Chemoprophylaxis and the epidemiological characteristics of re-emergent \textit{P. vivax} malaria in the Republic of Korea

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\textbf{Objective} In the Republic of Korea (ROK), soldiers stationed where there is a risk of contracting malaria have received antimalarial chemoprophylaxis since 1997. However, chemoprophylaxis may facilitate the development of drug resistance, and late primary attacks in individuals who have received chemoprophylaxis are becoming more frequent. We investigated the association between chemoprophylaxis and the epidemiological characteristics and effectiveness of treatment for re-emergent \textit{Plasmodium vivax} malaria, using a nationwide malaria database.

\textbf{Methods} Among soldiers at risk of malaria between 1999 and 2001, we reviewed all \textit{P. vivax} malaria cases (1158) that occurred before 31 December 2003. Early and late primary attacks were defined as cases occurring \textless{} 2 or \textgreater{} 2 months after the last day of exposure to risk of malaria, respectively.

\textbf{Findings} Of these cases, 634 (72.0\%) had received chemoprophylaxis, and 324 (28.0\%) had not. Cases occurred mostly in summer, with a peak in July–August. Stratification by chemoprophylaxis history revealed different times to onset. Early primary attacks were more prevalent in the group not receiving chemoprophylaxis, while in the group receiving chemoprophylaxis most cases were late primary attacks. Of the latter, 312 out of 461 (67.7\%) did not take primaquine regularly. After treatment of the first attack, 14 (1.2\%) of 1158 were re-treated; all re-treated cases were cured using the same doses and regimen used for the first treatment.

\textbf{Conclusion} In ROK, the increase in late primary episodes of re-emergent \textit{P. vivax} malaria is associated with the use of antimalarial chemoprophylaxis.

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\footnotesize{Voir page 833 le résumé en français. En la página 833 figura un resumen en español.}

\textbf{Introduction} \textit{Plasmodium vivax}, the causative agent of vivax malaria, has been endemic in the Republic of Korea (ROK) for centuries. The number of cases of endemic malaria began to decline in the 1960s, partly due to increased socioeconomic development, increased use of agricultural pesticides, and the efforts of the National Malaria Eradication Service. These factors contributed to the eradication of malaria in the ROK, resulting in the declaration by WHO in 1979 that the country was malaria-free.\textsuperscript{1} In 1993, one case of malaria attributed to autochthonous transmission was detected near the demilitarized zone (DMZ) that separates ROK (south) from the Democratic People’s Republic of Korea (north).\textsuperscript{2} Since 1993, the number of malaria cases has increased exponentially, particularly among soldiers based near the DMZ.\textsuperscript{1–5}

In ROK, healthy males aged over 18 years serve 26 months of mandatory military duty; most are stationed throughout their service near the DMZ, where the risk of malaria is highest. After finishing their military duty, the soldiers return from these risk areas to areas with little or no malaria. To reduce the occurrence of malaria among current and former soldiers, the military initiated antimalarial chemoprophylaxis in 1997.

Although chemoprophylaxis reduces the number of cases of malaria, long-term chemoprophylaxis can facilitate the development of drug resistance.\textsuperscript{6,7} Recently, although there have been no reports of treatment failure in ROK, an increase in late primary episodes of \textit{P. vivax} malaria among soldiers who had received chemoprophylaxis has raised doubts regarding its effectiveness. A recent study in ROK showed that prophylaxis with primaquine was not effective in preventing late primary attacks.\textsuperscript{8}

We investigated the association between chemoprophylaxis and the epidemiological characteristics and effectiveness of treatment for re-emergent \textit{P. vivax} malaria, using a nationwide malaria database.

\textbf{Methods} \textbf{Chemoprophylaxis} Chemoprophylaxis with hydroxychloroquine sulfate (400 mg, once per week) is started in early summer and continued throughout the transmission season. Fourteen-day prophylaxis with primaquine (15 mg of base, once per day) is started on the first day of the last week of chloroquine administration. During military duty, soldiers assigned to areas at risk of malaria experience two consecutive transmission seasons and receive chemoprophylaxis each season. In

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addition to chemoprophylaxis, in 1998 the military adopted the use of permethrin-treated battle-dress uniforms and bednets, and the application of mosquito vector-control agents. The number of soldiers receiving chemoprophylaxis and the amount of permethrin used have increased annually (Table 1).

