Chemoprophylaxis and the epidemiological characteristics of re-emergent *P. vivax* malaria in the Republic of Korea

Changsoo Kim,[a] Dong Chun Shin,[a] Tai Soon Yong,[b] Dae Kyu Oh,[c] Rock Kwon Kim,[d] Keeho Park,[c] & Il Suh[a]

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 *Plasmodium vivax* malaria, using a nationwide malaria database.

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

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.

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

Bulletin of the World Health Organization 2006;84:827-834.

Voir page 833 le résumé en français. En la página 833 figura un resumen en español.

يمكن الاطلاع على الملخص بالعربية في صفحة 833.

Introduction

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.[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).[2] Since 1993, the number of malaria cases has increased exponentially, particularly among soldiers based near the DMZ.[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.[6,7] Recently, although there have been no reports of treatment failure in ROK, an increase in late primary episodes of *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.[8]

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

Methods

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

[a] Department of Preventive Medicine, Yonsei University College of Medicine, 134 Shinchon-Dong, Seodaemun-Gu, Seoul 120-752, Seoul, Republic of Korea. Correspondence to Il Suh (email: isuh@yumc.yonsei.ac.kr).

[b] Department of Parasitology, Yonsei University College of Medicine, Seoul, Republic of Korea.

[c] Korea Center for Disease Control and Prevention, Seoul, Republic of Korea.

[d] The Armed Forces Medical Command, Seoul, Republic of Korea.

Ref No. **05-029546**

(*Submitted: 29 December 2005 – Final revised version received: 3 April 2006 – Accepted: 18 April 2006*)

Table 1. **Antimalarial chemoprophylaxis and insecticide-treated materials[a] received by soldiers in the Republic of Korea army**

Precaution	Year			
	1999	2000	2001	2002
Chemoprophylaxis (No. of soldiers)	61 772	90 000	109 476	141 780
Period of chemoprophylaxis:				
Chloroquine[b]	7 June–11 October	5 June–9 October	14 May–24 September	13 May–23 September
Primaquine[c]	12–25 October	3–16 October	18 September–1 October	17–30 September
Insecticide-treated materials[a] (No. of soldiers)	80 000	80 000	150 692	157 361

[a] Permethrin (6.4 g per person for 3 months) was used to treat battle-dress uniforms and bednets.
[b] Hydroxychloroquine sulfate at a weekly dose of 400 mg.
[c] Primaquine base at a daily dose of 15 mg.

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.[4,9] 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. Cases in soldiers who had entered the ROK army between 1 March and 30 April (who would retire during a malaria risk period) or who retired during a malaria risk period were excluded because we could not discriminate between early (individuals infected in the year of retirement) and late (individuals infected in the year before retirement) primary attacks. Therefore, the subjects exposed to risk of malaria for the first time between 1999 and 2001 were those who had entered military service between the beginning of October 1998, 1999, or 2000 and the end of the respective following February 1999, 2000 or 2001.

During the study period, 1215 cases of *P. vivax* malaria were reported. Of these, 56 in soldiers who had been in malaria risk areas after retirement (46 received chemoprophylaxis during military duty and 10 did not) and one case from Africa were excluded. Ultimately, 1158 cases were analysed.

Statistical analysis

Cohorts of individuals exposed to risk of malaria in each year between 1999 and 2001 were constructed. Early and late primary attacks were defined as cases occurring ≤ 2 or > 2 months after the last day of the malaria risk period, respectively.

This study included all cases that occurred among defined populations; we therefore fixed the denominator in the chemoprophylaxis and no-chemoprophylaxis groups such that the cases represent the epidemiological characteristics of *P. vivax* malaria in each group. To analyse the proportional difference in early and late primary attacks between the groups that did or did not receive chemoprophylaxis, we divided the 1158 cases into two groups according to the timing of symptom onset ("before" and "after" the second round of chemoprophylaxis began) because the number of soldiers receiving chemoprophylaxis changed each year. All cases that were primary attacks were followed until 31 December 2003 after treating the first attack.

Ethical issues

This study was approved by the Ethical and Security Committee for clinical research at Office of Surgeon General, Army Headquarters, Gyeryong, Republic of Korea.

