



# Transmission dynamics of vivax malaria in the republic of Korea: Effectiveness of anti-malarial mass chemoprophylaxis



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## HIGHLIGHTS

- Vivax malaria with short and long incubation period caused an epidemic in Korea.
- Effectiveness of chemoprophylaxis was assessed using the reproduction number.
- Renewal process was demonstrated to be useful for analyzing illness onset data.
- Best-fit model indicated an abrupt decline in secondary transmission in 1998.

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## ABSTRACT

**Background:** Vivax malaria with two distinct (short- and long-term) incubation periods has been prevalent in the Republic of Korea since its re-emergence in 1993. As part of countermeasures, mass chemoprophylaxis has been conducted since 1997 among military personnel, a high risk group. To assess the population effectiveness of chemoprophylaxis, the time-dependent reproduction number was estimated in the present study.

**Methods:** A renewal process has been employed, estimating the yearly effective reproduction number ( $R_y$ ) from 1993 to 2012 using a maximum likelihood estimation method. Akaike Information Criterion (AIC) was computed to identify the best-fit model with a time-dependent trend that coincides with the timing of mass chemoprophylaxis.

**Results:** The estimates of  $R_y$  revealed an overall declining trend from 1997 to 2012. Despite small fluctuations in 2005 and 2009,  $R_y$  was brought to be close to unity since 2000. An extrapolated model of the time-dependent reproduction number with the smallest AIC indicated that there was an abrupt decline in secondary transmission from 1997 to 1998.

**Conclusion:** The epidemic of vivax malaria in the Republic of Korea has been on the whole brought under control in the last decades. Mass chemoprophylaxis assisted the decline in secondary transmissions from its second year, which presumed to have reflected the effect of long incubation period and expansion of the coverage.

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## 1. Introduction

Vivax malaria is a protozoan disease caused by *Plasmodium vivax* and transmitted between human hosts through anopheline mosquitoes, e.g. *Anopheles sinensis* in the case of the Republic of Korea. Once sporozoites are introduced from the infectious vector to humans, they reach the liver hepatocyte via the blood stream and are known not

only to differentiate into schizonts and produce merozoites but also to develop into hypnozoites (latent forms) which can remain in the liver cells and induce a relapse at a later stage (Bray and Garnham, 1982; Cogswell, 1992; Krotoski, 1989). From a clinical point of view, vivax malaria has been considered to be a relatively benign form of malaria compared to those caused by *Plasmodium falciparum*. However, recent studies revealed that the burden of vivax malaria has been perhaps overlooked in the past (Galinski and John, 2008; Price et al., 2007; Baird, 2007).

Geographically, vivax malaria is prevalent in a wide geographic range of countries across the world, especially in South and Southeast Asia (World Health Organization, 2013). The endemic

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area extends to temperate countries, including the Republic of Korea (ROK; South Korea). Indigenous vivax malaria in the ROK had been once eliminated and the last reported case had been seen in 1984 (Chai et al., 1994). Nevertheless, the cases caused by local transmission have been continuously observed in the recent 20 years since the reemergence in 1993 (Chai et al., 1994; Korea Centers for Disease Control and Prevention, 2013; Park et al., 2009; Cho et al., 1994; Feighner et al., 1998; Chai, 1999). As the epidemic was initially localized to military personnel who had experienced duty nearby demilitarized zone (DMZ), the vivax epidemic in Korea is considered to have been the result from a geographic extension of the epidemic of the same disease in the Democratic People's Republic of Korea (DPRK; North Korea) (Chai, 1999; Han IIRee, 1998; Weon-Gyu Kho et al., 1999; Park et al., 2003). Ecologically speaking, the Korean strain of *P. vivax* has a fascinating feature. That is, the Korean strain has a short- (mean 26.6 days) and long-term (mean 48.2 weeks) incubation periods (Nishiura et al., 2007), so that the epidemic could last over years in the temperate zone where there is no transmission in winter season due to wintering mosquito vector (Chow, 1970).

As part of countermeasures against vivax malaria, anti-malarial chemoprophylaxis with hydroxychloroquine and primaquine has been conducted among military personnel since 1997 in the ROK. Hydroxychloroquine targets the blood-stage parasites, while primaquine targets hypnozoites in the liver. Since the dormant stage is not affected by hydroxychloroquine, primaquine is deemed essential as part of the prophylaxis against vivax malaria. A total of 15,981 soldiers underwent chemoprophylaxis in the first year, and subsequently the number of subjects increased year by year reaching 90,000 in 2000. The effectiveness of chemoprophylaxis on preventing epidemic has been assessed in case-based studies in the past (Yeom et al., 2005; Roy et al., 2013). However, the incidence of vivax malaria in a year in Korea is strongly dependent on the incidence in the previous year due to the long-term incubation period, and thus, the full clarification of the population effectiveness of chemoprophylaxis requires us to explicitly account for the transmission dynamics.