**Malaria surveillance**

In ROK, malaria cases in soldiers must be reported to the Armed Forces Medical Command, and cases in veterans and civilians must be reported to the Korea Center for Disease Control and Prevention. Malaria cases in veterans are defined as those experiencing a malaria attack within 24 months after retirement. Soldiers diagnosed with malaria are admitted to a military hospital for treatment and are interviewed by physicians; veterans are treated in community outpatient clinics and are interviewed by trained public-health specialists. All soldiers and veterans diagnosed with *P. vivax* malaria receive standard treatment: 2 g of hydroxychloroquine sulfate (1200, 400, and 400 mg on days 1 to 3, respectively) and 210 mg of primaquine (15 mg of base, once per day for 14 days).

Study subjects

We reviewed all cases of *P. vivax* malaria reported to the Armed Forces Medical Command and Korea Center for Disease Control and Prevention that occurred before 31 December 2003 in soldiers who had entered the ROK army during non-risk periods between 1 October 1998 and 28 February 2001 and who had been exposed to risk of malaria for the first time in military service between 1999 and 2001. We defined the malaria risk period as 1 May to 30 September.

Table 2. Cases of *P. vivax* malaria in soldiers and veterans of the Republic of Korea army, by exposure cohort

<table>
<thead>
<tr>
<th>First year of exposure</th>
<th>No. of patients</th>
<th>Onset of symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>First year</td>
</tr>
<tr>
<td>1999</td>
<td>590 (209)</td>
<td>28</td>
</tr>
<tr>
<td>2000</td>
<td>370 (138)</td>
<td>30</td>
</tr>
<tr>
<td>2001</td>
<td>198 (80)</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>1158 (427)</td>
<td>68</td>
</tr>
</tbody>
</table>

* Figures in parentheses are numbers of cases that occurred after retirement.
* In the first and second year of follow-up, all cases were among soldiers exposed to risk of malaria; in the third year of follow-up, no cases were exposed to risk of malaria.
* Cases that occurred in the first year of exposure.
Results

Of the 1158 cases, 634 (72.0%) had received chemoprophylaxis during military duty, and 324 (28.0%) had not. All cases were among soldiers stationed in malaria risk areas during military duty.

The year of symptom onset for each exposure cohort is shown in Table 2. Most cases occurred in summer (May–August), with a peak in July–August. In winter (December–February), only 12 cases (4, 7, and 1 in the first, second and third winters, respectively) occurred (Fig. 1). To investigate the monthly distribution of early and late primary attacks by history of chemoprophylaxis, we analysed the cases that occurred in the first and third years; cases that occurred in the second year were excluded in the analysis because early and late primary attacks occurred concurrently. Of the cases (mostly early primary attacks) that occurred in the first year, numbers in the notchemoprophylaxis group peaked before those in the chemoprophylaxis group, while the monthly distribution of cases (late primary attacks) that occurred in the third year was similar in the two groups (Fig. 2).

Of the 195 cases that occurred before the start of the second round of chemoprophylaxis, 195 (16.8%) occurred before, and 963 (83.2%) after the second round of chemoprophylaxis started. Stratification of the cases on the basis of history of chemoprophylaxis revealed different times to onset (Fig. 3). The number of malaria cases in the no-chemoprophylaxis group increased within 5 months of first exposure to malaria risk, as seen in Fig. 3a (72.2%) and Fig. 3b (77.3%). In the group receiving chemoprophylaxis, however, most cases occurred after 10 months, as seen in Fig. 3a (84.6%) and Fig. 3b (58.2%).

Of the 195 cases that occurred before the start of the second round of chemoprophylaxis, 107 (87.0%) of the 123 cases in the group receiving chemoprophylaxis and 20 (27.8%) of the 72 cases that did not receive chemoprophylaxis were late primary attacks (Table 3). All the cases in the group receiving chemoprophylaxis received chloroquine, and 44 (41.1%) of the 107 cases that were late primary attacks finished prophylaxis with primaquine. Of the 963 cases that occurred after the second round started, 354 (59.2%) of the 598 cases in the group receiving chemoprophylaxis and 79 (21.6%) of the 365 cases who did not receive the second chemoprophylaxis were late primary attacks. Of the 354 cases that were late primary attacks and who received the second chemoprophylaxis, 105 (29.7%) completed prophylaxis with primaquine.

After using the history of first chemoprophylaxis to stratify the 963 cases that occurred after the start of the second round, the proportion of late primary attacks was found to be significantly higher among cases who received the second chemoprophylaxis than among those who did not, regardless of first chemoprophylaxis history (Table 4, web version only, available from: http://www.who.int/bulletin).