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

First year of exposure	No. of patients[a]	Onset of symptoms[b]		
		First year[c]	Second year[a]	Third year[a]
1999	590 (209)	28	351 (2)	211 (207)
2000	370 (138)	30	201	139 (138)
2001	198 (80)	10	106	82 (80)
Total	**1158 (427)**	**68**	**657 (2)**	**432 (425)**

[a] Figures in parentheses are numbers of cases that occurred after retirement.
[b] 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.
[c] Cases that occurred in the first year of exposure.

Results

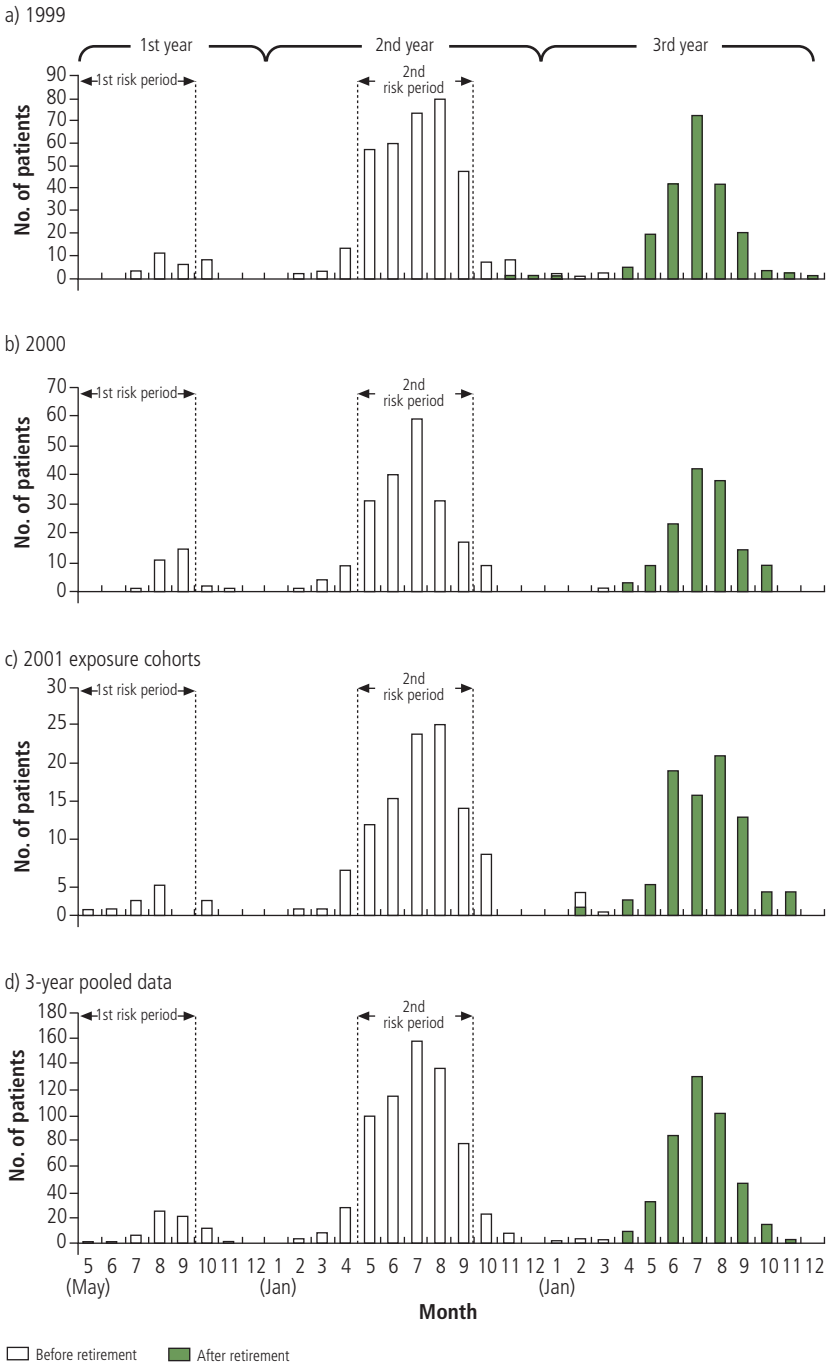
Of the 1158 cases, 634 (72.0%) had received chemoprophylaxis during military duty, and 324 (28.0%) had not. All cases were among soldiers stationed in malaria risk areas during military duty.