Mathematical modeling technique is useful for approximately capturing the underlying transmission dynamics and detecting any temporal changes. Recently several modeling studies took place, explicitly accounting for dormant stages of *P. vivax* in the model structure (White et al., 2014; Kim et al., 2006). In the present study, we estimated the time-dependent (effective) reproduction numbers from 1993 to 2012, using a renewal equation model and assessing the temporal trend of the transmission of vivax malaria in the ROK. In addition, we evaluated the population effectiveness of mass chemoprophylaxis, using the reproduction number and testing whether there was a detectable change in the trend of secondary transmission.

## 2. Materials and methods

### 2.1. Epidemiological data

Malaria is classified as one of the group III communicable diseases in the ROK, so all diagnosed cases are reported to the Division of Infectious Disease Surveillance (DIDS), Korea Centers for Disease Control and Prevention (KCDC). We used the number of notified vivax malaria cases by month from 1993 to 2013 (Fig. 1) (Korea Centers for Disease Control and Prevention, 2013). The cases were confirmed by parasitemia in peripheral blood smears (Park et al., 2003). In addition to the temporal frequency of illness onset, the distribution of the incubation period, time from infection to the first exhibition of symptoms expressed as a mixture of short- (proportion 63.1%) and long-term (36.9%), was extracted from the literature (Fig. 2) (Nishiura et al., 2007) and was assumed as known in the subsequent analyses.

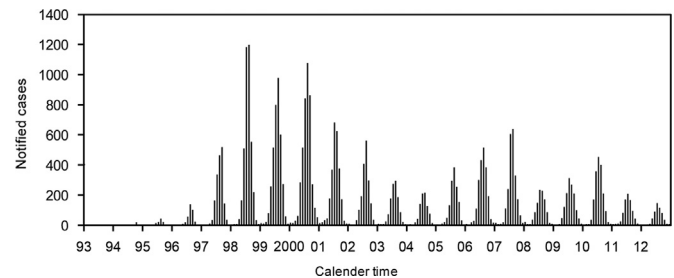


Fig. 1. Notified cases of vivax malaria in the Republic of Korea by month from 1993 to 2013.

Data source: Ref. Korea Centers for Disease Control and Prevention (2013).

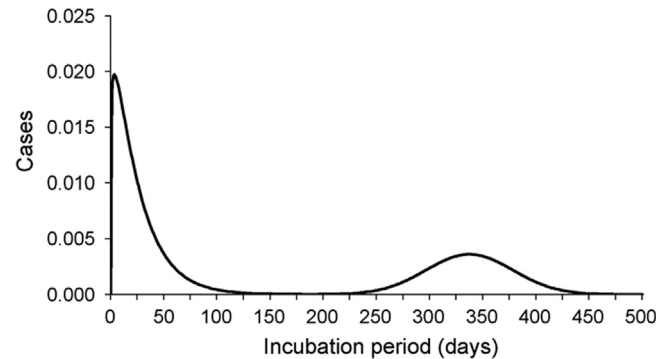


Fig. 2. Predicted distribution of the incubation period of *Plasmodium vivax* malaria in the Republic of Korea.

Citation: Ref. Nishiura et al. (2007).

In the ROK, symptomatic malaria is assumed to be properly treated, and thus, multiple relapses after the diagnosis can be left out from our consideration. Moreover, absence of transmission from November to April due to wintering season of *Anopheles sinensis* was adapted from the literature (Chow, 1970).

### 2.2. Renewal process model

This study is composed of two different parts of analysis. First, the time-dependent (effective) reproduction number, i.e., an indicator of the average number of secondary human cases caused by a single human case, was estimated from 1993 to 2012. Second, we examined whether there was a detectable change in the trend of transmission in and after 1997, when mass chemoprophylaxis was conducted among military personnel.

When formulating the malaria transmission model in the ROK, an extremely low entomologic inoculation rate (EIR) helped us to impose a key assumption: re-infection was assumed as negligible so that immunity in the population does not affect the reproduction number. Moreover, due to geographically extended transmission within the ROK, we assumed that there was no impact of immigration of infected mosquitoes from the DPRK. Since the epidemiological data are reported monthly, we use a discrete version of renewal process. Let  $i_t$  be the number of newly infected individuals in month  $t$ . The renewal process is described by

$$i_t = \sum_{\tau=1}^{t-1} A_{t,\tau} i_{t-\tau}, \quad (1)$$

where  $A_{t,\tau}$  represents the rate of secondary transmission per single primary case in month  $t$  and infection-age (i.e. the time since infection in the primary case)  $\tau$ . We assume that  $A$  is separable into the product of time-dependent and infection-age-dependent components, (i.e.,

