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Modeling of re-emerging *Plasmodium vivax* in the Northern Area of the Republic of Korea Based on a Mathematical Model

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Plasmodium vivax re-emerged in 1993 near the demilitarized zone (DMZ) in South Korea, although *P. vivax* malaria disappeared in South Korea in 1979. The re-emergence of malaria in South Korea is believed to have originated from infection by mosquitoes from North Korea across the DMZ. The principal vector of *P. vivax* in the Korean Peninsula is *Anopheles sinensis*. The density of *An. sinensis* has a peak during the second week of July. The North Korean strain of *P. vivax* has 2 characteristics: a wide distribution of the terms of relapse and a high rate of relapse. Therefore, we may well wonder why the incidence of malaria is concentrated in summer, especially in August. Mathematical models in North Korea and South Korea were constructed, in which the South Korean model was affected unidirectionally by the North Korean model. We carried out simulations of the model for the Paju-shi and Yonchon-gun situations near the DMZ region. The simulation results followed the time-course of the re-emergence of *P. vivax* there, and revealed the mechanism of the elevation of the incidence of *P. vivax* in summer.

Key words: *DMZ, Korea, model, Plasmodium vivax, re-emergence*

1. INTRODUCTION

Plasmodium vivax malaria was endemic in the Korean Peninsula for many centuries. Infection by *P. vivax* was common after the Korean War. Later, the National Malaria Eradication Service (NMES) was established in collaboration with the World Health Organization, and the WHO declared in 1979 that indigenous malaria had disappeared in South Korea (Paik *et al.*, 1987). In 1993, the first occurrence of the re-emergence of *P. vivax* was reported in Paju-shi of Kyonggi-do near the demilitarized zone (DMZ). Thereafter, the incidence of malaria increased exponentially, and in 2000, more than 4,000 cases of *P. vivax* infection were diagnosed. After 2000, the incidence of malaria decreased due to malaria control measures. It was suggested that the re-emerging malaria in South Korea originated from infection by mosquitoes from North Korea (Kho *et al.*, 1999). The North Korean strain of *P. vivax* has 2 characteristics: the terms of relapse after infection are widely distributed from several months to 1 or 2 years (Kim, 2001; Oh *et al.*, 2001; Bray *et al.*, 1982), and the rate of relapse is relatively high compared with that of other strains of *P. vivax* (Kim, 2001; Oh *et al.*, 2001; Bray *et al.*, 1982). Most cases of malaria in South Korea are observed in June-September, with especially high incidence in August.

There are 7 *Anopheles* species in Korea, and only 2 species, that is, *An. sinensis* and *An. yatsushiroensis*, are capable of acting as vectors for the transmission of *P. vivax* (Ree *et al.*, 1967). The principal vector of *P. vivax* is *An. sinensis*, and the density of *An. sinensis* has a peak during the second week of July (Lee *et al.*, 2002).

Mathematical models are useful for forecasting the prevalence of infections diseases and for evaluating control strategies. Such a model for *Plasmodium falciparum*, the DMT model, was constructed by Dietz *et al.* (1974). In the present study, a mathematical model of the re-emergence of malaria in South Korea was constructed based on the DMT model and using the characteristics of the North Korean strain of *P. vivax*, which include a wide distribution of the terms of relapse and a high rate of relapse. The model consisted of models in North Korea

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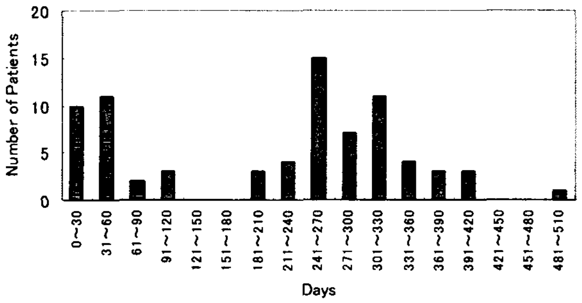

Fig. 1 The distribution of the latent period of the re-emergence of malaria in 77 patients in South Korea. Derived from Oh *et al.* (2001).

and South Korea. In the North Korean model, the population of individuals was divided into 5 epidemiological classes. On the other hand, in the South Korean model, the population of individuals was divided into 4 classes due to the different public health circumstances. The South Korean model was affected unidirectionally by the North Korean model.

