1 **Title**
2 Transmission dynamics of vivax malaria in the Republic of Korea: Effectiveness of
3 anti-malarial mass chemoprophylaxis
4
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14 Transmission dynamics of vivax malaria
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1 **Abstract**

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

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

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

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

21

22 **Keywords:** malaria, epidemiology, *Plasmodium vivax*, mathematical model,
23 effectiveness, prophylaxis

1 **Introduction**

2 Vivax malaria is a protozoan disease caused by *Plasmodium vivax* and transmitted
3 between human hosts through anopheline mosquitoes, e.g. *Anopheles sinensis* in the
4 case of the Republic of Korea. Once sporozoites are introduced from the infectious
5 vector to humans, they reach the liver hepatocyte via the blood stream and are known
6 not only to differentiate into schizonts and produce merozoites but also to develop into
7 hypnozoites (latent forms) which can remain in the liver cells and induce a relapse at a
8 later stage[1-3]. From a clinical point of view, vivax malaria has been considered to be a
9 relatively benign form of malaria compared to those caused by *Plasmodium falciparum*.
10 However, recent studies revealed that the burden of vivax malaria has been perhaps
11 overlooked in the past[4-6].

12 Geographically, vivax malaria is prevalent in a wide geographic range of countries
13 across the world, especially in South and Southeast Asia[7].The endemic area extends to
14 temperate countries, including the Republic of Korea (ROK; South Korea). Indigenous
15 vivax malaria in the ROK had been once eliminated and the last reported case had been
16 seen in 1984[8]. Nevertheless, the cases caused by local transmission have been
17 continuously observed in the recent 20 years since the reemergence in 1993[8-13]. As
18 the epidemic was initially localized to military personnel who had experienced duty

1 nearby demilitarized zone (DMZ), the vivax epidemic in Korea is considered to have
2 been the result from a geographic extension of the epidemic of the same disease in the
3 Democratic People's Republic of Korea (DPRK; North Korea)[13-16]. Ecologically
4 speaking, the Korean strain of *P. vivax* has a fascinating feature. That is, the Korean
5 strain has a short- (mean 26.6days) and long-term (mean 48.2 weeks) incubation periods
6 [17], so that the epidemic could last over years in the temperate zone where there is no
7 transmission in winter season due to wintering mosquito vector[18].

8 As part of countermeasures against vivax malaria, anti-malarial chemoprophylaxis
9 with hydroxychloroquine and primaquine has been conducted among military personnel
10 since 1997 in the ROK. Hydroxychloroquine targets the blood-stage parasites, while
11 primaquine targets hypnozoites in the liver. Since the dormant stage is not affected by
12 hydroxychloroquine, primaquine is deemed essential as part of the prophylaxis against
13 vivax malaria. A total of 15,981 soldiers underwent chemoprophylaxis in the first year,
14 and subsequently the number of subjects increased year by year reaching 90,000 in
15 2000. The effectiveness of chemoprophylaxis on preventing epidemic has been assessed
16 in case-based studies in the past[19, 20]. However, the incidence of vivax malaria in a
17 year in Korea is strongly dependent on the incidence in the previous year due to the
18 long-term incubation period, and thus, the full clarification of the population

1 effectiveness of chemoprophylaxis requires us to explicitly account for the transmission
2 dynamics.

3 Mathematical modeling technique is useful for approximately capturing the
4 underlying transmission dynamics and detecting any temporal changes. Recently
5 several modelling studies took place, explicitly accounting for dormant stages of *P.*
6 *vivax* in the model structure [21,22]. In the present study, we estimated the
7 time-dependent (effective) reproduction numbers from 1993-2012, using a renewal
8 equation model and assessing the temporal trend of the transmission of vivax malaria in
9 the ROK. In addition, we evaluated the population effectiveness of mass
10 chemoprophylaxis, using the reproduction number and testing whether there was a
11 detectable change in the trend of secondary transmission.

12 **Materials and Methods**

13 *Epidemiological data*

14 Malaria is classified as one of the group III communicable diseases in the ROK, so
15 all diagnosed cases are reported to the Division of Infectious Disease Surveillance
16 (DIDS), Korea Centers for Disease Control and Prevention (KCDC). We used the
17 number of notified vivax malaria cases by month from 1993-2013 (Figure 1) [9]. The
18 cases were confirmed by parasitemia in peripheral blood smears[16]. In addition to the

1 temporal frequency of illness onset, the distribution of the incubation period, **time from**
2 **infection to the first exhibition of symptoms** expressed as a mixture of short-
3 (proportion 63.1%) and long-term (36.9%), was extracted from literature (**Figure 2**) [17]
4 and was assumed as known in the subsequent analyses. **In the ROK, symptomatic**
5 **malaria is assumed to be properly treated, and thus, multiple relapses after the diagnosis**
6 **can be left out from our consideration.** Moreover, absence of transmission from
7 November to April due to wintering season of *Anopheles sinensis* was adapted from
8 literature[18].

