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VIVAX MALARIA: A CONTINUING HEALTH THREAT TO THE REPUBLIC OF KOREA

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Abstract. Vivax malaria reemerged in the Republic of Korea in 1993. Most of the cases occurred among soldiers in the region adjacent to the Demilitarized Zone (DMZ) until 1995. To determine the rate of dispersion of vivax malaria, we evaluated its epidemiologic characteristics. Of 13,903 cases of vivax malaria reported in 2000, 40.1% (5,577) were reported among Republic of Korea military personnel, 26.2% (3,641) among veterans discharged less than two years from the military, and 33.7% (4,685) among civilians. Cases of vivax malaria have rapidly increased annually among counties bordering the DMZ, and have spread to approximately 40 km south of the DMZ. Chemoprophylaxis administered to military personnel may have been responsible for the decreasing number of cases among the Republic of Korea military population. The first mosquito-transmitted cases appeared in early June. Therefore, chemoprophylaxis should be instituted in early April to reduce the number of infected mosquitoes. Extensive intervention is warranted to reduce the spread of vivax malaria in the Republic of Korea.

INTRODUCTION

Plasmodium vivax, the causative agent of vivax malaria (benign tertian malaria) in the Republic of Korea, was endemic on the Korean Peninsula for many centuries until the late 1970s, when the Republic of Korea was declared malaria free.[1] Temperate zone vivax malaria is able to survive cold winters due, in part, to its long incubation period of more than six 6 months (some reports indicate a period as long as 18 months) in some patients who become infected.[2–5] Malaria transmission is initiated annually when latent forms (stages) of *P. vivax* leave the liver and enter the blood of infected persons the following malaria season, resulting in disease, an increased reservoir population, and new mosquito infections. Most malaria transmission is attributed to latent malaria that emerges the following year, since data show that the proportion of asysmptomatic carriers is very low (0.05–0.4%) (Park J-W and others, unpublished data).

Vivax malaria is a major public health threat in the Republic of Korea that affects both civilian and military communities. During the Korean War (1950–1953), approximately 15% of all febrile illnesses among Republic of Korea army personnel were due to malaria.[6–8] From the beginning of the Korean War, U.S. soldiers were given chemoprophylaxis, so the severity of the malaria problem was not realized until 1951 when soldiers rotated home on leave and discontinued malaria suppression therapy.[8] However, in 1953 more than 3,000 U.S. soldiers and nearly 9,000 Republic of Korea army soldiers were diagnosed with malaria.[7,9] In 1954, following the signing of the armistice and reduced hostilities, malaria cases decreased to fewer than 6,000 among the Republic of Korea army soldiers. As socioeconomic conditions in the Republic of Korea improved and associated malaria control efforts were strengthened, the Republic of Korea was finally declared malaria free in 1979.[1] However, focal indigenous cases that originated from imported cases continued to be reported until 1984.[10]

In 1993, malaria reemerged in the Republic of Korea when the first case was diagnosed in a Republic of Korea army soldier stationed in Paju County, near the Demilitarized Zone (DMZ) that divides the Republic of Korea (South Korea) and the Democratic People's Republic of Korea (North Korea).[11] Since 1993, the annual incidence of vivax malaria has increased, with more than 2,000 cumulative cases reported by the end of 1997.[12] During this period, malaria has largely been confined to the northern part of Kyonggi Province and the northwestern part of Gangwon Province near the DMZ where many Republic of Korea army personnel are stationed.[12]

To meet the potential for a military incursion, large numbers of Republic of Korea soldiers and more than 10,000 U.S. soldiers are stationed along the DMZ. Most Republic of Korea soldiers are stationed in confined areas for their entire period of duty (26 months), while most U.S. soldier's tours of duty are 12 months. For U.S. personnel, patient travel history is reported and blood samples from malaria patients are taken for parasite DNA analysis to eliminate malaria that is acquired outside of Korea. Republic of Korea military veterans previously assigned to malaria-risk areas may directly impact the spread of malaria throughout the Republic of Korea because they travel to and reside in areas with little or no malaria. Civilians in the Republic of Korea who reside in and/or travel to high-risk areas also may become infected and contribute to the spread of malaria upon their return to areas of lower risk. Also, U.S. soldiers, after serving and training in high-risk malaria areas along the DMZ, may become ill several months after they return to United States, resulting in the reintroduction of vivax malaria.[13] To determine the rate of dispersion of vivax malaria, we evaluated the epidemiologic characteristics, i.e., geographic dispersion, monthly and annual incidence, and short incubation malaria cases in the Republic of Korea.