The simulation was carried out for the situations of Paju-shi and Yonchon-gun in Kyonggi-do with the initial condition that there were no infected individuals. The results of simulations in Paju-shi and Yonchon-gun followed the time-course of the re-emergence of *P. vivax*. They also revealed the mechanism by which the incidence of *P. vivax* is highest in the summer considering the above 2 characteristics of the North Korean strain of *P. vivax*.

In the near future, *Anopheles* mosquito vectors capable of malaria transmission may invade countries that are free from malaria because of the effect of global warming, and malaria may re-emerge. Our method will be useful for the prediction of the prevalence of malaria in countries in which malaria re-emerges.

2. MATERIALS AND METHODS

2-1 Relapses

The North Korean strain of *P. vivax* has the characteristics that the terms of relapse after infection are widely distributed from several months to 1 or 2 years (Kim, 2001; Oh *et al.*, 2001; Bray *et al.*, 1982). The surveillance of the incubation periods of relapse for 73 veterans receiving prophylaxis of chloroquine and 4 civilians who were diagnosed at 3 university hospitals, Seoul National University Hospital, Chungbuk National University Hospital and Chonnam National University Hospital (January 1, 1996 - December 31, 1999) is shown in Fig. 1 (Oh *et al.*, 2001). It was reported that there were no cases of relapse 4-6 months after infection and that the outbreak of relapse cases had 2 peaks at 1-2 months and 8-9 months after infection. Therefore, the distribution of the terms leading to relapse is grouped into 2 parts: 1 - 4 months after infection and more than 6 months after infection, which are called "short incubation period" and "long incubation period", respectively, while the cases who develop parasitemia within 1 month after infection are regarded as "primary infection". In this study, it was assumed that prophylaxis of chloroquine would not prevent relapses, while it prevents primary infections. In order to establish modeling of the relapse-distribution, the distribution of short incubation period would be applied to the exponential distribution for the regression curve (mean = 0.019 1/days), (Fig. 2-(b)), and the distribution of long incubation period would be applied to the log-normal distribution (mean = 288 days, mean ± S. D. =288-52, 288+64 days) (Fig. 2-(a)). A χ^2-value 13.37 (15.51, *d.f.* = 8) was accepted as statistically significant ($P < 0.05$) by the χ^2-fitness test.