$A_{t,\tau} = U_t g_\tau$ ), so that the equation can be rewritten as

$$i_t = U_t \sum_{\tau=1}^{t-1} i_{t-\tau} g_\tau, \quad (2)$$

where  $U_t$  is the average number of secondary transmissions per primary case in month  $t$  and  $g_\tau$  represents the probability mass function of generation time (per month), i.e., the relative frequency of secondary transmissions as a function of infection-age  $\tau$  in the primary case.  $U_t$  is considered to reflect both intrinsic and extrinsic factors that are involved in the transmission dynamics, e.g. vector density and the effect of chemoprophylaxis, and  $\sum_{\tau=1}^{t-1} i_{t-\tau} g_\tau$  on the right-hand side represents the effective number of human primary cases who could cause secondary transmission.

Since the data of  $i_t$  rests on infection event and cannot be directly observed, the Eq. (2) is rearranged. Let  $j_t$  be the number of incidence of clinical malaria (i.e. the incidence of illness onset) in month  $t$ , we have

$$j_t = \sum_{\tau=1}^{t-1} U_{t-\tau+1} j_{t-\tau} g_\tau. \quad (3)$$

See Appendix A for the derivation of the Eq. (3). The rearranged model (3) allows us to account for seasonality by decomposing  $U_t$  as

$$U_t = u_y w_m, \quad (4)$$

where the monthly time  $t$  is replaced by calendar month by  $t = 12y + m$  where  $y$  and  $m$  are natural numbers that represent calendar year and month, respectively. Decomposing  $U$  into the product of  $u$  and  $w$ , the yearly component of the reproduction number is extracted to assess the long-term trend in malaria transmission. To allow year-by-year assessment, we assume that the other component, i.e., seasonal forcing  $w_m$ , that represents the relative frequency of monthly variation in the transmissibility within a year, remains unchanged from 1993 to 2013. It should be noted that  $w_m$  is normalized so that  $u_y$  represents the yearly arithmetic mean of  $U_t$ . Using these parameters, the estimate of the yearly effective reproduction number  $R_y$  is obtained. We defined the  $R_y$  as the dominant eigenvalue of the following compartment

matrix which satisfies

$$\begin{bmatrix} \mathbf{i}_y \\ \mathbf{i}_{y-1} \end{bmatrix} = \begin{bmatrix} K_y & L_y \\ E & O \end{bmatrix} \begin{bmatrix} \mathbf{i}_{y-1} \\ \mathbf{i}_{y-2} \end{bmatrix}, \quad (5)$$

where  $\mathbf{i}_y$  is a 12-dimensional vector whose  $m$ -th component represents the number of secondary transmissions caused in month  $m$  in year  $y$  (See Appendix B for further details of the definition and computation of  $R_y$ ).

Letting  $\mathbf{u}$  and  $\mathbf{w}$  be vectors  $\{u_y\}$  and  $\{w_m\}$ , the Poisson-likelihood function to estimate parameters that govern these vectors,  $L$ , is

$$L(\mathbf{u}, \mathbf{w}; \mathbf{Z}) = \prod_t \frac{(E(j_t; Z_{t-1}))^{j_t} \exp(-E(j_t; Z_{t-1}))}{j_t!}, \quad (6)$$

where  $Z_t$  represents the observed data in and before month  $t$ .

### 2.3. Quantitative settings

In the present study, the generation time distribution  $g_\tau$  represents the time between two successive infections of human cases (i.e. the time from infection in human primary case to infection in secondary case).  $g_\tau$  is assumed to be modeled as mirroring the incubation period distribution  $f_\tau$  lagged by 1 month to the right (i.e.,  $g_0 = 0$  and  $g_\tau = f_{\tau-1}$  (for  $\tau \geq 1$ )), because the cases are infectious during the erythrocytic stage that coincides with symptomatic period (i.e. the incubation period is equated to the latent period of human primary case), and because we assume that the time from parasitemia in the primary case to infection in the secondary case is a constant (and is equal to 1 month). Fig. 3 schematically illustrates these assumptions in relation to the natural history. We believe that these assumptions are reasonable, because it takes about 20 days for the parasites to grow in the gut of anopheline mosquitoes (i.e., extrinsic incubation period (EIP)) and only after the maturation of sporozoites the infection in human secondary case can take place. The EIP was calculated using the formula given in elsewhere (Detinova, 1962) with the average temperature during six months of malaria season (from May to October) in the ROK (National climate data, 1981–2010). The incubation period distribution  $f(\tau)$  is calculated as a mixture of short- and long-term incubation periods expressed by gamma distribution and normal distribution, respectively (Nishiura et al., 2007). Using  $p$  as the weight of the short-term incubation period (0.63; 95% CI:

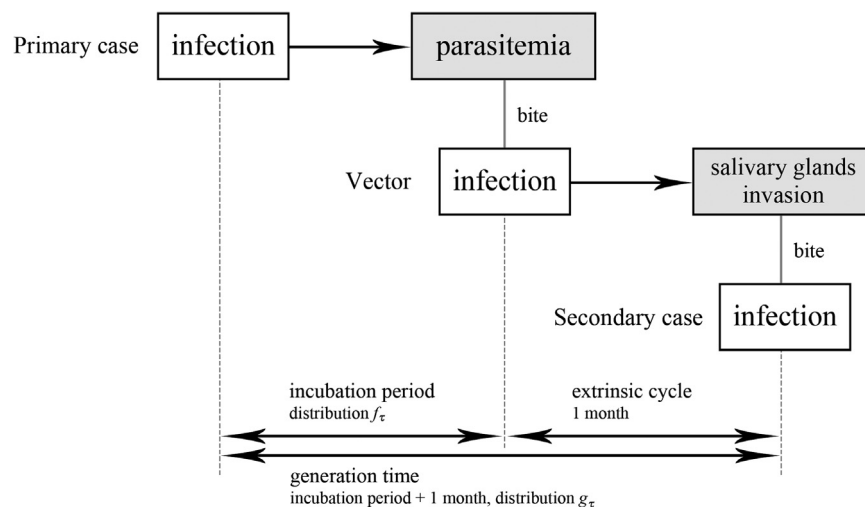


Fig. 3. Natural history of vivax malaria transmission.

Incubation period refers to the time from infection in human primary case to the onset of symptoms (parasitemia), which follows the distribution  $f_\tau$ . The time from parasitemia in human primary case to infection in human secondary case, denoted as “extrinsic cycle”, is assumed to be a constant (i.e. 1 month). Generation time  $g_\tau$ , the time interval between successive infections of cases, is therefore characterized as  $f_\tau$  lagged by 1 month to the right.

0.57–0.69),  $f(\tau)$  was computed as

$$f(\tau) = ps(\tau) + (1-p)l(\tau), \quad (7)$$

where  $s(\tau)$  and  $l(\tau)$  represent the probability density function of the short- and long- incubation periods, respectively. Since our transmission model has handled discrete-time events, the distribution  $f(\tau)$  was discretized by taking the monthly difference of the cumulative distribution function.

Seasonal forcing  $w_m$  was manually set at zero during the wintering season (when  $m=1, 2, 3, 4, 11$  and  $12$ ). The maximum likelihood estimates of  $u_y$  and  $w_m$  (for the remaining months) were obtained by minimizing the negative logarithm of the likelihood function,  $L(\mathbf{R}, \boldsymbol{\omega}; \mathbf{Z}, t)$ . The yearly effective reproduction number was subsequently calculated. The 95% confidence intervals (CI) of  $w_m$  were derived from the profile likelihood. The 95% CI of  $R_y$  was obtained by employing the parametric bootstrap method (Efron and Tibshirani, 1993), because  $R_y$  is not given in a closed-form. Monthly incidence has been generated by Poisson distribution whose mean is equal to the observed counts of cases for each loop (1000 repeats). A statistical package, R (<http://www.r-project.org/>) was used to carry out the estimation.

#### 2.4. Temporal trend of transmission

In addition to the abovementioned estimation procedure, we have fitted an extrapolated parametric function to  $u_y$ , the yearly component of the reproduction numbers, to statistically detect the trend of secondary transmission. More specifically, we employed a negative exponential curve mixed with an abrupt decline in the secondary transmission in order to detect the change in secondary transmissions due mainly to the effectiveness of mass chemoprophylaxis among military personnel.  $u_y$  was parametrically modeled as

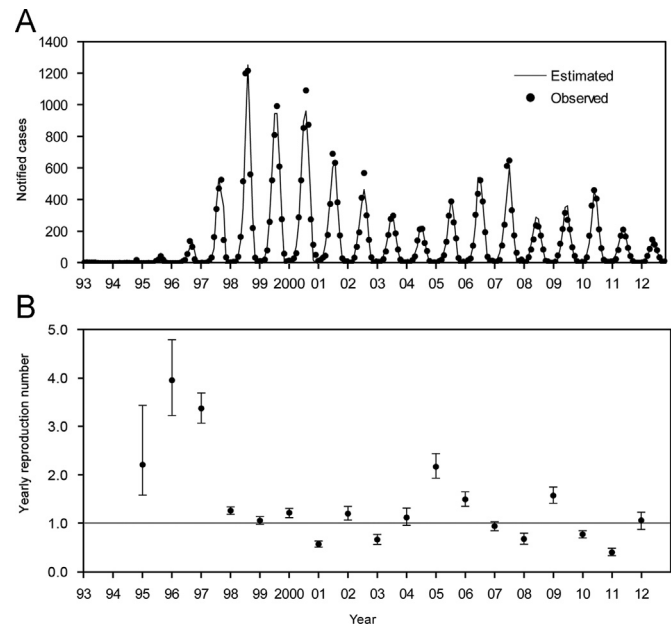
$$u_y = \begin{cases} u_0 e^{-ay} + b & (\text{for } y < y_d) \\ c(u_0 e^{-ay} + b) & (\text{for } y \geq y_d) \end{cases} \quad (8)$$

