4, few or no patients with primary infections appeared for any of the 1,000-iterations because of the low mosquito density (Table 4). In scenarios 1 and 2, some of the patients appeared just after the introduction of the index patients in summer because of the high mosquito density, and the epidemic terminated in autumn for all 1,000-iterations because of the low mosquito density (Table 6; Fig. 3 (b)).

The influence of a decrease in the inoculation rate on the occurrence of patients among residents and tourists and

the proportion of extinction were investigated. The number of patients with primary infections derived from the index patient, together with the incidence among tourists, and probabilities of extinction decreased in correlation to the RI in all scenarios except several inverted value sets, which were insignificant (significance level, 0.05): P-value=41% (Table 4, scenario 2, RI=1, 0.5, mean), 49% (Table 5, scenario 1, RI=1, 0.5, mean), 46% (Table 6, scenario 3, RI=0.5, 0.25, within 1 month).

In Taiwan, one and two patients were recognized as having autochthonous *P. falciparum* infection in 2001 and 2003, respectively, and there were 258 patients of imported *P. falciparum* infection during 1999-2008 [38]. Meanwhile, 61-83 persons infected with *P. falciparum* malaria abroad enter Japan every year (2002-2006) [39]. Although there is a low possibility of the occurrence of *P. falciparum* infection in the situation where RI=0.25 (3.2.2), global warming may accelerate the expansion of the habitat of *An. minimus* and consequently the occurrence of *P. falciparum* infection. Therefore, it is necessary to establish a continuous monitoring system for the detection of *P. falciparum* malaria infection and surveillance for *An. minimus*.

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