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

Akira Endo [a], Hiroshi Nishiura [a,b,*]

[a] Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[b] CREST, Japan Science and Technology Agency, Saitama, Japan

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.

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

* Correspondence to: Graduate School of Medicine, The University of Tokyo, Medical Building No. 3, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. Tel: +81 3 5841 3688; fax: +81 3 5841 3637.
E-mail address: nishiurah@m.u-tokyo.ac.jp (H. Nishiura).

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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 26.6days) 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.

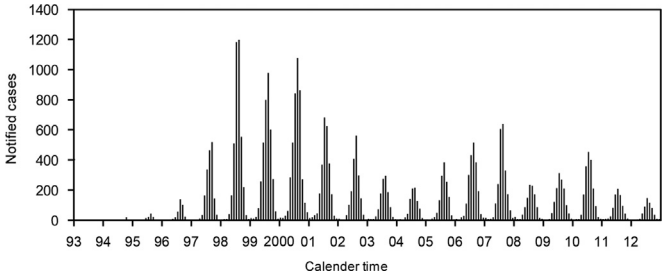

Fig. 1. Notified cases of vivax malaria in the Republic of Korea by month from 1993 to 2013.
Data source: Ref. Korea Centers for Disease Control and Prevention (2013).

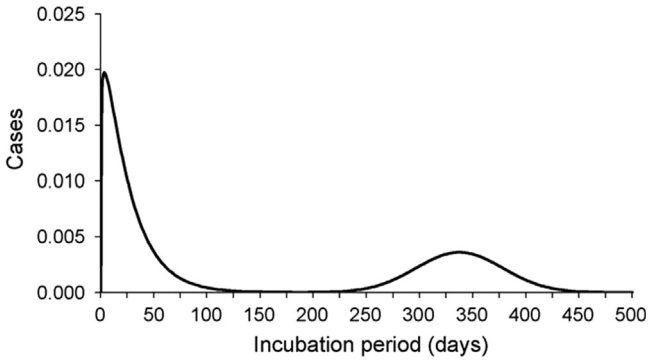

Fig. 2. Predicted distribution of the incubation period of *Plasmodium vivax* malaria in the Republic of Korea.
Citation: Ref. Nishiura et al. (2007).

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

$$i_t = \sum_{\tau=1}^{t-1} A_{t,\tau} i_{t-\tau}, \tag{1}$$

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) τ. We assume that A is separable into the product of time-dependent and infection-age-dependent components, (i.e.,