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 no-chemoprophylaxis 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 1158 cases, 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.

Fig. 1. **Monthly distribution for cases of *P. vivax* malaria in soldiers and veterans of the army of the Republic of Korea, for each exposure cohort**



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 *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.

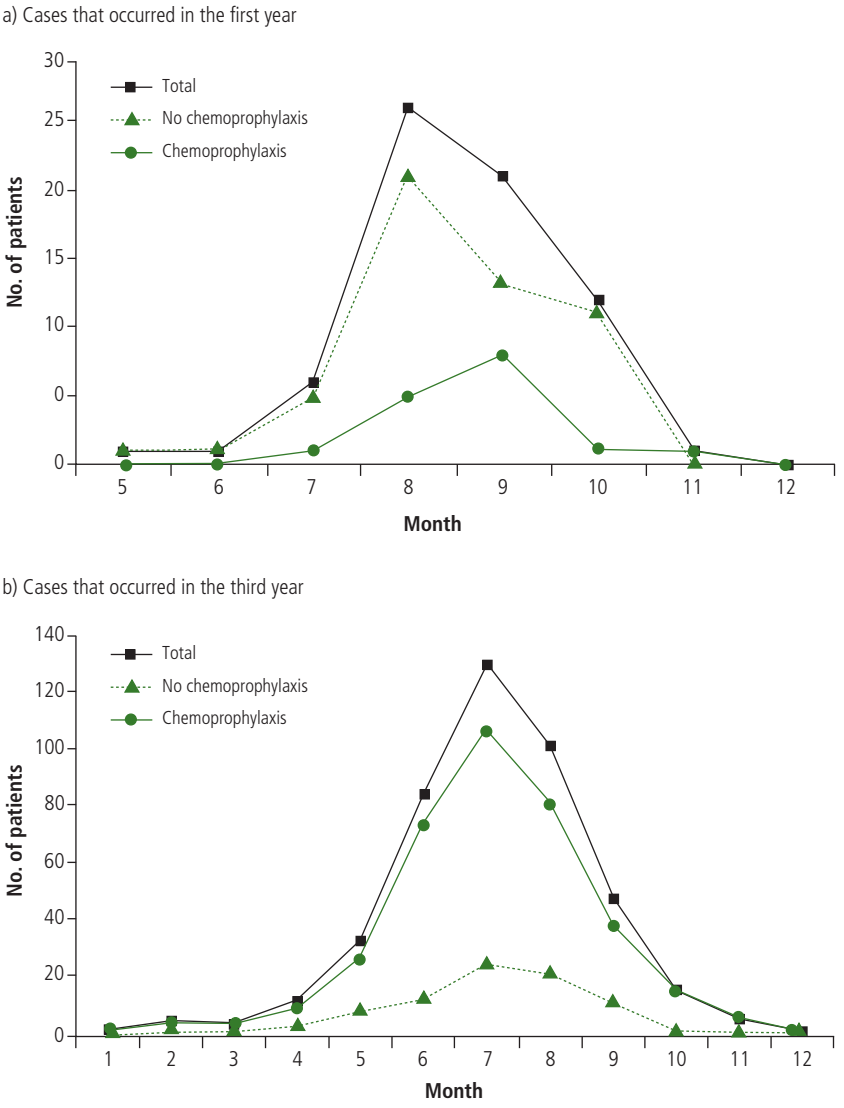
Discussion

Early primary attacks are usually defined as cases occurring ⩽ 1 month after exposure[10,11]; however, to investigate the epidemiological characteristics of re-emergent *P. vivax* malaria, we defined early onset as cases occurring ⩽ 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.[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 *P. vivax* malaria had both short and long latency periods and that most cases had a long latency, characteristic of *P. vivax* malaria in temperate regions.[13–15] A recent study also suggested that two-thirds of re-emergent cases of *P. vivax* malaria had a long latency, with a mean duration of 10 months, although long-latency forms of *P. vivax* malaria might have been overrepresented because only cases that occurred after retirement were included.[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 *P. vivax* malaria has epidemiological characteristics that differ from those of the *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.