Resurgence of *Plasmodium vivax* Malaria in the Republic of Korea during 2006–2007

Gyo Jun,† Joon-Sup Yeom,‡ Jee-Young Hong, E-Hyun Shin, Kyu-Sik Chang, Jae-Ran Yu, Sejoong Oh, Hyeok Chung, and Jae-Won Park⁎

Departments of Biochemistry and Microbiology, Graduate School of Medicine, Gachon University of Medicine and Science, Incheon, Republic of Korea; Department of Preventive Medicine, Konyang University College of Medicine, Daejeon, Republic of Korea; Division of Medical Entomology and Malaria and Parasitic Diseases, Korea Centers for Disease Control and Prevention, Seoul, Republic of Korea; Korean Armed Forces Medical Command, Gyeonggi-do, Republic of Korea

Abstract. *Plasmodium vivax* malaria, which re-emerged in the Republic of Korea (ROK) in 1993, had decreased since 2001. However, case numbers began to increase again in 2005. The number of cases rose 54.0% in 2006, but the rate of increase slowed down in 2007. Among the total of 4,206 cases of *P. vivax* malaria during 2006–2007, 756 cases (18.0%) were ROK military personnel, 891 cases (21.2%) were veterans, and 2,559 cases (60.8%) were civilians. The rapid increase during this period was mostly contributed by the western part of the malaria-risk areas that is under the influence of adjacent North Korea. Local transmission cases in ROK have also increased gradually and the transmission period seemingly became longer. Chemoprophylaxis in the military should be re-assessed in view of chloroquine-resistance. Continuous surveillance and monitoring are warranted to prevent further expansion of *P. vivax* malaria caused by climate change in ROK.

INTRODUCTION

*Plasmodium vivax* malaria was endemic on the Korean Peninsula for many centuries. Its biologic characteristics, including the relapse pattern, were widely studied during the Korean War (1950–1953), and the regimen of presumptive anti-relapse therapy with primaquine was also established during this period. Through improved national economic conditions and continuous malaria control programs, *P. vivax* malaria cases in the Republic of Korea (ROK) tapered off in the 1960s and 1970s, and, finally, ROK was declared malaria-free in 1979.

However, *P. vivax* malaria re-emerged in ROK in 1993, and its annual incidence rapidly increased up to more than 4,000 cases in 2000, fell to 864 cases in 2004, and rose again in 2005. During the early period of re-emergence, *P. vivax* malaria in ROK may have been mostly caused by infected Anopheline mosquitoes originating from the Democratic People’s Republic of Korea (DPRK; North Korea) near the Demilitarized Zone (DMZ), as evidenced by epidemiologic and demographic data. However, as the proportion of *P. vivax* malaria cases among civilians increased with the geographic expansion into cities and counties located further from the DMZ, local transmission cases also increased. During these years, intense efforts were made by the Korean government to control/eliminate malaria. In the military sector, since 1997, the Korean Ministry of National Defense initiated a chemoprophylaxis program using chloroquine and primaquine for soldiers stationed in the malaria-risk areas. Soldiers were given 400 mg hydroxychloroquine sulfate orally once a week from June until early October followed by 15 mg primaquine phosphate orally once a day for 2 weeks. Other measures such as wearing permethrin-treated uniforms and using permethrin-treated bed nets during the transmission season were also taken. In private sectors, the government performed education programs for healthcare personnel (doctors/nurses/medical technicians) and provided rapid detection tests for early detection/treatment of patients. Preventive measures such as spraying insecticides and eliminating mosquito habitats were also taken during the transmission season.

In this situation, resurgence of *P. vivax* malaria cases in ROK in 2005 highlights the importance of continuous analysis of epidemiologic characteristics of *P. vivax* malaria in ROK. In this study, we evaluated the epidemiologic characteristics, i.e., number of cases and their monthly and annual incidence, geographic distribution of the cases, compliance of military patients to chemoprophylaxis, seasonal pattern of the first late primary attack cases, and the number of Anophelees mosquitoes from one of the malaria-risk areas in ROK from 2006 through 2007 to analyze the current malaria situation in ROK.