The natural trend in  $u_y$  is assumed to have been captured by the negative exponential term, while  $u_y$  is lowered by  $c$  (which should ideally satisfy  $c < 1$ ) after the year of prophylaxis  $y_d$  (which is supposed to be 1997 or later corresponding to the year in which the population impact of chemoprophylaxis is considered to be observed). Using the parametric model, the negative log likelihood with the number of parameters (including those for seasonal forcing) is obtained, permitting us to calculate Akaike Information Criterion (AIC) for each model. The AIC was compared among different models with an assumed change point  $y_d$  in 1997, 1998, 1999 or 2000. AIC of another model without such change was also computed and compared against others. A sensitivity analysis of model fit with  $y_d$  yielding the smallest AIC in the baseline was carried out to account for uncertainty in  $p$ , the weight of short-term incubation period when modeling the bimodal incubation period distribution.  $p$  was varied from its lower to upper bound of the 95% confidence interval (CI), i.e., 56.8% and 69.4%, and any change in an abrupt decline in  $u_y$  was sought.

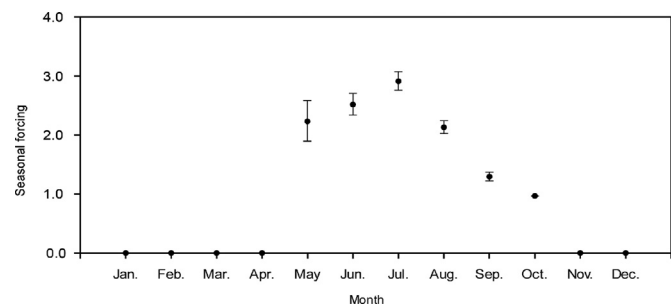
### 3. Results

#### 3.1. Yearly reproduction number

Fig. 4A compares observed and predicted temporal distribution of vivax malaria cases. From visual inspection, the model has captured both seasonal and long-term patterns of monthly incidence in the ROK. Fig. 4B shows the estimated yearly effective reproduction number of vivax malaria. Overall, the estimates of  $R_y$  revealed a gradual decline with a few small temporary increases



**Fig. 4.** Temporal distribution of vivax malaria cases and the estimated yearly reproduction numbers of vivax malaria in the Republic of Korea, from 1993 to 2012. (A) Comparison of the predicted and observed numbers of vivax malaria cases by month. The number of cases from 1996 to 2012 is predicted. (B) Estimated yearly effective reproduction numbers of vivax malaria. The maximum likelihood estimate (dots) and the 95% confidence intervals (whisker). The horizontal gray line represents the value of  $R_y=1$  below which yearly incidence is considered to be declining.



**Fig. 5.** Seasonal forcing of vivax malaria in the Republic of Korea. The maximum likelihood estimate (dots) and the 95% confidence intervals (whisker) are shown. The estimates are normalized and thus the yearly average is equal to 1. Vivax malaria in the Republic of Korea is transmitted by *Anopheles sinensis*, and the seasonal forcing during the winter season (from October to April) is manually set at zero.

around 2005 and 2009. The estimates were mostly below or close to unity, supporting an overall decrease in the long-term.

Fig. 5 shows the estimated seasonal forcing expressed as the relative frequency of secondary transmission in each month. The estimates revealed a clear seasonal pattern in the transmission of malaria in the temperate zone.

#### 3.2. Trend and sensitive analysis

Table 1 compares the model fit results with variable change point  $y_d$  varied from 1997 to 2000. AIC was smallest for  $y_d=1998$ . For this model, the factor of abrupt decline in secondary transmission,  $c$ , was estimated at 0.659. The second smallest AIC was seen in the model with  $y_d=1997$ . Fig. 6 shows the yearly reproduction



**Table 1**  
Model fit with variable change point  $y_d$  in the secondary transmission of vivax malaria.

Change point ( $y_d$ )	% Short term incubation period ( $p$ )	Number of parameters	Negative log-likelihood	AIC <sup>†</sup>	ΔAIC
None	63.1	8	2692.53	5401.06	97.78
1997	63.1	9	2667.67	5353.34	50.06
1998	63.1	9	2642.64	5303.28	0
1999	63.1	9	2684.67	5387.34	84.06
2000	63.1	9	2692.51	5403.01	99.73

<sup>†</sup> AIC; Akaike Information Criterion.