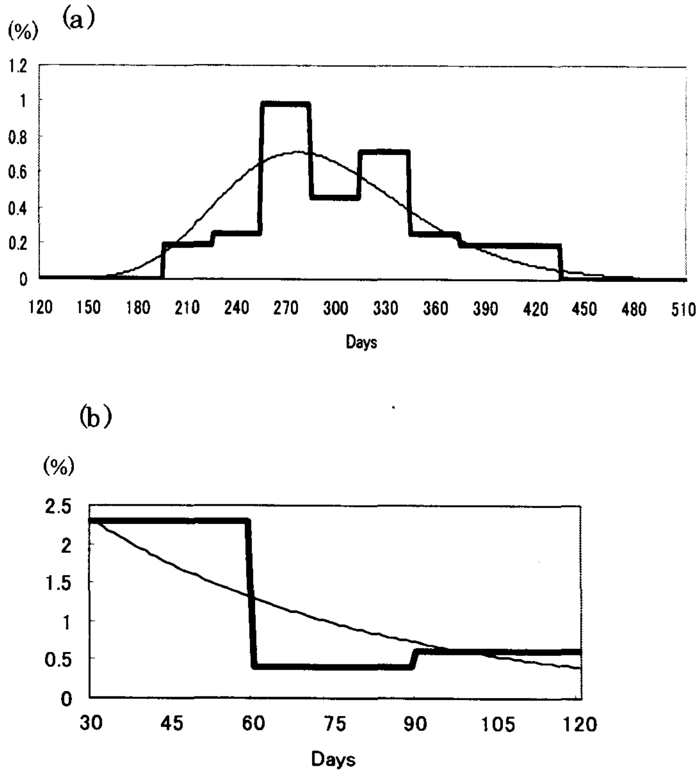

Fig. 2 The distribution of long incubation period (a) and short incubation period (b). The log-normal distribution (thin curve) (a) and the exponential distribution (thin curve) (b) compared with the surveillance data (thick line).

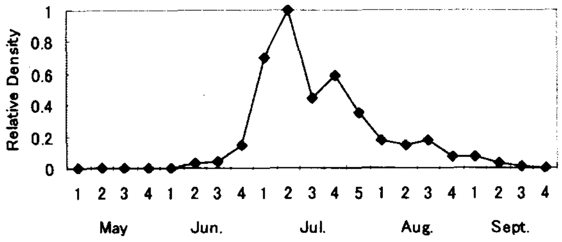

Fig. 3 The relative variation of the weekly density of female mosquitoes to the highest density in August. Derived from Lee *et al.* (2002).

2-2 The ratio of primary infection to relapse

The North Korean strain of *P. vivax* has the characteristics that the rate of relapse is relatively high compared with that of other strains of *P. vivax*. Kim (2001) observed that only 4 cases (8%) were primary infection while 52 cases (92%) were relapse. Moreover, Park *et al.* (2003) reported that the number of people infected with malaria in the military was 393 during 1993 - 2000 and that 56 cases had been in the non-endemic region of *P. vivax*. Therefore, it is speculated that the rate of primary infection is at least 14% of the total cases. Oh *et al.* (2001) also indicated that the numbers of primary infection and relapse were 10 (13%) and 67 (87%), respectively. We adopted 87% as the average rate of relapse based on the above 3 reports.

2-3 The seasonal fluctuation of *Anopheles sinensis*

It is known that there are 7 species of *Anopheles* in Korea, and that only 2 species, that is, *An. sinensis* and *An. yatsushiroensis*, are capable of acting as vectors for the transmission of *P. vivax*. (Ree *et al.*, 1967). *An. sinensis*, the principal malaria vector, comprises more than 80% of total malaria vectors (Cho *et al.*, 2002). Therefore, it is assumed that malaria in Korea would be transmitted only by *An. sinensis* species. The population of *An. sinensis* rises steeply from the second week of June, reaches a peak during the second week of July, and then gradually decreases through the fourth week of September (Lee *et al.*, 2002). The seasonal fluctuation of relative density compared with the peak week (the second week of July) is shown in Fig. 3.

2-4 The seasonal pattern of the incidence of *P. vivax*

The monthly time-course of malaria cases in 1993-1994 and 1998-2000 is shown in Fig. 4 (National Institute of Health, Korea, 2003). Most cases of malaria were observed in June-September, with an especially high incidence in August from 1995 to 2003, whereas an elevated incidence of malaria cases was not observed in the summer in 1993-1994. The seasonal pattern of the incidence was also noted in an old report (Hasegawa, 1913) stating that the incidence of *P. vivax* was highest in June - October. Given these 2 characteristics, that is, the wide distribution of terms to relapse (1-16 months) and the high relapse rate (87%), why is the incidence of malaria concentrated in the summer, especially in August?