MATERIALS AND METHODS

Malaria is classified as one of the group III communicable diseases in ROK. Cases detected in private hospitals and clinics are reported to local public health centers operated by the government. The case definition of malaria includes any febrile illness with demonstration of *P. vivax* parasites in peripheral blood smears. A case report usually contains the patient’s name, age, sex, address, the date of onset of illness, the date of malaria diagnosis, and the possible area where infection occurred. Data collected in public health centers are sent to the Division of Infectious Disease Surveillance (DIDS) at the Korea Centers for Disease Control and Prevention (KCDC). Most of the cases reported through this system are civilians and veterans, although some soldiers who were diagnosed while they were on vacation might be included. However, DIDS contacts every reported patient for exact epidemiologic information. Any wrong information reported from hospitals and clinics are corrected during this process.

All malaria cases among military personnel must be reported to the Korean Armed Forces Medical Command and the Korean Ministry of National Defense. The Korean Armed Forces Medical Command sends military malaria data to
DIDS at KCDC. Cases among military veterans were defined as those who had a malaria attack within 24 months of discharge from military service, and those who had been stationed in a malaria-risk area. Classification of all reported cases into civilian/veteran/soldier and the exact numbers of reported cases are finalized by DIDS at KCDC.

The annual geographic distribution of *P. vivax* malaria in ROK military personnel, veterans, and civilians was determined by the location where they were stationed or where they lived when the diagnosis was made. The seasonal incidence was analyzed by grouping cases according to 10-day intervals. The seasonal incidence of civilians in 2006 was compared with that of 2002 to analyze the change in the malaria transmission season. Seasonal distribution of the first late primary attack was analyzed by the date of the first symptom onset of veteran patients and the date of their discharge from the military. Data on the compliance of military personnel to chemoprophylaxis during 2005–2007 were obtained from the Korean Armed Forces Medical Command.

The numbers of Anopheline mosquitoes were monitored using a light trap in Ganghwa County, one of the malaria-risk areas in ROK, during the malaria transmission season of 2006 and 2007. Trapping was conducted twice a week on Monday and Tuesday between 8 PM and 7 AM of the following day from May until October. A trap was set up at the same location and the length of trapping time was kept constant to ensure consistency. Anopheline mosquitoes were separated morphologically and counted regardless of the blood-fed status or sporozoite content. The average of the numbers of trapped Anopheline mosquitoes for 2 days was taken as a representative value of the week.

**RESULTS**

In 2006 and 2007, the number of *P. vivax* malaria cases in ROK increased. The incidence of malaria in 2006 was 54% higher than in 2005, and increased by a further 8.3% in 2007 (Table 1). Among the total of 4,206 cases of *P. vivax* malaria that occurred during 2006 and 2007, 756 cases (18.0%) were reported among military personnel, 891 cases (21.2%) among veterans who had served in malaria-risk areas, and 2,559 cases (60.8%) among civilians (Table 1). The proportion of civilians among the total annual cases reached over 60% in 2006, but lowered slightly to 58.6% in 2007.

During 2006 and 2007, *P. vivax* malaria cases among both military personnel and civilians increased mainly in the western part of the malaria-risk areas compared with the previous year (Figure 1). In particular, the increase of civilian cases was marked in the western part of the malaria-risk areas including Ganghwa County, Gimpo, Goyang, Incheon, and Paju Cities in 2006. The rapid increase of the total cases in 2006 was mostly contributed by the increase of the cases in these areas. In Incheon City and Ganghwa County, the incidence among civilians soared 221% and 75% higher than in 2005, respectively, and in Gimpo, Goyang, and Paju Cities, it also increased markedly (68%, 48%, and 40%, respectively). In 2007, the incidence among civilians was similar to the previous year in Ganghwa County, Gimpo, Goyang, and Incheon Cities, whereas 20% fewer cases were reported in Paju City. The cases of military personnel showed similar geographic distribution to the civilian cases during this period despite fewer cases. A notable feature of the malaria incidence among military personnel was that, in 2007, the number of cases in Gimpo City increased by 5 times of the previous year, but such a pattern was not observed in other cities or counties. Unlike civilians, the incidence among military personnel in Yeoncheon, Cheolwon, and Hwacheon Counties kept increasing in 2006 and 2007. Yeoncheon County showed 26% and 100% increase in 2006 and 2007, respectively, and Cheolwon County showed a 96% increase in 2006. In Hwacheon County, the number of cases among military personnel was five in 2004 and one in 2005, but increased to 11 in 2006 and 10 in 2007. Despite the rapid resurgence of the total cases during this period, the eastern part of the malaria-risk areas showed almost no change in incidence among both military personnel and civilians (Figure 1).