After the first attack had been treated, 14 (1.2%) out of 1158 cases were re-treated for P. vivax malaria. All the first attacks occurred during military duty; in seven cases, a second attack occurred after retirement. A third episode of P. vivax malaria occurred in one case within 1 month after the second attack during military duty. After excluding...
the cases that occurred in 2003 (relapses would have occurred in 2004 or later), 484 out of 1076 cases were not exposed to risk of malaria after the first diagnosis. Of the 484 cases, 2 (0.4%) were re-treated as \textit{P. vivax} malaria > 6 months (204 and 351 days) after the first attack. All re-treated cases were cured using the same doses and regimen used for the first treatment.

\section*{Discussion}

Early primary attacks are usually defined as cases occurring $\leq 1$ month after exposure \cite{10,11}; however, to investigate the epidemiological characteristics of re-emergent \textit{P. vivax} malaria, we defined early onset as cases occurring $\leq 2$ months after the last day of the malaria risk period (before December). Cases that occurred in the first year (i.e. cases infected in the first year) and third year (i.e. cases with infections from the previous year) showed a typical unimodal peak in summer, regardless of the history of chemoprophylaxis, and only a few cases occurred in winter (Fig. 2). Thus it is obvious that early primary attacks occurred before winter. The cases that occurred in November might have been caused by infection in late September or early October; therefore, we categorized all the cases that occurred in November as early primary attacks.

In this study, most cases occurred in summer, with a peak in July–August, and the monthly distribution paralleled the density of the mosquito population.\cite{12} After stratification by history of chemoprophylaxis, symptom onset in cases occurring in the first year was delayed in the group receiving chemoprophylaxis compared with that in the no-chemoprophylaxis group, while it was similar in both groups for the cases that occurred in the third year. This suggests that blood-stage schizonticide (by chloroquine) is associated with delayed symptom onset and that the latency period of late primary attack is not related to chemoprophylaxis.

Studies conducted between about 1950 and the 1970s demonstrated that Korean \textit{P. vivax} malaria had both short and long latency periods and that most cases had a long latency, characteristic of \textit{P. vivax} malaria in temperate regions.\cite{13-15} A recent study also suggested that two-thirds of re-emergent cases of \textit{P. vivax} malaria had a long latency, with a mean duration of 10 months, although long-latency forms of \textit{P. vivax} malaria might have been overrepresented because only cases that occurred after retirement were included.\cite{16} Unlike previous studies, most cases in this study involving soldiers and veterans that did not receive chemoprophylaxis were early primary attacks, while most cases that received chemoprophylaxis were late primary attacks. These findings suggest that re-emergent \textit{P. vivax} malaria has epidemiological characteristics that differ from those of the \textit{P. vivax} malaria that was in existence between about 1950 and the 1970s, but that are similar to those of tropical strains, which have a short latency period before symptom onset.\cite{15} Moreover, the use of antimalarial chemoprophylaxis can change the pattern of malaria occurrence. Although genetic evidence suggests that re-emergent \textit{P. vivax} has a Chinese or Democratic People’s Republic of Korean origin,\cite{17,18} genetic variation might have arisen in response to chemoprophylaxis or climate change. A recent study demonstrated that the merozoite surface protein (MSP) gene nucleotide sequence of \textit{P. vivax} in ROK is similar to that of Thai isolates.\cite{19} However, we cannot conclude that our results show evidence of tropical strains in ROK because strain characterization was not performed. To identify the biological characteristics and origin of re-emergent \textit{P. vivax} malaria, further molecular epidemiological analysis is needed.
Most late primary attacks (312 of 461 cases, or 67.7%) in the group receiving chemoprophylaxis were in soldiers who had not taken primaquine prophylaxis regularly, implicating non-adherence to prophylaxis as a major cause of the increase in late primary attacks. Two additional factors might have affected the observed increase in late primary attacks among those who had received chemoprophylaxis.

First, primaquine may not effectively reduce late primary attacks; a recent study in ROK reported that the effectiveness of primaquine prophylaxis against late primary attacks was 32%, and that the doses of primaquine used in ROK would be considered inadequate in other countries. In this study, late primary attacks occurred in individuals who had received primaquine prophylaxis regularly, and it is thus possible that factors such as inadequate primaquine dosage and absorption are associated with P. vivax malaria. However, only 0.4% of those receiving the standard prophylactic dose of primaquine were retreated for relapse, suggesting that primaquine effectively reduces the incidence of late primary attacks.