MATERIALS AND METHODS

Malaria is one of the communicable diseases (Group III) that are reportable to the Ministry of Health and Welfare in

the Republic of Korea. All cases of malaria in military personnel must be reported to the Office of the Surgeon General, Army Headquarters, and the Ministry of Health and Welfare. The case definition of malaria includes any febrile illness[1] and demonstration of *P. vivax* parasites in peripheral blood smears.[2] All cases of vivax malaria that were reported by the Korean Ministry of National Defense from January 1, 1993 through December 31, 2000 were reviewed and their epidemiologic characteristics (duty station, time of year at diagnosis, and time in service prior to diagnosis) were analyzed. Military populations assigned to areas near the DMZ remained constant throughout the study period. However, these populations and their distributions are not reported due to national security.

Malaria case data among Republic of Korea military veterans and civilians were collected by the Department of Epidemiology, National Institute of Health (Seoul, Republic of Korea). Cases among military veterans were defined as those who 1) had a malaria attack within 24 months after discharge from military service, and 2) had been stationed in a malaria-risk area. Otherwise, veterans are reported as civilians. Malaria-risk areas were defined as those areas where malaria cases were reported during the preceding year(s). Data for veterans and civilians were analyzed in the same way as the Republic of Korea Army data. Because of the mandatory 26-month Republic of Korea military duty, most veterans who were stationed in malaria-risk areas were exposed to malaria-infected mosquitoes for two consecutive transmission seasons (May through October).

Epidemiologic investigations for the Eighth U.S. Army personnel who contracted and were diagnosed with malaria in the Republic of Korea were conducted. Additionally, U.S. soldiers diagnosed with malaria in the United States that was attributed to exposure in the Republic of Korea are reported. Suspected areas of transmission were identified through reported travel/training history in malaria-risk areas.

The annual geographic distribution of malaria in Republic of Korea military personnel and veterans was determined by grouping malaria cases by city and/or county where the patients were stationed when the malaria diagnosis was made. The geographic distribution of malaria for the civilian population was determined by grouping cases by city and/or county where the patients had resided when the diagnosis was made. For U.S. military members with duty/training in malaria-risk areas and diagnosed with vivax malaria in the Republic of Korea, the most likely locations of transmission were reported.

The overall history of chloroquine and primaquine chemoprophylaxis among the Republic of Korea Army soldiers and Eighth U.S. Army soldiers was reviewed and compared with annual malaria rates.

RESULTS

A total of 13,903 cases of vivax malaria were reported from January 1, 1993 through December 31, 2000 (Table 1). Of these, 40.1% (5,577) were reported among Republic of Korea military personnel, 26.2% (3,641) were reported among veterans who had been in malaria-risk areas and were discharged from military service for two or less years, and 33.7% (4,685) were reported among civilians and veterans who were discharged from military service for more than two years. Since the reintroduction of vivax malaria in 1993 through 1996, more than 80% of the reported malaria cases occurred among Republic of Korea soldiers. From 1996 onward, the number of cases among the group of veterans increased annually through 2000, when it paralleled that of Republic of Korea soldiers. Similar annual trends were observed in the civilian populations through 1998. For 1999 and 2000, civilian cases exceeded those of Republic of Korea soldier and veteran populations.

TABLE 1

Annual incidence of vivax malaria among Republic of Korea Army military personnel, veterans (retired/discharged soldiers), and civilian personnel

	1993	1994	1995	1996	1997	1998	1999	2000	Total
Soldiers	1	18	88	287	1,155	1,655	1,085	1,288	5,577
Veterans*	0	1	12	25	207	1,127	996	1,273	3,641
Civilians†	0	2	7	46	361	1,148	1,541	1,580	4,685
Total	1	21	107	358	1,723	3,930	3,622	4,141	13,903

* Veterans include soldiers who were retired or discharged from the miliary for ≤2 years and previously assigned to a malaria-risk area.
† Civilians include veterans who were discharged from the military for >2 years.

The first case of vivax malaria attributed to exposure in the Republic of Korea among U.S. military personnel was reported in 1994. Although no cases were reported in 1995, 14 cases (diagnosed in the Republic of Korea and the United States) were reported in 1996. The number of annual cases increased through 1999, but decreased in 2000 (Table 2). Most malaria cases in U.S. military personnel were suspected to have been contracted during training at sites within 25 km of the DMZ.