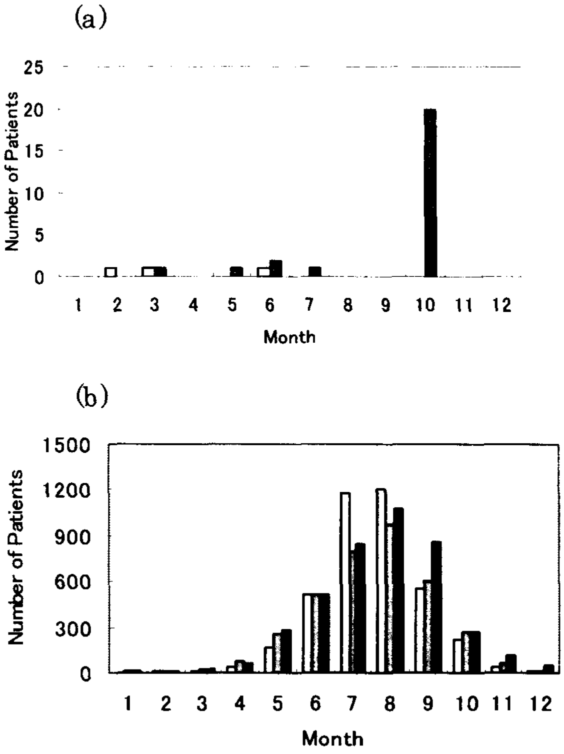

Fig. 4 The monthly incidence of *P. vivax* in South Korea (a) in 1993 (white bars) and 1994 (gray bars) and (b) in 1998 (white bars), 1999 (gray bars) and 2000 (black bars).

2-5 Malaria cases in the northern part of South Korea

In 2 regions near the DMZ, Paju-shi, where the first case of the re-emergence of malaria was discovered, and Yonchon-gun, where most of the cases of malaria were observed in the beginning of re-emergence of malaria, the incidence of *P. vivax* increased until 1999, but it subsequently decreased thereafter (CDMR, 2003). Fig. 5 shows the civilian cases of malaria in Paju-shi (1994-2002) and Yonchon-gun (1995-2002), where the surveillance data was derived from CDMR (2003); Moon (2001); Lee (1998); Park (2003).

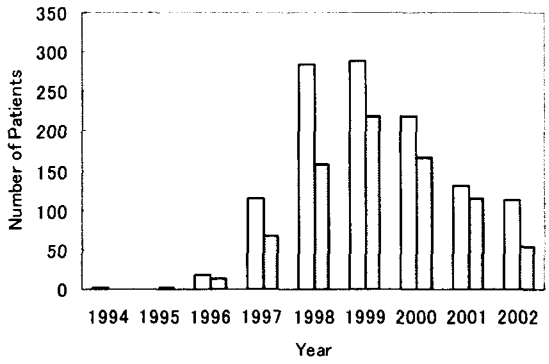

Fig. 5 Cases of malaria in civilians in Paju-shi (white bars) and Yonchon-gun (gray bars) in 1994 – 2002. The vertical axis represents the number of cases per 100,000.

2-6 Re-emergence of *P. vivax*

In 1993, *P. vivax* malaria re-emerged in South Korea, although WHO declared in 1979 that indigenous malaria had disappeared. The first possibility regarding this re-emergence was that in the beginning of the 1990's, immigrant workers from countries with endemic malaria provided a nidus for re-establishment of the epidemic of *P. vivax*. The second possibility was that mosquitoes infected with *P. vivax* came to South Korea across the DMZ. The facts that most of the cases in the beginning of the re-emergence occurred in military personnel who served near the DMZ, and that the cases of malaria spread from the DMZ toward the south supported the second possibility (Kho *et al.*, 1999). In this study, it was assumed that the infected mosquitoes will come across the DMZ at a constant rate based on the second possibility.

2-7 Mathematical model

The mathematical model in South Korea and North Korea was established on the basis of the DMT model (Dietz *et al.*, 1974). The South Korean model is affected unidirectionally by the North Korean model, because the infected mosquitoes will come to South Korea across the DMZ.