9 [---Figures 1 & 2 inserted about here---]

10 ***Renewal process model***

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

16 When formulating the malaria transmission model in the ROK, an extremely low
17 entomologic inoculation rate (EIR) helped us to impose a key assumption: re-infection
18 was assumed as negligible **so that immunity in the population does not affect the**

1 **reproduction number**. Moreover, due to geographically extended transmission within the
 2 ROK, we assumed that there was no impact of immigration of infected mosquitoes from
 3 the DPRK. Since the epidemiological data are reported monthly, we use a discrete
 4 version of renewal process. Let i_t be the number of newly infected individuals in month
 5 t . The renewal process is described by

$$6 \quad i_t = \sum_{\tau=1}^{t-1} A_{t,\tau} i_{t-\tau}, \quad (1)$$

7 where $A_{t,\tau}$ represents the rate of secondary transmission per single primary case in
 8 month t and infection-age (i.e. the time since infection in the primary case) τ . We
 9 assume that A is separable into the product of time-dependent and
 10 infection-age-dependent components, (i.e., $A_{t,\tau} = U_t g_\tau$), so that the equation can be
 11 rewritten as

$$12 \quad i_t = U_t \sum_{\tau=1}^{t-1} i_{t-\tau} g_\tau, \quad (2)$$

13 where U_t is the average number of secondary transmissions per primary case in month t
 14 and g_τ represents the probability mass function of generation time (per month), i.e.,
 15 the relative frequency of secondary transmissions as a function of infection-age τ in
 16 the primary case. **U_t is considered to reflect both intrinsic and extrinsic factors that are**
 17 **involved in the transmission dynamics, e.g. vector density and the effect of**

1 chemoprophylaxis, and $\sum_{\tau=1}^{t-1} i_{t-\tau} g_{\tau}$ on the right-hand side represents the effective
 2 number of human primary cases who could cause secondary transmission.

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

$$6 \quad j_t = \sum_{\tau=1}^{t-1} U_{t-\tau+1} j_{t-\tau} g_{\tau}. (3)$$

7 See Appendix 1 for the derivation of the equation (3). The rearranged model (3) allows
 8 us to account for seasonality by decomposing U_t as

$$9 \quad U_t = u_y w_m, (4)$$

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

1 of the yearly effective reproduction number R_y is obtained. We defined the R_y as the
 2 dominant eigenvalue of the following compartment matrix which satisfies

$$3 \quad \begin{bmatrix} \mathbf{i}_y \\ \mathbf{i}_{y-1} \end{bmatrix} = \begin{bmatrix} K_y & L_y \\ E & O \end{bmatrix} \begin{bmatrix} \mathbf{i}_{y-1} \\ \mathbf{i}_{y-2} \end{bmatrix}, \quad (5)$$

4 where $\mathbf{i}_y$ is a twelve-dimensional vector whose m -th component represents the number
 5 of secondary transmissions caused in month m in year y (See Appendix 2 for further
 6 details of the definition and computation of R_y).

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

$$9 \quad L(\mathbf{u}, \mathbf{w}; \mathbf{Z}) = \prod_t \frac{(E(j_t; Z_{t-1}))^{j_t} \exp(-E(j_t; Z_{t-1}))}{j_t!}, \quad (6)$$

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

11 *Quantitative settings*

12 In the present study, the generation time distribution, g_τ represents the time
 13 between two successive infections of human cases (i.e. the time from infection in
 14 human primary case to infection in secondary case). g_τ is assumed to be modeled as
 15 mirroring the incubation period distribution f_τ lagged by 1 month to the right (i.e.,
 16 $g_0=0$ and $g_\tau=f_{\tau-1}$ (for $\tau \geq 1$)), because the cases are infectious during the erythrocytic
 17 stage that coincides with symptomatic period (i.e. the incubation period is equated to the
 18 latent period of human primary case), and because we assume that the time from

1 parasitemia in the primary case to infection in the secondary case is a constant (and is
2 equal to 1 month). Figure 3 schematically illustrates these assumptions in relation to the
3 natural history. We believe that these assumptions are reasonable, because it takes about
4 20 days for the parasites to grow in the gut of anopheline mosquitoes (i.e., extrinsic
5 incubation period (EIP)) and only after the maturation of sporozoites the infection in
6 human secondary case can take place. The EIP was calculated using the formula given
7 in elsewhere [23] with the average temperature during six months of malaria season
8 (from May to October) in the ROK[24]. The incubation period distribution $f(\tau)$ is
9 calculated as a mixture of short- and long-term incubation periods expressed by gamma
10 distribution and normal distribution, respectively[17]. Using p as the weight of the
11 short-term incubation period (0.63;95% CI: 0.57-0.69), $f(\tau)$ was computed as

$$12 \quad f(\tau) = ps(\tau) + (1 - p)l(\tau), \quad (7)$$

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

17 [---Figure 3 inserted about here---]