The reemergence of malaria was first reported in Paju County in July 1993 and expanded geographically annually (Figure 1). During 1994 and 1995, the majority of malaria cases were reported for soldiers that had been exposed in the northern areas of Gimpo, Paju, and Yeoncheon Counties near the DMZ. In 1996, malaria increased and expanded both laterally along the DMZ to include Gangwha (west coast) and Cheolwon (central region) Counties and south to Goyang and Inchon Counties, bordering northwest Seoul. By 1997, malaria was endemic in the Republic of Korea, with the number of cases continuing to increase throughout the malaria-risk areas and expanding southeast into Hwacheon County. By 1998, malaria cases expanded into northeastern areas of Yanggu and Inje Counties, and limited foci of vivax malaria developed along the east coast near the DMZ of Goseong County. Through 2000, the annual number of malaria patients reported from counties bordering Seoul continued to in-

TABLE 2

Number of malaria cases among United States Eighth Army personnel and Korean Augmentees to the U.S. Army from 1993 through 2000

	1993	1994	1995	1996	1997	1998	1999	2000
Diagnosed in Korea	0	1	0	12	27	22	20	16
Diagnosed in United States	0	0	0	2	7	25	28	24
Total	0	1	0	14	34	47	48	40

crease, with transmission reported to occur in developing areas surrounding Seoul, approximately 40 km south of the DMZ.

Similar increases in the distribution of malaria cases were observed among civilian populations. These were associated with the geographic distribution and increases among Republic of Korea military personnel. However, while malaria cases among the civilian population increased through 2000 in most counties, they decreased in the Republic of Korea Army population adjacent to the DMZ during 1999 (Paju, Yeonchon, and Cheolwon Counties) and 2000 (Paju, Goyang, and Gimpo Counties). Although malaria cases in the Republic of Korea Army increased in Yeonchon and Cheolwon Counties in 2000, they were still less than the numbers of cases detected in 1998.

Most malaria cases were diagnosed from June through September, with a unimodal peak in August–September (Figure 2). However, during 1999 and 2000, the incidence reached its peak in late May, decreased by late/mid June after chemoprophylaxis was initiated in military populations, then peaked again in mid-July, and maintained a high level until late August when the number of cases decreased, as in previous years.

To determine when malaria transmission from humans to mosquitoes to humans had begun to occur, we examined cases with a short incubation period among Republic of Korea Army soldiers who 1) contracted malaria and 2) had been exposed to malaria for only one season (they entered military service in or after November of the previous year). The results show that the first cases of malaria with a short incubation period due to infected mosquitoes occurred in early June (Figure 3).

The Republic of Korea military initiated chloroquine chemoprophylaxis to nearly 16,000 soldiers in 1997 (Table 3). The number of soldiers given chemoprophylaxis increased annually thereafter until more than 90,000 soldiers were given chemoprophylaxis by 2000. At the annual termination of chloroquine chemoprophylaxis, a two-week regimen of 15 mg of primaquine was provided to soldiers who were given chloroquine chemotherapy to eliminate latent liver parasite stages.

Similarly, the Eighth U.S. Army provided limited chemoprophylaxis to its military personnel during 1997 and initiated a chemoprophylaxis policy that expanded drug usage for U.S. soldiers in 1998, with 8,780 soldiers given chemoprophylaxis by 1999 (Table 3). However, the chemoprophylaxis policy was changed in 2000 to include only those soldiers (1,159) who resided north of the Imjin River. The numbers of U.S. military personnel given chemoprophylaxis were reduced to include only those that resided in a high-risk area, identified as north of the Imjin River. Soldiers who resided in low-risk areas trained in this area for brief periods, and there appeared to be more cases of malaria imported into the United States as a result of chemoprophylaxis use.