Civilian malaria incidence per 100,000 population in the western risk areas was 16.4 (15.3–17.5) in 2006, 71% higher than in 2005 (Table 2). There was no evidence of decline in incidence in 2007, despite the slightly lower point estimate of 15.7 (14.7–16.7). Nationwide civilian incidence per 100,000 population in ROK was 1.6 (1.5–1.7), 2.6 (2.5–2.7), and 2.6 (2.5–2.7) in 2005, 2006, and 2007, respectively, marking a 63% increase in 2006 and kept at the same level in 2007.

Most of the *P. vivax* malaria cases occurred from June through September, with a peak from early July to mid-September in 2006 and from early July to late August in 2007 (Figure 2). The 10-day incidence reached a maximum between late July and mid-August in 2006. However, it reached the highest point in early September in civilians, for whom intensive interventions like chemoprophylaxis were not performed in 2006, which was unusual when compared with other years with a peak in July or August. In 2007, the 10-day incidence was highest in late July. The 10-day incidence peak of civilian cases reached over 100 cases in 2006 and over 120 cases in 2007.

Anopheline mosquitoes, the major transmission vectors of malaria, were collected and counted on a weekly basis in

<table>
<thead>
<tr>
<th>Annual incidence of <em>Plasmodium vivax</em> malaria among Republic of Korea (ROK) military personnel, veterans, and civilians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soldiers</td>
</tr>
<tr>
<td>Veterans</td>
</tr>
<tr>
<td>Civilians</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

*The first numerical values in parentheses represent the proportion of each group among the total annual cases, and the second numerical values in parentheses represent the rate of increase compared with the annual incidence of the previous year. Previously, a total of 1,304 cases were reported for the year 2005 (230 soldiers, 317 veterans, and 757 civilians) because one soldier case, four veteran cases, and two civilian cases occurred in 2005 and were reported belatedly in the following year. Therefore, the number of cases in 2005 should be corrected from 1,304 to 1,311.
†Numerical values in parentheses represent the proportion of each group among the total cases during 2006–2007.
‡Veterans include those who have been discharged from the military for ≥ 2 years and previously stationed to a malaria-risk area.
§Civilians include veterans who have been discharged from the military for > 2 years.
Ganghwa County from 2006 through 2007. The weekly numbers of Anopheline mosquitoes during August and September in 2006 were much greater than the same period in 2007 (Figure 3). The first late primary attack cases among veterans mainly occurred during the first transmission season after their discharge, with the peak apparent between mid-June and mid-August (Figure 4). Its seasonal pattern was quite similar to a previous study.2 Out of 646 veteran patients investigated in this study, 636 (98.5%) had the first late primary attack during the year after their discharge. The 10-day incidence of civilians in 2006 showed a wider peak than in 2002 (Figure 5),7 because of case increases in June, September, and October that were the base of the peak in 2002. Among soldiers who were admitted to military hospitals because of P. vivax malaria during 2005 and 2007, less than a quarter followed a regular chemoprophylaxis schedule (Table 3).

DISCUSSION

Plasmodium vivax malaria in ROK kept the increasing trend in 2006 and 2007, dashing the hope that the resurgence in 2005 might be a temporary phenomenon.8 The increase during this period was mostly contributed by the western part of the malaria-risk areas of ROK that could be influenced by the malaria situation in DPRK. In 2000 and 2001, the number of P. vivax malaria cases in DPRK reached the highest peak ever, with nationwide prevalence of the disease except in the northern mountainous areas.9,10 After 2001, total annual cases had dropped, with the geographic distribution shrinking to the southwestern part of DPRK that harbor many rice fields.11