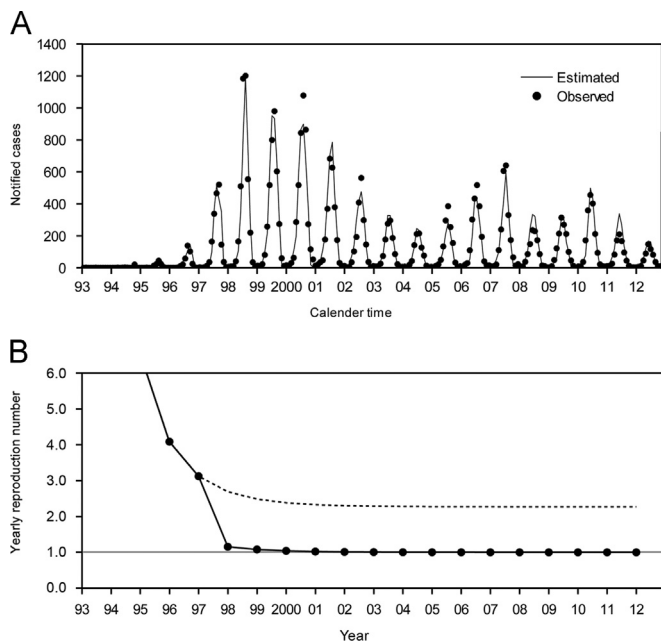
ΔAIC; difference of AIC value from that obtained with change point in 1998.

**Table 2**  
Sensitivity analysis of  $y_d$  (1998) to variable weight of the short-term incubation period  $p$ .

Change point ( $y_d$ )	Weight of the short-term incubation period ( $p$ )	Number of parameters	Negative log-likelihood	AIC	ΔAIC
No	63.1	8	2692.53	5401.06	97.78
Yes	63.1	9	2642.64	5303.28	0
No	69.4	8	2687.23	5390.46	63.98
Yes	69.4	9	2654.24	5326.48	0
No	56.8	8	2739.85	5495.70	148.17
Yes	56.8	9	2664.77	5347.53	0

<sup>†</sup> AIC; Akaike Information Criterion.

ΔAIC; difference of AIC value from that obtained with change point.



**Fig. 6.** Predicted temporal distribution of vivax malaria cases and estimated yearly reproduction numbers of vivax malaria in the Republic of Korea (ROK) from 1993 to 2012. (A) Predicted and observed numbers of vivax malaria cases in the Republic of Korea from 1993 to 2012 (note that the model employed is exponential-fitted and different from Fig. 4 (A)). The number of cases from 1999 to 2012 is predicted by using the yearly average of the reproduction number fitted to an exponential curve mixed with an abrupt decline in the estimate from 1997, as shown in (B). (B) The yearly reproduction numbers obtained by fitting the yearly component of the reproduction number,  $u_y$ , to an exponential curve mixed with an abrupt decline in the estimate from 1997, which we assume reflects the effect of mass chemoprophylaxis among military personnel in the ROK. The dotted line shows the reproduction numbers extrapolated from those before the decline.

number with the yearly component  $u_y$  parametrically modeled as

$$u_y = \begin{cases} 1.84\exp(-0.65y) + 0.88 & (y \leq 1997) \\ 1.21\exp(-0.65y) + 0.58 & (y \geq 1998) \end{cases} \quad (9)$$

As has been indicated by the estimate of  $c$ , the model reflects an abrupt decline in  $u_y$  which has been reduced by 34% in 1998 and later.

Table 2 shows the result of sensitivity analysis. Setting  $y_d$  at 1998, AIC of each model was calculated with variable  $p$  (weight of the short-incubation period). For any of the three  $p$ , AIC of models with change point in 1998 appeared to be smaller than others, indicating that the abrupt decline in  $u_y$  is robust to variation in the weight of bimodal incubation period.

#### 4. Discussion

Transmission dynamics of vivax malaria in the ROK has been modeled by employing the renewal process model, estimating the yearly effective reproduction number ( $R_y$ ) from 1993 to 2012 and assessing the trend in secondary transmission in relation to the timing of introducing mass chemoprophylaxis. The estimates of  $R_y$  revealed an overall declining trend from 1993 to 2012 with a few temporary increases around 2005 and 2009. Moreover, we assessed the possible population impact of mass chemoprophylaxis on the trend of secondary transmission by parametrically modeling the yearly component of the reproduction number and comparing AIC among models with different timings of abrupt time-dependent change in transmission. The best model appeared to be the model with abrupt decline in secondary transmission by 34% from 1998, coinciding with the expansion of chemoprophylaxis. The effectiveness of vector control interventions has been assessed using a periodic model in the previous study (Chitnis et al., 2012), but to our knowledge, our study is the first to have explicitly assessed the population impact of mass chemoprophylaxis against vivax malaria in the temperate country.