[13] Moreover, the use of antimalarial chemoprophylaxis can change the pattern of malaria occurrence. Although genetic evidence suggests that re-emergent *P. vivax* has a Chinese or Democratic People's Republic of Korean origin,[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 *P. vivax* in ROK is similar to that of Thai isolates.[19] However, we can not 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 *P. vivax* malaria, further molecular epidemiological analysis is needed.

Fig. 2. **Monthly distribution of cases of *P. vivax* malaria during the first and third years of follow-up in soldiers and veterans of the army of the Republic of Korea**



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.

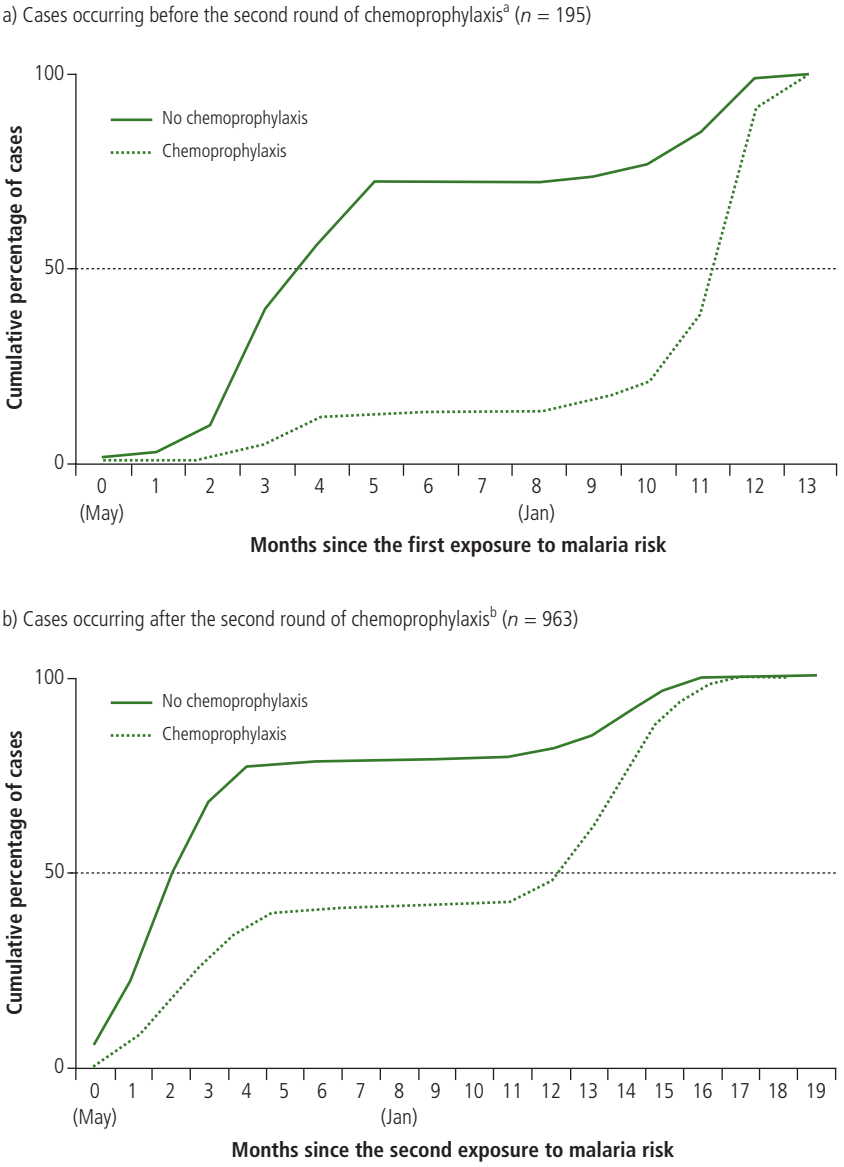
First, primaquine may not effectively reduce late primary attacks; a recent study in ROK reported that the effectiveness of primaquine prophylaxis against late primary attacks was 32%,[8] and that the doses of primaquine used in ROK would be considered inadequate in other countries.[20–24] In this study, 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 re-treated 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.[25] If the effects of chloroquine are not considered, the efficacy of prophylaxis with primaquine could be significantly underestimated owing to symptom onset delay.[8]