Table 2

<table>
<thead>
<tr>
<th>Area</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Population</td>
<td>Incidence/10^5</td>
</tr>
<tr>
<td>West risk areas†</td>
<td>504</td>
<td>5,273,742</td>
<td>9.6 (8.8–10.4)</td>
</tr>
<tr>
<td>East risk areas†</td>
<td>26</td>
<td>531,016</td>
<td>4.9 (3.0–6.8)</td>
</tr>
<tr>
<td>Other areas</td>
<td>229</td>
<td>42,878,283</td>
<td>0.5 (0.4–0.6)</td>
</tr>
<tr>
<td>ROK overall</td>
<td>759</td>
<td>48,683,040</td>
<td>1.6 (1.5–1.7)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses represent 95% confidence intervals.
† West risk areas include Yeonchon, Pocheon, Gapyeong, and other cities/counties west of them except Seoul. East risk areas include Cheolwon, Hwacheon, Chooncheon, and other cities/counties east of them (see Figure 1).
However, in the mid-2000s, regional incidences in some areas adjacent to the DMZ remained as high or even higher than in 2000 and 2001,\textsuperscript{11,12} which might have influenced the rapid increase of malaria cases in the western malaria-risk areas of ROK.

Besides the direct influence from DPRK, elevated local transmission might be another cause for the increase of \textit{P. vivax} malaria cases during this period. Although civilians generally reside south of military bases, civilian cases exceeded 60\% of the total annual cases in 2006. Traditionally, \textit{P. vivax} malaria cases in Ganghwa County were largely confined to the northern part of the island close to DPRK, and most cases occurring in the southern part of the island involved people who had a travel history to the northern part of the island or other malaria-risk areas adjacent to the DMZ. From the mid-2000s, however, malaria cases were reported among civilians of the southern Ganghwa County who had never been to the areas adjacent to the DMZ during the past 2 years. This was coincident with the occurrence of \textit{P. vivax} malaria cases in Yeongjong Island that is located several kilometers south of the southern seashore of Ganghwa County.\textsuperscript{8} During 2006 and 2007, annual incidence reached about 20 cases for two consecutive years in Yeongjong Island, where the Incheon International Airport is located. Precautions should be implemented to prevent expansion of \textit{P. vivax} malaria to the International Airport. In Gimpo, Goyang, Incheon, and Paju Cities, where the number of civilian cases rapidly increased, many apartment complexes had been built in parts of the formerly farming areas. Accordingly, the increased population density surrounded by unchanged rice fields might have raised contact frequencies between the residents and Anopheline mosquitoes.

In 2007, the number of \textit{P. vivax} malaria cases among military personnel increased by more than 40\%, whereas the incidence among civilians and veterans was generally unchanged. In particular, Gimpo City had 71 military personnel patients in 2007, marking a 5 times increase compared with 2006. Presumably, such a dramatic change was not caused by a simple increase...
Compliance of military personnel patients to chemoprophylaxis with hydroxychloroquine and primaquine in Republic of Korea during 2005–2007

<table>
<thead>
<tr>
<th>Year</th>
<th>Status of chemoprophylaxis</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
<td>No. of patients (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Regular †</td>
<td>48 (25.0)</td>
<td>63 (30.1)</td>
<td>76 (18.4)</td>
<td>187 (23.0)</td>
</tr>
<tr>
<td></td>
<td>Irregular ‡</td>
<td>116 (60.4)</td>
<td>130 (62.2)</td>
<td>294 (71.2)</td>
<td>540 (66.3)</td>
</tr>
<tr>
<td></td>
<td>None §</td>
<td>28 (14.6)</td>
<td>16 (7.7)</td>
<td>43 (10.4)</td>
<td>87 (10.7)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>192 (100)</td>
<td>209 (100)</td>
<td>413 (100)</td>
<td>814 (100)</td>
</tr>
</tbody>
</table>

*Note: Of the 987 military personnel patients during 2005–2007, those answered the survey are included in this table.
† Regular administration of both drugs.
‡ Irregular administration of either of the drugs.
§ Chemoprophylaxis was not performed for this group.

in malaria cases but to an amended case report system of the ROK Army. Even though battalions and regiments are supposed to report all the malaria cases to the Medical Command of the ROK Army and must refer the patients to local military hospitals, not all the military units faithfully carried out the reportage and referred the patients. Instead, they treated patients in their own medical offices. Such negligence in reporting malaria cases occurred most widely in 1999 when the incidence of malaria among the military personnel reached its peak (J-W Park and J-S Yeom, personal communication). Later on, military authorities started strict supervision on the case report system, which might have contributed to the sharp rise in malaria cases among soldiers in Gimpo City.