18

1 Seasonal forcing w_m was manually set at zero during the wintering season
2 (when $m=1, 2, 3, 4, 11$ and 12). The maximum likelihood estimates of u_y and w_m (for the
3 remaining months) were obtained by minimizing the negative logarithm of the
4 likelihood function, $L(\mathbf{R}, \boldsymbol{\omega}; \mathbf{Z}, t)$. The yearly effective reproduction number was
5 subsequently calculated. The 95% confidence intervals (CI) of w_m were derived from
6 the profile likelihood. The 95% CI of R_y was obtained by employing the parametric
7 bootstrap method [25], because R_y is not given in a closed-form. Monthly incidence has
8 been generated by Poisson distribution whose mean is equal to the observed counts of
9 cases for each loop (1,000 repeats). A statistical package, R (<http://www.r-project.org/>)
10 was used to carry out the estimation.

11 *Temporal trend of transmission*

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

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

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

16 **Results**

17 ***Yearly reproduction number***

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

3 [---Table 1 & Figure 6 inserted about here---]

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

9 [---Table 2 inserted about here---]

10 **Discussion**

11 Transmission dynamics of vivax malaria in the ROK has been modeled by
 12 employing the renewal process model, estimating the yearly effective reproduction
 13 number (R_y) from 1993-2012 and assessing the trend in secondary transmission in
 14 relation to the timing of introducing mass chemoprophylaxis. The estimates of R_y
 15 revealed an overall declining trend from 1993-2012 with a few temporary increases
 16 around 2005 and 2009. Moreover, we assessed the possible population impact of mass
 17 chemoprophylaxis on the trend of secondary transmission by parametrically modeling
 18 the yearly component of the reproduction number and comparing AIC among models

1 with different timing of abrupt time-dependent change in transmission. The best model
2 appeared to be the model with abrupt decline in secondary transmission by 34% from
3 1998, coinciding with the expansion of chemoprophylaxis. The effectiveness of vector
4 control interventions has been assessed using a periodic model in the previous study[26],
5 but to our knowledge, our study is the first to have explicitly assessed the **population**
6 **impact** of mass chemoprophylaxis against vivax malaria in the temperate country.

7 Estimates of R_y has indicated that the epidemic of vivax malaria in the ROK since
8 1993 has been, on the whole, brought under control, as R_y has been below or slightly
9 above unity since 2000. Of technical note, R_y has been explicitly defined and derived
10 using Floquet analysis as **shown in Appendix 2. Similar methodology** has been
11 employed elsewhere [27, 28, 29]. **In contrast with such published studies that have been**
12 **focused on the basic reproduction number, a constant quantity over time,** we believe that
13 the present study is the first to have extended such concept to the time-dependent
14 (effective) reproduction number in the presence of seasonality. **Our proposed effective**
15 **reproduction number reflects yearly change in transmission dynamics in the most**
16 **appropriate theoretical manner.** Of course, our model has imposed rough assumptions,
17 including the ignorance of re-infection and transmission from the DPRK or the
18 assumption of homogeneous transmission between vectors and humans (which can lead

1 to underestimation of the reproduction number[30]).These points remain to be resolved
2 in future studies. Despite these essential unsupported assumptions, it should be
3 emphasized that the proposed approach to assessing the longitudinal temporal dynamics
4 with the prolonged incubation period has been very unique and most appropriately
5 realized by employing renewal equation that can rest on illness onset data.

6 In addition, the best model informed by AIC indicated that the mass
7 chemoprophylaxis against vivax malaria in the ROK has most likely induced the abrupt
8 decline in the yearly component of secondary transmission. The decline in the
9 transmission is likely to have been detectable since 1998, because the population impact
10 of the chemoprophylaxis since 1997 was not totally visible in 1997 due to the limited
11 coverage and the existence of the long-term incubation period. The chemoprophylaxis
12 has been subsequently expanded, and thus, the effectiveness has become detectable and
13 grown greater in the following years (which we believe to have been captured by the
14 exponentially decreasing trend in secondary transmissions). Although the population
15 effectiveness of chemoprophylaxis against vivax malaria in the ROK is very difficult to
16 be assessed using case data alone (due mainly to the presence of long-term incubation
17 period), our renewal process model actually rested on the dynamics of illness onset (as
18 demonstrated in Appendix 1) and this should be regarded as a great technical

1 advancement in assessing the temporal dynamics of infection with the exact timing of
2 intervention using observable case data.