Second, symptom onset might be masked in patients receiving chemoprophylaxis because of blood-stage schizonticidal activity; consequently, the number of late primary attacks might increase. This hypothesis is supported by two findings: (1) the stratification of cases by history of chemoprophylaxis revealed delayed symptom onset in early primary attacks and a different proportion in late primary attacks; and (2) 32.3% of late primary attacks in the group receiving chemoprophylaxis were in men who had taken chloroquine and primaquine. Interestingly, in this study, cases of delayed symptom onset did not occur immediately after the end of chloroquine prophylaxis and convert into late primary attacks. Owing to design limitations, we could not find any determinants associated with the latency of P. vivax malaria, and further investigations are needed.

For these two reasons, the increase in late primary attacks in the group receiving chemoprophylaxis may be largely associated with patient non-adherence to primaquine and a delay in symptom onset attributable to chemoprophylaxis. These findings are important not only for planning chemoprophylaxis programmes for areas with little or no malaria risk, because late primary attacks can directly affect the spread of malaria, but also for assessing the effectiveness of prophylaxis with primaquine, because chloroquine is a powerful potential confounding factor. If the effects of chloroquine are not considered, the efficacy of prophylaxis with primaquine could be significantly underestimated owing to symptom onset delay.

Primaquine is the only available drug that eliminates liver-stage parasites, although other drugs such as tafenoquine and malarone are being tested. Primaquine is a long-term medication (usually 14 days), and low compliance can be a problem. To increase compliance, the ROK military requires that all soldiers take antimalarial drugs under direct supervision and sign a drug administration checklist. In addition, to reduce late primary attacks occurring after retirement, all soldiers who were stationed in risk areas and retiring during the malaria risk period receive primaquine prophylaxis before retirement. Nevertheless, for a variety of reasons, low compliance with chemoprophylaxis remains a major problem.
The situation in ROK is unusual because sporozoite-infected mosquitoes moving from north to south across the DMZ caused the re-emergence of malaria.30,31 Although malaria has spread south of the DMZ, most cases still occur near the DMZ.32 Moreover, a state of military confrontation still exists along the DMZ. For these reasons, the goals of chemoprophylaxis in the ROK military are to reduce the number of malaria cases and to limit the spread of malaria into non-risk areas. On the basis of our results, it is impossible to determine whether chemoprophylaxis should be encouraged or discouraged to reduce the number of late primary attacks. If chemoprophylaxis were to be discontinued, the number of late primary attacks would increase with the total number of malaria cases. Conversely, although no report on treatment failure has been issued, the continuation of long-term chemoprophylaxis might enhance resistance or tolerance to antimalarial drugs. Given that most cases occurring during April and May are late primary attacks from the previous year, chemoprophylaxis and other prevention measures should be started at the beginning of April to reduce the potential for transmission to humans. However, the best way to control P. vivax malaria in the Korean peninsula is to ensure that malaria eradication programmes are performed in the Democratic People’s Republic of Korea and in ROK. Although the ROK Government has supported malaria-prevention programmes in the Democratic People’s Republic of Korea since 2001, and in 2005 provided the equivalent of US$ 877 000 of malaria-related aid and equipment via WHO,33 support for aid programmes must be continued and extended.

Our study has several limitations. First, misclassification bias could be a major limitation. Both early and late primary attacks occurred concurrently during the malaria risk period in the second year, and the second-year cases were categorized as early or late according to the timing of symptom onset. However, many of the cases that occurred between May and early June (before chemoprophylaxis started) in the second year might actually have been late primary attacks in individuals infected in the first year, given that only two cases occurred between May and June in the first year. Considering the cases that occurred before the second round of chemoprophylaxis and excluding 87 cases (76 in the chemoprophylaxis group; 11 in the no-chemoprophylaxis group) that occurred after 1 May in the second year, the proportion of late primary attacks was also significantly higher in the chemoprophylaxis group (66.0% versus 14.8%). It was impossible to distinguish early and late primary attacks during and after the malaria risk period in the second year. However, among the cases presenting before the second round of chemoprophylaxis, late primary attacks were more prevalent in the group receiving chemoprophylaxis, suggesting that the proportional difference between the chemoprophylaxis and no-chemoprophylaxis groups in late primary attacks occurring after the start of the second round can be considered to be a conservative estimate, and thus it appears that our results are not greatly affected by misclassification bias.