DISCUSSION

Vivax malaria in Korea is classified as unstable malaria because conditions usually do not support widespread disease. Areas with unstable malaria usually have low rates of disease, but can occasionally have local epidemics due to climatic change, topography, agricultural change (reduction of livestock), inefficient vector control, and socioeconomic changes.[14] Contributing factors to malaria transmission instability include the short transmission season (May through October), high vector populations, and the zoophilic behavior of the principal malaria vector *Anopheles sinensis*.[14]

Because vivax malaria in the Republic of Korea has both a short incubation period and a longer 6–18-month long incubation (latent) period, many soldiers who were infected while serving near the DMZ did not experience a malaria attack until they were discharged and returned home or traveled to other parts of the Republic of Korea.[15] Because of the mandatory 26-month military duty, most veterans who were stationed in malaria-risk areas were exposed to malaria-infected mosquitoes for two consecutive transmission seasons (May through October). From the time the first case of reemerging vivax malaria was reported in 1993, more than 3,400 veterans developed malaria by 2000. These veterans, as well as civilians who traveled to and from malaria-endemic areas, potentially serve as a source of secondary infections among civilian populations located in areas where malaria-risk was low or had not been previously reported. So far, however, there have been no known cases contracted in either military or civilian personnel south of the Han River.

Patients are infective to mosquitoes several days prior to febrile episodes, as well as during and after the febrile period. Even after treatment with chloroquine, patients are infective for up to 36 hours after initial treatment. However, if chloroquine and primaquine are given concurrently, patients are infective for less than four hours after treatment.[16] While the mean time from the onset of symptoms to diagnosis has decreased from 23.6 days in 1995 to 8 days in 2000,[17] delay in diagnosis continues to provide reservoir populations for potential transmission from humans to mosquitoes.

The topography of Korea is comprised of approximately 70% mountains with intermittent valleys of various sizes. The Taebaeck Mountain Range is located in the northeastern half of Korea, extending from the Sino-Korean border through the DMZ and south, and dividing the east coast area from central Korea. The Kwangju Mountain Range forms a branch of the Taebaeck Mountain Range in North Korea, extending south and forming a central region barrier near the DMZ. The northwestern half of South Korea has fertile valleys where rice agriculture is the principal economic product, and forms the western corridor and the fertile western shore areas, including Inchon. These discrete valleys create the potential for geographic malaria foci that were shown to occur prior to the eradication of malaria from the Republic of Korea and since its reintroduction in 1993.

In addition, greater numbers of military personnel assigned to guard the DMZ are concentrated in valley areas (rice-growing regions) in preparation for armed intrusions, and are constantly exposed to biting mosquitoes while on patrol, training exercises, and other military operations. Troop movements from one foci to previously non-malarious areas or areas of low transmission of malaria increase the potential for the spread of malaria throughout the Republic of Korea.

Our data demonstrate that the geographic distribution of vivax malaria rapidly expanded since the first case appeared in 1993, following a long hiatus of autochthonous transmission. Initially, most of the cases were reported from areas adjacent to the mid-western part of the DMZ (Gimpo, Paju,