Estimates of  $R_y$  has indicated that the epidemic of vivax malaria in the ROK since 1993 has been, on the whole, brought under control, as  $R_y$  has been below or slightly above unity since 2000. Of technical note,  $R_y$  has been explicitly defined and derived using Floquet analysis as shown in Appendix B. Similar methodology has been employed elsewhere (Bacaër and Dads el H, 2012; Bacaër, 2009; Bacaër and Guernaoui, 2006). In contrast with such published studies that have been focused on the basic reproduction number, a constant quantity over time, we believe that the present study is the first to have extended such concept to the time-dependent (effective) reproduction number in the presence of seasonality. Our proposed effective reproduction number reflects yearly change in transmission dynamics in the most appropriate theoretical manner. Of course, our model has imposed rough assumptions, including the ignorance of re-infection and transmission from the DPRK or the assumption of homogeneous transmission between vectors and humans (which can lead to underestimation of the reproduction number (Smith et al., 2007)). These points remain to be resolved in future studies. Despite these essential unsupported assumptions, it should be emphasized that the proposed approach to assessing the longitudinal temporal dynamics with the prolonged incubation period has been very unique and most appropriately realized by employing renewal equation that can rest on illness onset data.

In addition, the best model informed by AIC indicated that the mass chemoprophylaxis against vivax malaria in the ROK has most likely induced the abrupt decline in the yearly component of secondary transmission. The decline in the transmission is likely to have been detectable since 1998, because the population impact of the chemoprophylaxis since 1997 was not totally visible in 1997 due to

the limited coverage and the existence of the long-term incubation period. The chemoprophylaxis has been subsequently expanded, and thus, the effectiveness has become detectable and grown greater in the following years (which we believe to have been captured by the exponentially decreasing trend in secondary transmissions). Although the population effectiveness of chemoprophylaxis against vivax malaria in the ROK is very difficult to be assessed using case data alone (due mainly to the presence of long-term incubation period), our renewal process model actually rested on the dynamics of illness onset (as demonstrated in [Appendix A](#)) and this should be regarded as a great technical advancement in assessing the temporal dynamics of infection with the exact timing of intervention using observable case data.

Several limitations other than the absence of re-infection and ignorance of DPRK should be noted. First, spatial profile of the dataset has not been taken into account due to data limitation. We plan to incorporate this component and analyze the spatiotemporal dynamics in the future. Second, the case data that we analyzed rested on the notification report and such data must face the issue of ascertainment bias (that stems from underdiagnosis and underreporting). However, as long as those coverage approximately remain constant over time, the renewal equation still permits us to obtain valid maximum likelihood estimates of the reproduction number. Third, we assumed that the proportion and length of short- and long-term incubation period are known. A recent study has raised a concern over the possible extension of the incubation period ([Park, 2011](#)). Moreover, it is pointed out that the risk of relapse might be triggered by systemic illnesses including malaria itself ([White, 2011](#)). In light of these biological features, it should be emphasized that our model is perhaps too simplistic. Nevertheless, the result of the sensitivity analysis indicated that our conclusion about the existence of change point is robust to variation in the proportion  $p$ .

Despite the limitations mentioned above, we believe that our study demonstrates that the modeling approach to malaria using renewal process can potentially be a useful tool to assess the temporal dynamics, and the similar framework can be extended for other vector borne diseases. Such assessment can be used for evaluating effectiveness or necessity of control measures. In this sense, we believe the present study gives an important step to boosting similar frameworks for assessing epidemics dynamics.

## Conflict of interests

The authors have declared that no conflict of interest exists.

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## Appendix A. Renewal equation using case data

Using the renewal equation model, the number of newly infected individuals at calendar time  $t$ ,  $i_t$ , satisfies

$$i_t = U_t \sum_{s=1}^{t-1} i_{t-s} g_s, \quad (A1)$$

Assuming that the incubation period is independently and identically distributed (i.i.d.), the number of new illness onsets at calendar time  $t$ ,  $j_t$ , is the convolution of the incubation period and the incidence

of infection  $i_t$ .