North Korean model

In the North Korean model, the population of individuals is divided into 5 epidemiological classes: susceptible (S), dormant hypnozoites without parasitemia (H), latent for primary infection (Pr), positive with gametocytes (In) and positive without gametocytes (Po). Moreover, H, Pr, In, Po classes are subdivided into 3 subclasses which are denoted by the suffix i (i=0, 1, 2) according to the number of hypnozoites in their livers. We introduce the epidemiological parameters: inoculation rate (h), the onset rate of symptoms with infection (α), the rate of loss of infection (β) and the rate of recovery taking account of superinfection (R). Moreover, ε and μ are the ratio of primary infection and that of relapse, respectively (ε+μ=1). The classes H_i, Pr_i and In_i, (i=1, 2) transfer into the class In_{i-1} when the individuals of these classes relapse into parasitemia. Moreover, the class Po_i (i=1, 2) transfers into the class Po_{i-1} when the individuals of this class relapse into parasitemia. The scheme of the model in North Korea is illustrated in Fig. 6-(a).

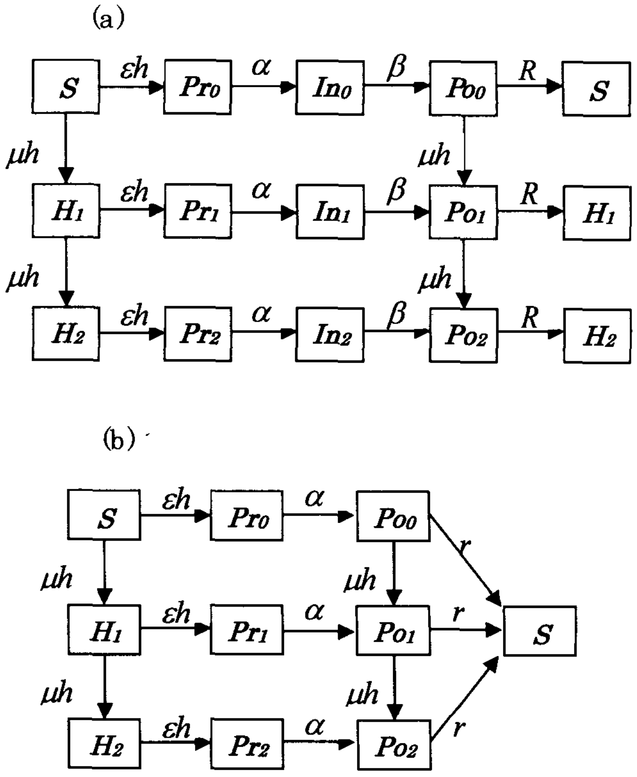

Fig. 6 The scheme of models in North Korea (a) and South Korea (b).

South Korean model

Although the North Korean strain of *P. vivax* prevails in both North Korea and South Korea, the model for transmission in South Korea is modified compared to that for North Korea due to the different public health circumstances. In South Korea, cases of malaria usually recover in about 1 week upon treatment with chloroquine, and therefore the positive with gametocytes class (In) is combined with the positive without gametocytes class (Po). Since the radical treatment results in the clearance of hypnozoites in the malaria patients, it is assumed that the class (Po) transfers to the class (S) on recovery.

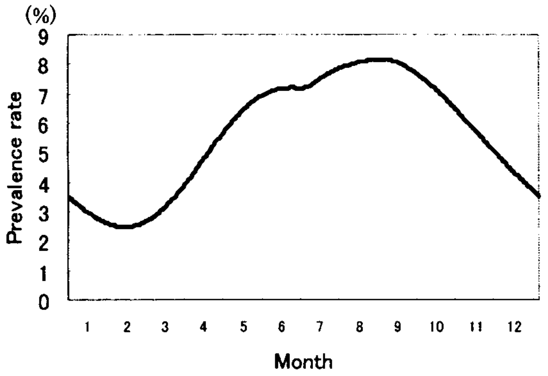

Fig. 7 The time-course of the prevalence in North Korea predicted by simulation by the model (the average rate of prevalence being 5.6%).

It is assumed that there are no infected individuals at the initial time in South Korea and that the infected mosquitoes come across the DMZ from North Korea, the number of which depends on the distance from the DMZ. The scheme of the model for South Korea is illustrated in Fig. 6-(b).