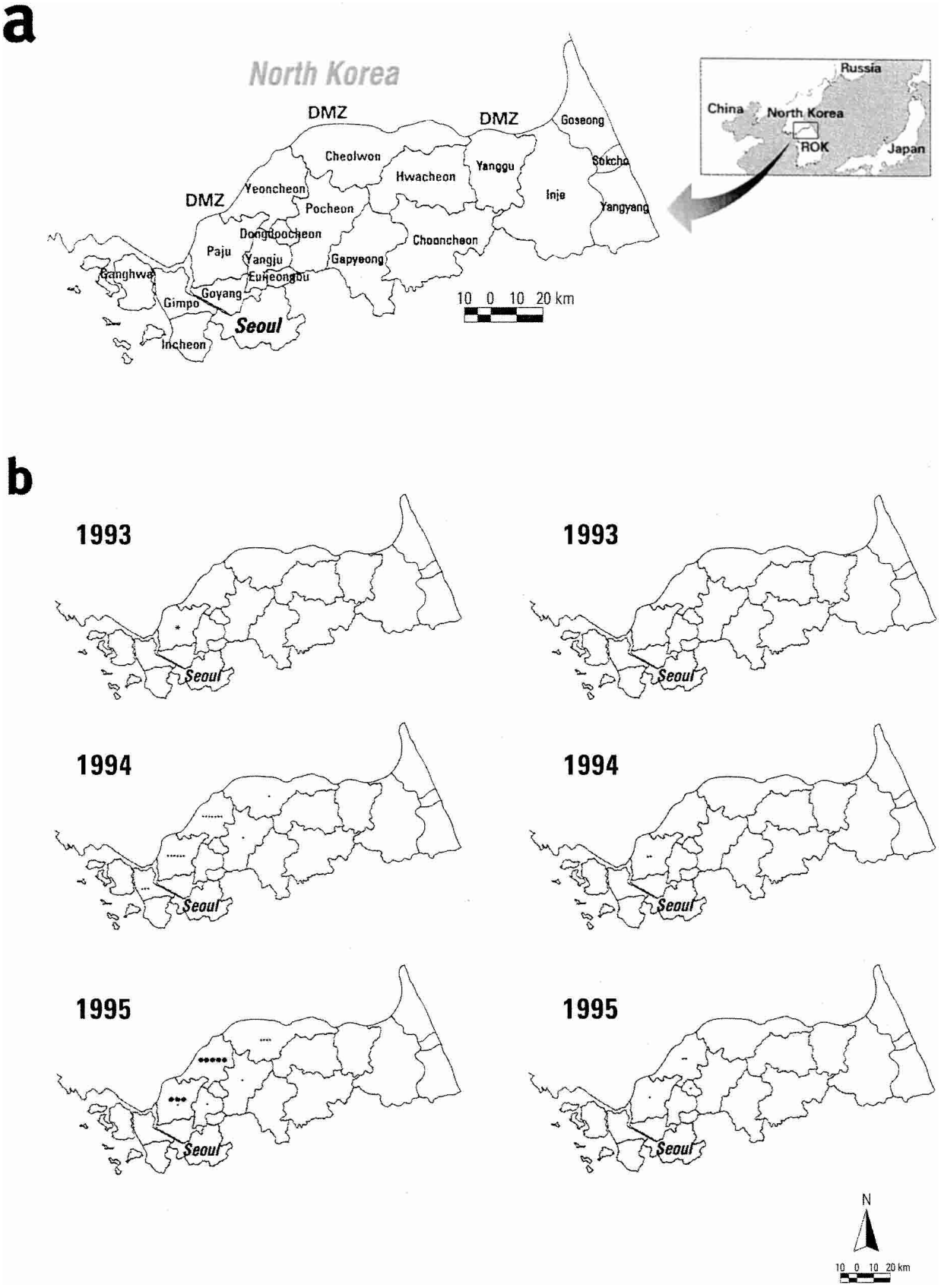

FIGURE 1. Distribution of reported malaria cases among Republic of Korea (ROK) military personnel north of Seoul/Han River in the Republic of Korea. **a**, Political boundaries of the Republic of Korea north of the Han River. DMZ = Demilitarized Zone. **b**, Annual malaria cases among military personnel (**left panels**) and civilians (**right panels**). Large dots represent 100 cases, medium dots represent 10 cases, and small dots represent 1 case. The asterisk in the 1993 military personnel map represents the first case.