Primaquine is the only available drug that eliminates liver-stage parasites, although other drugs such as tafenoquine and malarone are being tested.[20,26,27] Primaquine is a long-term medication (usually 14 days), and low compliance can be a problem.[28] 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

Fig. 3. **Cumulative percentage of *P. vivax* malaria cases that occurred before and after the start of the second round of chemoprophylaxis**



[a] Using the history of first chemoprophylaxis.
[b] Using the history of second chemoprophylaxis.

Table 3. **Cases of *P. vivax* malaria that occurred before or after the start of the second round of chemoprophylaxis in soldiers and veterans of the Republic of Korea army**

Chemoprophylaxis		No. of patients	Latency period		*P*-value[a]
			Early	Late	
Before[b]	Yes	123 (100)[c]	16 (13.0)	107 (87.0)	<0.001
	No	72 (100)	52 (72.2)	20 (27.8)	
	Total	195 (100)	68 (34.9)	127 (65.1)	
After[d]	Yes	598 (100)	244 (40.8)	354 (59.2)	<0.001
	No	365 (100)	286 (78.4)	79 (21.6)	
	Total	**963 (100)**	**530 (55.0)**	**433 (45.0)**	

[a] χ^2 test.
[b] History of first chemoprophylaxis.
[c] Figures in parentheses are percentages.
[d] History of second chemoprophylaxis.

in ROK. In this study, most of those who had late primary attacks had not taken primaquine regularly. Thus, to effectively reduce malaria among soldiers and veterans, a continuing education programme and strict compliance with chemoprophylaxis are essential.

Some studies have suggested that, because mass antimalarial chemoprophylaxis in endemic areas dose not reduce malaria transmission, other preventive measures such as insecticide-treated battle dress uniforms and bednets, and residual spraying are critical for controlling transmission.[6,7,29] 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 over-estimated 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.[5]

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. ■

Acknowledgments

We thank Terry A Klein, Minh C Hoang, Youngkeun Kim, and Donghoon Ko for their comments on an early version of the manuscript.

Competing interests: none declared.

Résumé

Chimioprophylaxie et caractéristiques épidémiologiques du paludisme à *P. vivax* réémergent en République de Corée

Objectif En République de Corée, les soldats stationnés dans des zones où ils étaient exposés à un risque de contracter le paludisme reçoivent une chimioprophylaxie antipalustre depuis 1997. Cependant, ce traitement peut faciliter le développement d'une pharmacorésistance et les accès primaires tardifs deviennent de plus en plus fréquents chez les individus l'ayant reçu. On a étudié les possibilités d'associations entre cette chimioprophylaxie d'une part et les caractéristiques épidémiologiques du paludisme à *Plasmodium vivax* réémergent et l'efficacité du traitement d'autre part en utilisant une base de données mondiale sur le paludisme.
Méthodes Parmi les soldats exposés à un risque de paludisme entre 1999 et 2000, on a étudié tous les cas de paludisme à *P. Vivax* (1158) apparus avant le 31 décembre 2003. Les accès précoces et tardifs ont été définis respectivement comme les cas survenant dans un délai $\leqslant$ 2 mois ou $>$ 2 mois après le dernier jour d'exposition au risque de paludisme.
Résultats Parmi ces cas, 634 (72,0 %) avaient reçu une chimioprophylaxie antipalustre et 324 (28,0 %) non. Les cas de paludisme sont apparus principalement en été, avec un pic en juillet-août. La stratification par antécédents de chimioprophylaxie a fait apparaître des différences dans les délais d'apparition. Une plus forte prévalence des accès précoces a été relevé dans le groupe n'ayant pas reçu de chimioprophylaxie, tandis que dans le groupe traité, la plupart des cas correspondaient à des accès primaires tardifs. Parmi ces derniers, 312 parmi 461 (67,7 %) ne prenaient pas régulièrement leur primaquine. Après le traitement du premier accès, 14 individus (1,2 %) parmi 1158 ont dû être retraités ; tous les cas retraités ont été guéris en utilisant la même posologie et le même schéma thérapeutique que pour le premier traitement.
Conclusion En République de Corée, il existe une association entre l'augmentation des cas d'accès primaires de paludisme à *P. Vivax* réémergent et l'utilisation d'une chimioprophylaxie antipalustre.