$$j_t = \sum_{\tau=0}^{t-1} i_{t-\tau} f_{\tau} \quad (A2)$$

In our study, we have imposed two assumptions that enabled us to assume that the probability density function of the incubation period  $f_{\tau}$  is associated with the generation time distribution, and can even be replaced by  $g_{\tau+1}$ , as described in the main text. We have

$$j_t = \sum_{\tau=0}^{t-1} i_{t-\tau} g_{\tau+1}. \quad (A3)$$

Substituting  $i_{t-\tau}$  in the right-hand side of (A3) with that in (A1), we get

$$j_t = \sum_{\tau=0}^{t-1} g_{\tau+1} U_{t-\tau} \sum_{s=1}^{t-\tau-1} i_{t-\tau-s} g_s. \quad (A4)$$

Eq. (A4) is identical to

$$j_t = \sum_{\tau=0}^{t-1} g_{\tau+1} U_{t-\tau} \sum_{s=0}^{t-\tau-2} i_{t-\tau-s-1} g_{s+1}. \quad (A5)$$

Substitute the inner summation of (A5) with the left-hand side of (A3), we obtain

$$j_t = \sum_{\tau=1}^t U_{t-\tau} j_{t-\tau-1} g_{\tau+1} = \sum_{\tau=1}^{t-1} U_{t-\tau+1} j_{t-\tau} g_{\tau}, \quad (A6)$$

because  $g_0=0$ . Eq. (A6) is identical to (3) in the main text and can be regarded as the renewal process model that can rest on illness onset data.

## Appendix B. Definition and computation of the yearly reproduction number

Let  $\mathbf{i}_y$  be a twelve-dimensional vector of monthly incidence in year  $y$ , which corresponds to the discrete renewal equation by months, i.e., using the renewal equation

$$i_t = U_t \sum_{\tau} i_{t-\tau} g_{\tau}, \quad (A7)$$

where  $i_t$  is grouped every 12 months as a vector. The  $m$ -th component of  $\mathbf{i}_y$  represents the number of secondary transmissions caused in month  $m$  in year  $y$ . When  $t$  is decomposed to be  $12y+m$  and  $U_t$  as  $u_y w_m$ , and by truncating  $g_{\tau}=0$  for  $\tau > 24$ ,  $\mathbf{i}_y$  is determined by  $\mathbf{i}_{y-1}$  and  $\mathbf{i}_{y-2}$  only. To define the yearly reproduction number  $R_y$  of malaria, the 12-by-12 matrices  $K_y$  and  $L_y$  are considered

$$\mathbf{i}_y = K_y \mathbf{i}_{y-1} + L_y \mathbf{i}_{y-2}, \quad (A8)$$

where the matrices  $K_y$  and  $L_y$  with  $(i, j)$ -elements  $k_{ij}^y$  and  $l_{ij}^y$  are respectively

$$k_{ij}^y = \begin{cases} u_{y,i} g_{12+i-j} & (\text{for } i=1) \\ u_{y,i} \left( g_{12+i-j} + \sum_{s=1}^{i-1} g_{i-s} k_{sj}^n \right) & (\text{for } i \geq 2) \end{cases} \quad (A9)$$

$$l_{ij}^y = \begin{cases} u_{y,i} g_{24+i-j} & (\text{for } i=1) \\ u_{y,i} \left( g_{12+i-j} + \sum_{s=1}^{i-1} g_{i-s} l_{sj}^n \right) & (\text{for } i \geq 2) \end{cases} \quad (A10)$$

(A7) can be rewritten as

$$l_i^y = \begin{cases} u_{y,i} \left( \sum_{j=1}^{12} l_i^{y-1} g_{12+i-j} + \sum_{j=1}^{12} l_i^{y-2} g_{24+i-j} \right) & (\text{for } i = 1) \\ u_{y,i} \left( \sum_{j=1}^i l_i^y g_{i-j} + \sum_{j=1}^{12} l_i^{y-1} g_{12+i-j} + \sum_{j=1}^{12} l_i^{y-2} g_{24+i-j} \right) & (\text{for } i \geq 2) \end{cases} \quad (\text{A11})$$

where  $l_i^y$  represents the  $i$ th component of the vector  $\mathbf{l}_y$ .

Using  $K_y$  and  $L_y$ , a recurrence relation of concatenated vector that is made of  $\mathbf{l}_y$  and  $\mathbf{l}_{y-1}$  is obtained, i.e.,

$$\begin{bmatrix} \mathbf{l}_y \\ \mathbf{l}_{y-1} \end{bmatrix} = \begin{bmatrix} K_y & L_y \\ E & O \end{bmatrix} \begin{bmatrix} \mathbf{l}_{y-1} \\ \mathbf{l}_{y-2} \end{bmatrix} \quad (\text{A12})$$

where  $E$  is an identity matrix and  $O$  is a zero matrix of size 12. The yearly effective reproduction number  $R_y$  is defined as the dominant eigenvalue of the 24-by-24 block matrix shown above (note that  $R_y$  is derived from the reproduction numbers only in year  $y$ ).

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