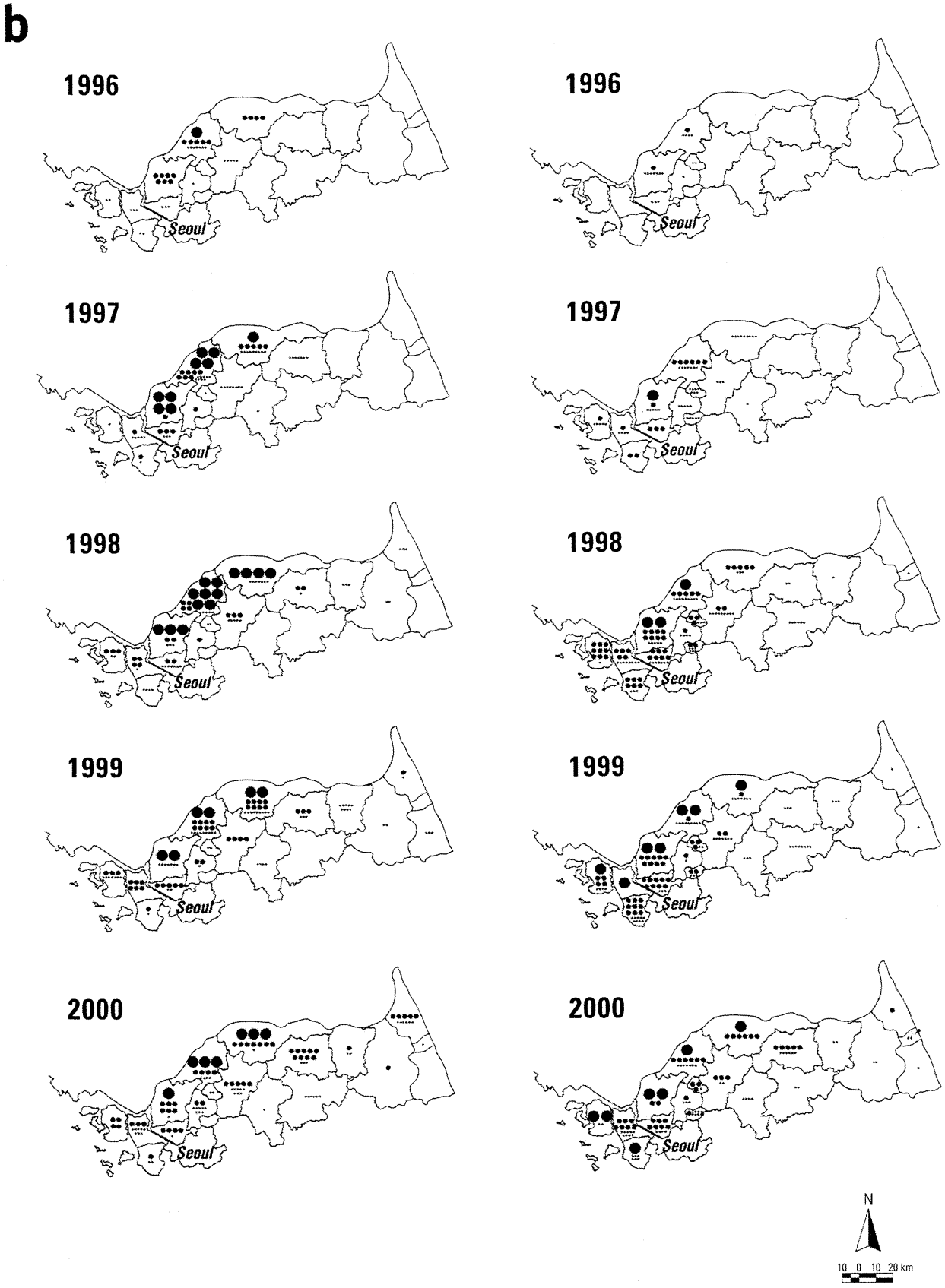

FIGURE 1. Continued.