Resumen

Quimioprofilaxis y epidemiología de la malaria reemergente por *P. 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 1997. Sin embargo, la quimioprofilaxis puede facilitar la aparición de farmacorresistencia, 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* (1158) registrados antes del 31 de diciembre de 2003. Se definieron como ataques primarios tempranos o tardíos los casos ocurridos $\leqslant$ 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 retratados 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.

ملخص

الوقاية الكيميائية والخصائص الوبائية للملاريا المنبعثة من جديد الناجمة عن المتصورات النشيطة في جمهورية كوريا

الهدف: يتلقَّى الجنود الذين يعسكرون في مناطق يسودها خطر العدوى بالملاريا في جمهورية كوريا الوقاية الكيميائية من الملاريا منذ عام 1997؛ إلا أن المعالجة الكيميائية قد تسهل من حدوث المقاومة للأدوية مما يؤدي لازياد ظهور هجمات بدئية متأخرة لدى أفراد سبق لهم أن تلقوا وقاية كيميائية. وقد استقصينا ترافق الوقاية الكيميائية بالخصائص الوبائية وبفعالية المعالجة للملاريا المنبعثة من جديد الناجمة عن المتصورات النشيطة، بالاستفادة من قاعدة معطيات وطنية عن الملاريا.
الطريقة: استعرضنا جميع حالات الملاريا الناجمة عن المتصورات النشيطة التي حدثت في الفترة بين عامي 1999 و2001 بين صفوف الجنود المعرَّضين لخطر الإصابة بالملاريا، ووجدنا أن عدد هذه الحالات التي وقعت قبل 31 كانون الأول/ديسمبر من عام 2003 قد بلغ 1158 حالة. وقد عُرِّفت الهجمات البدئية الباكرة بأنها الحالات التي تقع قبل شهرين أو أقل من آخر يوم للتعرض لخطر الإصابة بالملاريا، فيما عُرِّفت الهجمات البدئية المتأخرة بأنها الحالات التي تقع بعد أكثر من شهرين من آخر يوم للتعرض لخطر الإصابة بالملاريا.
الموجودات: من بين الحالات التي بلغ تعدادها 1158 حالة، كان 634 حالة (72%) قد تلقَّى وقاية كيميائية، و324 حالة (28%) لم تتلق معالجة كيميائية. وقد حدثت معظم الحالات في الصيف، وبلغت أقصاها في شهرَيْ تموز/يوليو وآب/أغسطس. ولدى تحليل قصة الوقاية الكيميائية إلى طبقات تبين أن البدء بها كان في أوقات متفاوتة. وكانت الهجمات البدئية الباكرة أكثر شيوعاً لدى المجموعة التي لم تتلق وقاية كيميائية، فيما كانت معظم الحالات التي تلقت الوقاية الكيميائية من الهجمات البدئية المتأخرة؛ ومن هؤلاء المصابين بالهجمات البدئية المتأخرة كان 312 حالة من بين 461 حالة (67.7%) لم يتلقوا البريماكين بشكل منتظم. وبعد معالجة الهجمة الأولى أعيدت معالجة (14) حالة من بين 1158 حالة (1.2%) وتحقق شفاء جميع الحالات التي أعيدت معالجتها باستخدام نفس الجرعات والنظم العلاجية التي استخدمت في المعالجة الأولى.
الاستنتاج: هناك ازدياد في الهجمات البدئية المتأخرة للملاريا المنبعثة من جديد الناجمة عن المتصورات النشيطة في جمهورية كوريا، وترافق باستخدام الوقاية الكيميائية.