3. RESULTS

North Korean model

The average prevalence rate is estimated as 5.6% by the simulation based on the transmission model of *P. vivax* in North Korea (Fig. 7).

Seasonal change of incidence

The seasonal change of incidence in South Korea is obtained through the simulation, where we take account of the distribution of relapse terms, the rate of relapse, the seasonal fluctuation of *An. sinensis* and the average prevalence rate in North Korea (Fig. 8). The simulation indicates that the prevalence is maintained at a high level from March to September, and has 2 peaks in April – May and July – August. In spite of the wide distribution of relapse terms and high rate of relapse, the simulation succeeded in modeling the peak incidence of malaria cases in the summer.

Re-emergence of malaria in Paju-shi and Yonchon-gun

A comparison of the surveillance data of cases of malaria in Paju-shi and Yonchon-gun in 1996 – 2002 and the prediction of the simulations is shown in Fig. 9-(a) and (b). The results of simulations followed the time-course of the re-emergence of *P. vivax* in 1996-1999 for both regions. On the other hand, the time-courses of the actual prevalence in Paju-shi and Yonchon-gun deviated from the predictions of the model simulation after 2000, because the model did not take into account any malaria control measures.

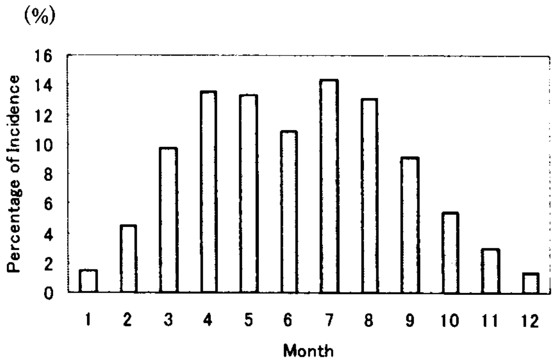

Fig. 8 The monthly incidence predicted by simulation using the model.

4. DISCUSSION

In this study, we assumed that the southward movement of infected mosquitoes across the DMZ caused the re-emergence of *P. vivax* in South Korea. Mosquitoes that had been released 21 days before in Kyonggi-do were recaptured at rates of 37.1%, 29.4%, 21.1%, 10.3% and 2.1% at 1, 3, 6, 9 and 12 km from the release point, respectively, namely, about 90% of the mosquitoes were recaptured within 6 km from the release point (Cho *et al.*, 2002). Therefore, it is reasonable for mosquitoes to fly across the DMZ because the DMZ is about 2 km wide.

The 2 mathematical models in North Korea and South Korea could be constructed with 4 epidemiological parameters. It was difficult to decide the rate of prevalence in North Korea in the beginning of the 1990's, because there was little and uncertain information about the cases of malaria in North Korea. In the parasite survey implemented in South Korea in 1960, the year after the Korean War, 212 blood smears were positive among 18,697 collected blood smears (the average parasite rate being 1.1%), and the highest prevalence detected was 5% (Paik *et al.*, 1987). Therefore, we presume the prevalence in North Korea to be 5%. The transmission model for South Korea is modified from that for North Korea due to the different public health circumstances. We succeeded in evoking the re-emergence of *P. vivax* in Paju-shi and Yonchon-gun near the DMZ in South Korea, through 2 cooperative models in which the South Korean model was unidirectionally affected by the North Korean model.