3 Several limitations other than the absence of re-infection and ignorance of DPRK
4 should be noted. First, spatial profile of the dataset has not been taken into account due
5 to data limitation. We plan to incorporate this component and analyze the
6 spatiotemporal dynamics in the future. Second, the case data that we analyzed rested on
7 the notification report and such data must face the issue of ascertainment bias (that
8 stems from underdiagnosis and underreporting). However, as long as those coverage
9 approximately remain constant over time, the renewal equation still permits us to obtain
10 valid maximum likelihood estimates of the reproduction number. Third, we assumed
11 that the proportion and length of short- and long-term incubation period are known. A
12 recent study has raised a concern over the possible extension of the incubation
13 period[31]. Moreover, it is pointed out that the risk of relapse might be triggered by
14 systemic illnesses including malaria itself[32]. In light of these biological features, it
15 should be emphasized that our model is perhaps too simplistic. Nevertheless, the result
16 of the sensitivity analysis indicated that our conclusion about the existence of change
17 point is robust to variation in the proportion p .

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

8

9 **Appendix 1**

10 **Renewal equation using case data**

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

$$13 \qquad i_t = U_t \sum_{s=1}^{t-1} i_{t-s} g_s. \qquad (A1)$$

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

$$17 \qquad j_t = \sum_{\tau=0}^{t-1} i_{t-\tau} f_{\tau} \qquad (A2)$$

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

$$5 \quad j_t = \sum_{\tau=0}^{t-1} i_{t-\tau} g_{\tau+1}. \quad (\text{A3})$$

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

$$7 \quad j_t = \sum_{\tau=0}^{t-1} g_{\tau+1} U_{t-\tau} \sum_{s=1}^{t-\tau-1} i_{t-\tau-s} g_s. \quad (\text{A4})$$

8 The equation (A4) is identical to

$$9 \quad j_t = \sum_{\tau=0}^{t-1} g_{\tau+1} U_{t-\tau} \sum_{s=0}^{t-\tau-2} i_{t-\tau-s-1} g_{s+1}. \quad (\text{A5})$$

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

$$11 \quad j_t = \sum_{\tau=1}^t U_{t-\tau} j_{t-\tau-1} g_{\tau+1} = \sum_{\tau=1}^{t-1} U_{t-\tau+1} j_{t-\tau} g_\tau, \quad (\text{A6})$$

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

14

15 **Appendix 2**

16 **Definition and computation of the yearly reproduction number**

17 Let i_y be a twelve-dimensional vector of monthly incidence in year y , which corresponds
 18 to the discrete renewal equation by months, i.e., using the renewal equation

$$i_t = U_t \sum_{\tau}^{t-1} i_{t-\tau} g_{\tau}, \quad (A7)$$

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,

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

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

(A7) can be rewritten as

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

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

Using K_y and L_y , a recurrence relation of concatenated vector that is made of

$\mathbf{i}_y$ and $\mathbf{i}_{y-1}$ is obtained, i.e.,

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

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

1 matrix shown above (note that R_y is derived from the reproduction numbers only in year
2 y).

3

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1 Table 1 – Model fit with variable change point y_d in the secondary transmission of vivax
2 malaria

Change point (y_d)	%Short term incubation period (p)	Number of parameters	Negative log-likelihood	AIC [†]	Δ AIC
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

3

4 [†] AIC; Akaike Information Criterion.

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

6

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

3

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

4

5 † AIC; Akaike Information Criterion.

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

7

8

1 **Figure legend**

2 Figure 1 - Notified cases of vivax malaria in the Republic of Korea by month from
3 1993-2013.

4 Data source: ref. [9].

5

6 Figure 2 - Predicted distribution of the incubation period of *Plasmodium vivax* malaria
7 in the Republic of Korea.

8 Citation: ref. [17].

9

10 Figure 3 – Natural history of vivax malaria transmission.

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

17

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

8
9 Figure 5 – Seasonal forcing of vivax malaria in the Republic of Korea.
10 The maximum likelihood estimate (dots) and the 95% confidence intervals (whisker)
11 are shown. The estimates are normalized and thus the yearly average is equal to 1.
12 Vivax malaria in the Republic of Korea is transmitted by *Anopheles sinensis*, and the
13 seasonal forcing during the winter season (from Oct.-Apr.) is manually set at zero.

14
15 Figure 6 – Predicted temporal distribution of vivax malaria cases and estimated yearly
16 reproduction numbers of vivax malaria in the Republic of Korea (ROK) from
17 1993-2012.

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

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6