References

1. World Health Organization. Synopsis of the world malaria situation, 1979. *Wkly Epidemiol Rec* 1981;56:145-9.
2. Chai IH, Lim GI, Yoon SN, Oh WI, Kim SJ, Chai JY. Occurrence of tertian malaria in a male patient who has never been abroad. [In Korean.]. *Korean J Parasitol* 1994;32:195-200.
3. Lee JS, Lee WJ, Cho SH, Ree HI. Outbreak of vivax malaria in areas adjacent to the demilitarized zone, South Korea, 1998. *Am J Trop Med Hyg* 2002;66:13-7.
4. Park JW, Klein TA, Lee HC, Pacha LA, Ryu SH, Yeom JS, et al. Vivax malaria: a continuing health threat to the Republic of Korea. *Am J Trop Med Hyg* 2003;69:159-67.
5. Korea Center for Disease Control and Prevention. Epidemiology of malaria in Korea, 2003. *CDMR* 2004;15:85-91.
6. Seidlein L, Greenwood B. Mass administrations of antimalarial drugs. *Trends Parasitol* 2003;19:452-60. Medline doi:10.1016/j.pt.2003.08.003
7. Greenwood B. The use of anti-malarial drugs to prevent malaria in the population of malaria-endemic areas. *Am J Trop Med Hyg* 2004;70:1-7.
8. Park K, Kang JK. Effectiveness of primaquine terminal prophylaxis against late primary attacks of *P. vivax* malaria: a case-control study among troops of the Republic of Korea Army. *Trans R Soc Trop Med Hyg* 2003;97:441-2. Medline doi:10.1016/S0035-9203(03)90083-6
9. Yeom JS, Ryu SH, Oh S, Choi DH, Song KJ, Oh YH, et al. Evaluation of anti-malarial effects of mass chemoprophylaxis in the Republic of Korea army. *J Korean Med Sci* 2005;20:707-12.
10. Gilles HM, Warrell DA. *Bruce-Chwatt's essential malariology*. Third Edition. Boston: Edward Arnold Press; 1993. p. 127-31.
11. Schwartz E, Parise M, Kozarsky P, Cetron M. Delayed onset of malaria — implications for chemoprophylaxis in travelers. N Engl J Med 2003; 349:1510-6. Medline doi:10.1056/NEJMoa021592
12. Kim HC, Lee KW, Miller WB, Strickman D. Seasonal prevalence of mosquitoes collected from light traps in Korea (1997–1998). Korean J Entomol 2001; 31:7-13.
13. Cogswell FB. The hypnozoite and relapse in primate malaria. *Clin Microbiol Rev* 1992;5:26-35.
14. Shute PG, Lupascu G, Branzei P, Maryon M, Constantinescu P, Bruce-Chwatt LJ, et al. A strain of *Plasmodium vivax* characterized by prolonged incubation: the effect of numbers of sporozoites on the length of the prepatent period. *Trans R Soc Trop Med Hyg* 1977;70:474-81. Medline doi:10.1016/0035-9203(76)90132-2
15. Tiburskaja NA, Vrublevskaja OS. T*he course of infection caused by the North Korean strain of vivax malaria.* Geneva: World Health Organization; 1977. WHO document WHO/MAL/77.895.
16. Oh MD, Shin H, Shin D, Kim U, Lee S, Kim N, et al. Clinical features of vivax malaria. *Am J Trop Med Hyg* 2001;65:143-6.
17. Kho WG, Park YH, Chung JY, Kim JP, Hong ST, Lee WJ, et al. Two new genotypes of *Plasmodium vivax* circumsporozoite protein found in the Republic of Korea. *Korean J Parasitol* 1999;37:265-70.
18. Han ET, Park JH, Shin EH, Choi MH, Oh MD, Chai JY. Apical membrane antigen-1 (AMA-1) gene sequences of re-emerging *Plasmodium vivax* in South Korea. *Korean J Parasitol* 2002;40:157-62.