In 2006, the peak 10-day incidence of malaria among civilians occurred in early September, which was unusual considering the seasonal incidence pattern of the previous years. The seasonal incidence pattern of 2006 revealed a plateau on a wide peak, whereas that of 2002 showed a typical unimodal peak. For recent *P. vivax* malaria in ROK, most early primary attack cases via short incubation period occurred after July. The increase in *P. vivax* malaria cases during September and October in 2006 means that early primary attack cases due to transmission by mosquitoes during the same season actively occurred, implying a longer transmission period in 2006 than in 2002. The increase in early primary attack cases in 2006 was consistent with the increased number of Anopheline mosquitoes in August and September of 2006. Further surveillance is necessary to monitor whether the lengthened transmission period is a temporary phenomenon or the consequence of more permanent factors such as climate change.

The peak of the 10-day incidence of civilians in 2007 was higher than in 2006, which might be ascribed to increased transmission during August and September of 2006. The 10-day incidence peak of 2007 was higher but much narrower than that of 2006, which resulted from the decrease in early primary attack cases via a short incubation period in 2007. To cope with the rapid resurgence of *P. vivax* malaria in DPRK, large-scale chemoprophylaxis with primaquine was performed on approximately 5 million individuals in May 2007 with the support of ROK. The chemoprophylaxis would be expected to reduce late primary attack cases via a long incubation period in DPRK, which might be the primary source of infection to ROK in 2007, subsequently resulting in the decrease of early primary attack cases in 2007. Even if local transmission cases in ROK have increased gradually, the status of *P. vivax* malaria in ROK has been greatly influenced by the situation in DPRK. The rapid decrease in the cases during September and October of 2007 seems related to the large-scale chemoprophylaxis in DPRK in that year.

The seasonal pattern of the first late primary attack of *P. vivax* malaria in veterans is quite similar to that observed during the Korean War, which means that the basic biologic characteristics of *P. vivax* with regard to relapse has been maintained for several decades on the Korean Peninsula. Although our study was limited to the patients, compliance of ROK military personnel to chemoprophylaxis was very poor, which is similar to previous results. Mass chemoprophylaxis contributed to the decrease in malaria cases among military personnel, and the chemoprophylaxis program was expanded annually from 16,000 in 1997 to more than 200,000 in 2007 despite poor compliance of soldiers. Prophylactic failure cases with high enough plasma concentrations of hydroxychloroquine have constantly occurred possibly because of the mass chemoprophylaxis, and chloroquine-resistant *P. vivax* malaria cases have been recently reported in ROK, suggesting a scale down of chemoprophylaxis. Continuous surveillance and monitoring are warranted to prevent further expansion of *P. vivax* malaria in ROK.

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Authors’ addresses: Gyo Jun, Department of Biochemistry, Graduate School of Medicine, Gachon University of Medicine and Science, 354-2 Yeonsu-dong, Yeonsu-gu, Incheon 460-799, Republic of Korea. Joon-Sup Yecom, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 108 Pyung-dong, Chongno-gu, Seoul 110-746, Republic of Korea. Jee-Young Hong, Department of Preventive Medicine, Konyang University College of Medicine, 685 Gasuwon-dong, Seo-gu, Daejeon 302-718, Republic of Korea. E-Hyun Shin and Kyu-Sik Chang, Division of Medical Entomology, Korea Centers for Disease Control and Prevention, 194 Tongil-ro, Eunpyung-gu, Seoul 122-701, Republic of Korea. Jae-Ran Yu, Division of Malaria and Parasitic Diseases, Korea Centers for Disease Control and Prevention, 194 Tongil-ro, Eunpyung-gu, Seoul 122-701, Republic of Korea. Sejoong Oh, Korean Armed Forces Medical Command, P.O.B. (No.) 100, Yool-dong, Bundang-gu, Seongnam-si, Gyeonggi-do 463-040, Republic of Korea. Hyeok Chung, Department of Microbiology, Graduate School of Medicine, Gachon University of Medicine and Science, 534-2 Yeonsu-dong, Yeonsu-gu, Incheon 406-799, Republic of Korea. Jae-Won Park, Department of Medical Research Institute (no. C-A8-218-1).

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