The second limitation is that the number of late primary attacks might have been underestimated because gametocyte-bearing subjects can reintroduce malaria to mosquitoes outside the risk area. However, the number of secondary and tertiary transmitted cases was probably small and is unlikely to have affected our results, because no cases among soldiers and few civilian cases (23 out of 609 cases in 2003) were reported in non-risk areas during the study period, and most of those cases had a history of travel to malaria risk areas.34

Conclusions

Despite its limitations, our study demonstrates that re-emergent P. vivax malaria in ROK shows epidemiological characteristics that differ from those of the P. vivax malaria that existed between about 1950 and the 1970s, and that the increase in late primary episodes of re-emergent P. vivax malaria is significantly associated with the use of antimalarial chemoprophylaxis. Although no treatment failures have been reported in ROK, further investigations of malaria-prevention strategies are needed to ensure control of late primary episodes of P. vivax malaria and to prevent the development of resistance or tolerance to antimalarial drugs.

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Competing interests: none declared.
Quimioprofilaxis y epidemiología de la malaria reemergente por *Plasmodium vivax* en la República de Corea

**Objetivo** En la República de Corea, los soldados emplazados en zonas con riesgo de malaria vienen recibiendo quimioprofilaxis antimalárica desde 1999. Sin embargo, la quimioprofilaxis puede facilitar la aparición de farmacorésistencia, y la observación de ataques primarios tardíos en personas que han recibido quimioprofilaxis es cada vez más frecuente. Investigamos la relación existente entre la quimioprofilaxis y las características epidemiológicas y la eficacia del tratamiento de la malaria reemergente por *Plasmodium vivax*, usando para ello una base de datos de ámbito nacional sobre la malaria.

**Métodos** Entre los soldados expuestos al riesgo de contraer malaria entre 1999 y 2001, estudiamos todos los casos de malaria por *P. vivax* registrados antes del 31 de diciembre de 2003. Se definieron como ataques primarios tempranos o tardíos los casos ocurridos ≤ 2 o > 2 meses después del último día de exposición al riesgo de malaria, respectivamente.

**Resultados** De esos casos, 634 (72.0%) habían recibido quimioprofilaxis, y 324 (28.0%) no. Los casos se produjeron sobre todo en verano, con un máximo en julio/agosto. La estratificación en función de los antecedentes de quimioprofilaxis reveló distintos intervalos de incubación de la enfermedad. Los ataques primarios tempranos fueron más frecuentes en el grupo no sometido a quimioprofilaxis, mientras que en el grupo sometido a ella la mayoría de los casos fueron ataques primarios tardíos. De estos últimos, 312 de 461 (67.7%) no tomaban primaquina de forma regular. Tras el tratamiento del primer ataque, 14 (1,2%) de 1158 casos fueron tratados de nuevo; todos los casos retrotratados se curaron con las mismas dosis y pautas usadas en el primer tratamiento.

**Conclusiones** En la República de Corea, el aumento de ataques primarios tardíos de malaria reemergente por *P. vivax* aparece asociado a la quimioprofilaxis antimalárica.
References


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Table 4. Cases of *P. vivax* malaria that occurred in soldiers and veterans of the Republic of Korea army after the start of the second round of chemoprophylaxis, stratified by history of chemoprophylaxis.

<table>
<thead>
<tr>
<th>Chemoprophylaxis received</th>
<th>No. of patients</th>
<th>Latency period</th>
<th>P-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Early</td>
<td>Late</td>
</tr>
<tr>
<td></td>
<td></td>
<td>220 (49.7)</td>
<td>223 (50.3)</td>
</tr>
<tr>
<td>First year</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>443 (100)&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>220 (49.7)</td>
<td>0 (0.0)</td>
<td>223 (50.3)</td>
</tr>
<tr>
<td>Total</td>
<td>556 (100)</td>
<td>333 (59.9)</td>
<td>223 (40.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24 (15.5)</td>
<td>131 (84.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>155 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>179 (100)</td>
<td>131 (84.5)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>252 (100)</td>
<td>173 (68.7)</td>
<td>79 (31.3)</td>
</tr>
<tr>
<td></td>
<td>407 (100)</td>
<td>197 (48.4)</td>
<td>210 (51.6)</td>
</tr>
</tbody>
</table>

<sup>a</sup> χ² test.

<sup>b</sup> Figures in parentheses are percentages.