19. Lim CS, Kim SH, Kwon SI, Song JW, Song KJ, Lee KN. Analysis of *Plasmodium vivax* merozoite surface protein-1 gene sequences from resurgent Korean isolates. *Am J Trop Med Hyg* 2000;62:261-5.
20. Baird JK, Hoffman SL. Primaquine therapy for malaria. *Clin Infect Dis* 2004; 39:1336-45. Medline doi:10.1086/424663
21. Rajgor DD, Gogtay NJ, Kadam VS, Kamtekar KD, Dalvi SS, Chogle AR, et al. Efficacy of a 14-day primaquine regimen in preventing relapses in patients with *Plasmodium vivax* malaria in Mumbai, India. *Trans R Soc Trop Med Hyg* 2003;97:438-40. Medline doi:10.1016/S0035-9203(03)90082-4
22. Looareesuwan S, Buchachart K, Wilairatana P, Chalermrut K, Rattanapong Y, Amradee S, et al. Primaquine-tolerant vivax malaria in Thailand. *Ann Trop Med Parasitol* 1997;91:939-43. Medline doi:10.1080/00034989760338
23. Baird JK, Fryauff DJ, Hoffman SL. Primaquine for prevention of malaria in travelers. *Clin Infect Dis* 2003;37:1659-67. Medline doi:10.1086/379714
24. Yi KJ, Chung MH, Kim HS, Kim CS, Pai SH. A relapsed case of imported tertian malaria after a standard course of hydroxychloroquine and primaquine therapy. *Korean J Parasitol* 1998;36:143-6.
25. Barid JK. Rieckmann. Can primaquine therapy for vivax malaria be improved? *Trends Parasitol* 2003;19:115-20. Medline doi:10.1016/S1471-4922(03)00005-9
26. Brueckner RD, Lasseter KC, Lim ET, Schuster BG. First-time-in humans safety and pharmacokinetics of WR238605, a new antimalarial. *Am J Trop Med Hyg* 1998;58:645-9.
27. Lell B, Faucher JF, Missinou MA, et al. Malaria chemoprophylaxis with tafenoquine: a randomized study. *Lancet* 2000;355:2041-5. Medline doi:10.1016/S0140-6736(00)02352-7
28. Kotwal RS, Wenzel RB, Sterling RA, Porter WD, Jordan NN, Petruccelli BP. An outbreak of malaria in US army rangers returning from Afghanistan. *JAMA* 2005;293:212-6. Medline doi:10.1001/jama.293.2.212
29. Hung le Q, Vries PJ, Giao PT, Nam NV, Binh TQ, Chong MT, et al. Control of malaria: a successful experience from Viet Nam. *Bull World Health Organ* 2002;80:660-6.
30. Chai JY. Re-emerging *Plasmodium vivax* malaria in the Republic of Korea. *Korean J Parasitol* 1999;37:129-43.
31. Kho WK, Jang JY, Hong ST, Lee HW, Lee WJ, Lee JS. Border malaria characters of reemerging vivax malaria in the Republic of Korea. *Korean J Parasitol* 1999;37:71-6.
32. Yeom JS, Ryu SH, Oh S, Lee WJ, Kim TS, Kim KH, et al. Status of *Plasmodium vivax* malaria in the Republic of Korea during 2001-2003. *Am J Trop Med Hyg* 2005;73:604-8.
33. Korea Center for Disease Control and Prevention. Support for malaria control in North Korea. *CDMR* 2005;16:108.

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**

Chemoprophylaxis received		No. of patients	Latency period		*P*-value[a]
First year	Second year		Early	Late	
Yes	Yes	443 (100)[b]	220 (49.7)	223 (50.3)	< 0.001
	No	113 (100)	113 (100.0)	0 (0.0)	
	Total	556 (100)	333 (59.9)	223 (40.1)	
No	Yes	155 (100)	24 (15.5)	131 (84.5)	< 0.001
	No	252 (100)	173 (68.7)	79 (31.3)	
	Total	407 (100)	197 (48.4)	210 (51.6)	

[a] χ^2 test.
[b] Figures in parentheses are percentages.