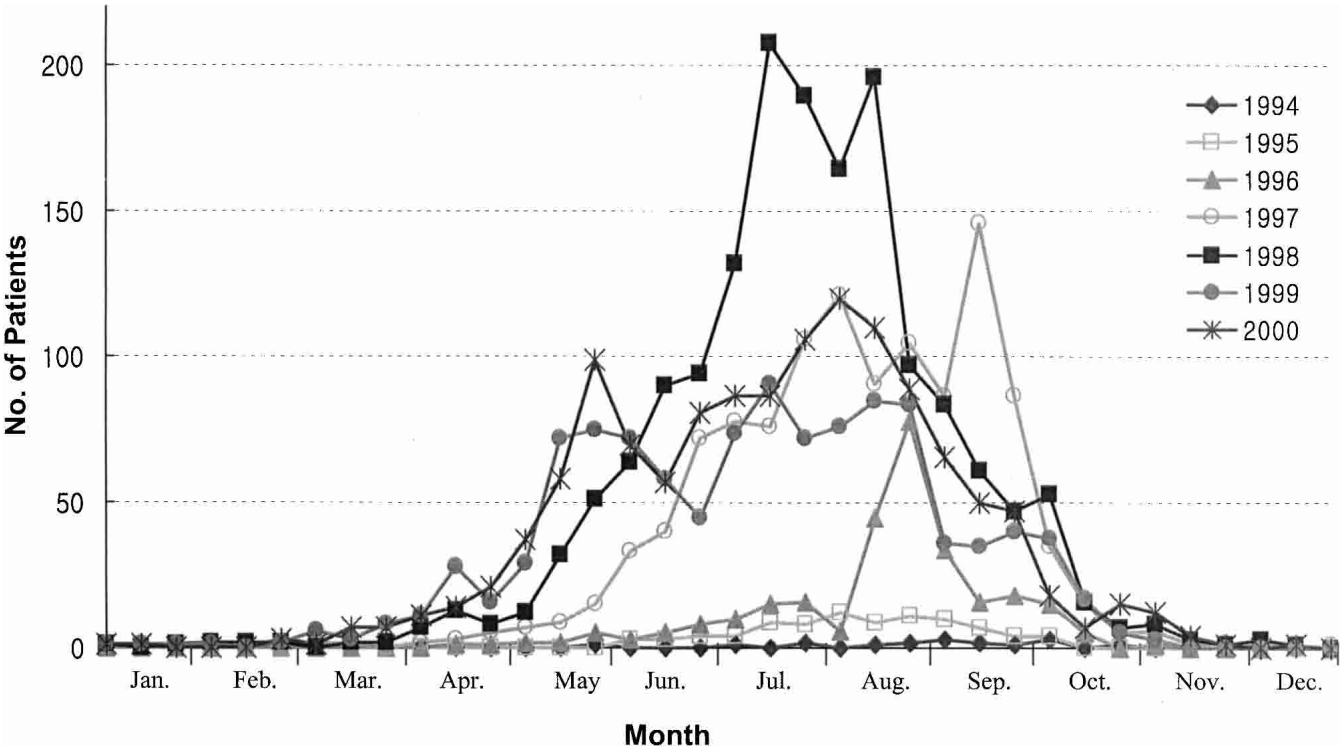

FIGURE 2. Number of malaria cases, reported at 10-day intervals, from 1994 through 2000 in the study area in the Republic of Korea. The first case occurred in mid-July 1993.

Yeoncheon, and Cheolwon Counties) through 1995.[18] Due to the initial concentration of malaria cases near the DMZ and its subsequent geographic distribution, it was suggested that the reemergence of vivax malaria resulted from infected mosquitoes originating from North Korea near the DMZ. While the DMZ separates North Korea and South Korea by approximately 2 km, at Panmunjom where official United Nations and other meetings are held, dignitaries, guards, and visitors from each country are separated by only a few meters. This increases the potential for transmission when infected persons and mosquitoes cohabitat. Although data are not available from North Korea, large quantities of chloroquine requested from the World Health Organization suggest that there is an ongoing outbreak of vivax malaria in North Korea.[19] Several investigators have suggested that 1) heavy rainfall in July 1993 and August 1995, 2) very low numbers of livestock (cattle/swine) in North Korea, 3) malnutrition, and 4) near collapse of their health care system are contributing factors to a probable epidemic of malaria in North Korea. Lack of data for malaria infection rates and epidemiology in North Korea prevent our full understanding of the epidemiology of malaria in South Korea.[18]

The western part of the DMZ was one of the three endemic areas where active transmission of vivax malaria persisted longer than in other parts of the country up until the late 1960s.[8] It has been suggested that malaria remained endemic and was maintained undetected in this area at very low levels until 1993, when the first reemergent case occurred, with a subsequent explosive increase in malaria cases. The other possibility for the source of reemergence could include malaria introduced from external sources. Recent studies demonstrated that genetic characterization of *P. vivax* parasites detected in Korean patients were similar to strains from North Korea, China, and east Asia,[20,21] suggesting such introduced malaria as the source of reemergence.

By 1996, malaria in the Republic of Korea had expanded southward to Inchon, Goyang, Yangju, and Pocheon, which are several kilometers south of the DMZ (Figure 1), and beyond the normal flight range of mosquito vectors from North Korea.[22,23] Cases of indigenous malaria were also reported in children who lived in Ilsan,[24,25] a satellite city near the northern part of Seoul, and who had no travel history to malaria-risk areas near the DMZ for at least two years. Therefore, the occurrence of malaria in these areas strongly suggests that malaria had become endemic by 1996 with local transmission, regardless of its origin of introduction.

Until 1998, malaria had not expanded further eastward to Hwacheon, where the Taebaeck Mountains run from north to south, forming a geographic barrier to infected mosquitoes. However, cases have increased steadily in the Taebaeck Mountain area (Yanggu, Inje, Gapyeong, and Chooncheon Counties) since 1998. The initial introduction and spread of malaria in this region may have been due to soldiers/civilians introducing malaria into those areas after travel/assignment to malaria-risk areas. While transmission of vivax malaria among military personnel was limited south of the Han River, annual increases have been observed among civilian populations since 1997. These increases are alarming as malaria becomes better established and slowly spreads south.