In South Korea, *P. vivax* malaria has re-emerged since

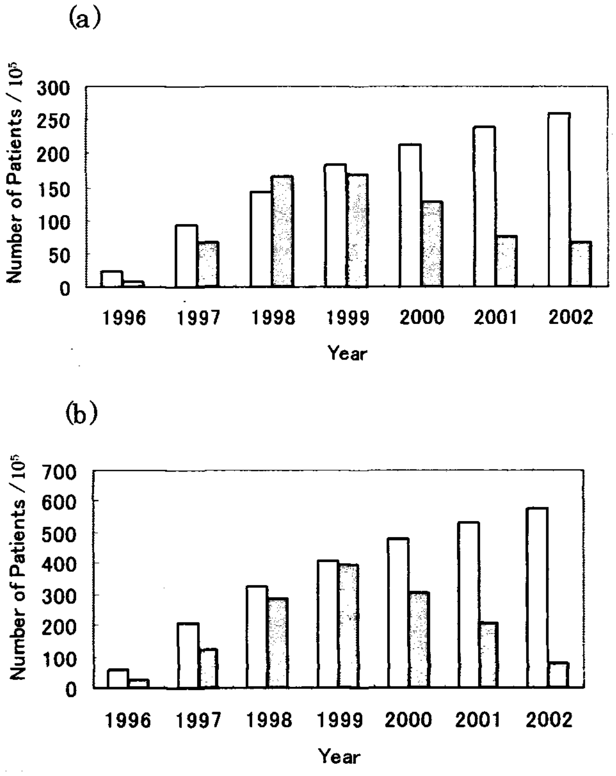

Fig. 9 The comparison of the prevalence between actual surveillance and the results of simulation in Paju-shi (a), Yonchon-gun (b). The time-courses of malaria cases per 100,000 obtained from surveillance and from the results of simulation are shown as gray bars and white bars, respectively.

1993 and the prevalence increased yearly until 2000. The incidence of *P. vivax* was highest in summer (June - September) in spite of the 2 characteristics of North Korean strain of *P. vivax* described in the text, that is, the high relapse rate and the wide distribution of relapse terms (Kim, 2001; Park *et al.*, 2003; Oh *et al.*, 2001; Bray *et al.*, 1982). The incidence in Korea had 2 peaks (April – May, July - August) in the simulation using our model. The simulation results revealed the mechanism by which the incidence of *P. vivax* was highest in summer, assuming the above 2 characteristics of *P. vivax*. The seasonal pattern of incidence would be affected by the incubation period. The first peak (April - May) and the second peak (July - August) would be related to the long incubation period and the short incubation period, respectively. If the average of the long incubation period would be prolonged from 288 days to 1 year, the incidence of *P. vivax* would be concentrated in summer and have a peak in August. However, the reason for the divergence of the peaks of the incidence of *P. vivax* in South Korea between the surveillance and the simulation is unknown.

The long incubation period (6 – 16 months) would be applied to the log-normal distribution, where the χ^2-value 13.37 was accepted as statistically significant (15.51, *d. f.* = 8, $P < 0.05$) by the χ^2-fitness test. The log-normal distribution was selected because of the long incubation period. The skewness (G) and the kurtosis (H) of the logarithmic transformation of 50 surveillance data are estimated as G=0.257 (0.533, P<0.05) and H=0.127 (0.99, P<0.05), respectively, which lead to fitting the distribution of the long incubation period to the log-normal distribution.

The number of civilian malaria cases increased until 1999 in Paju-shi and Yonchon-gun, where the malaria cases in these 2 regions accounted for 60-70% of the total malaria cases in Korea from 1993 to 1997. We succeeded in modeling the re-emergence of *P. vivax*. The time-courses of the true prevalence in Paju-shi and Yonchon-gun diverged from the time-course predicted by the model simulation after 2000, because the model took no account of any malaria control measures. The rate of contact with infected mosquitoes may be reduced by public health education and the use of window screens, while chemoprophylaxis prevents malaria infection. Early diagnosis and treatment may reduce the prevalence. In order to accurately predict the prevalence of *P. vivax* in South Korea, it would be necessary to incorporate the effect of malaria control measures in the South Korean model.

In the coming years, *Anopheles* mosquito vectors capable of malaria transmission may invade countries that are free from malaria because of the effect of global warming, and may cause the re-emergence of malaria. Our method will be useful for prediction of the prevalence in countries in which malaria re-emerges.

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