In 1997, the Republic of Korea military initiated chloroquine chemoprophylaxis to nearly 16,000 soldiers (Table 3). The number of Republic of Korea soldiers given chemoprophylaxis increased annually until 2000, when more than 90,000 soldiers assigned to malaria high-risk areas were in the

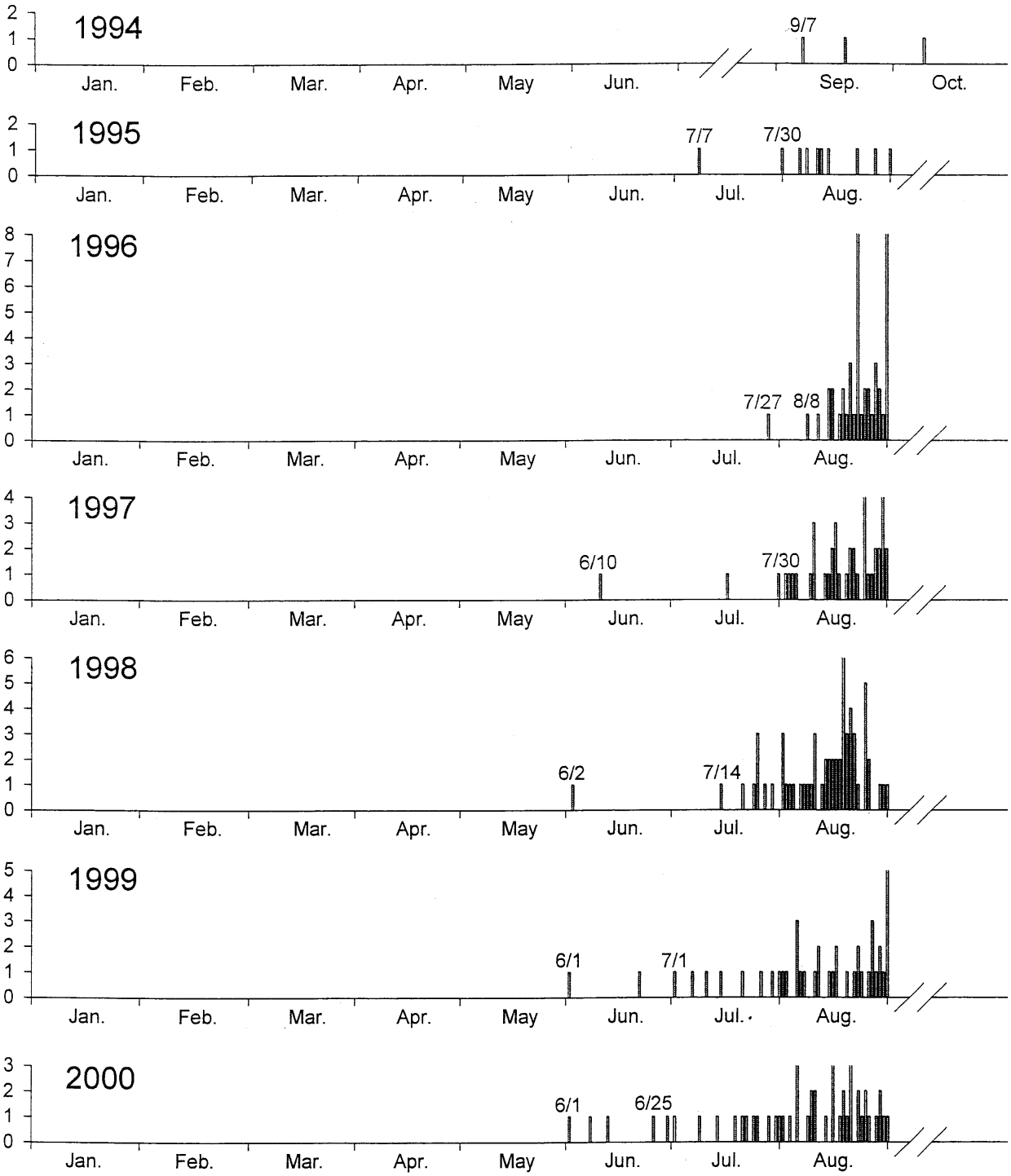

FIGURE 3. Date of diagnosis for Republic of Korea military personnel without previous exposure to malaria the preceding year. The y-axis of each graph represents the number of patients.

program. It was recommended that military commanders and their staff ensure that all soldiers took their chloroquine under direct observation to be effective. However, all administration of chloroquine was not conducted under direct observation, resulting in solders developing malaria as a result of either not taking the chloroquine as directed, or not taking it at all.[18] Similarly, when compliance was observed in U.S. troops, no cases were reported. It is unknown whether soldiers discontinued prophylaxis, the levels of chloroquine in the blood of these soldiers were insufficient to kill the parasites, or whether endemic strains of *P. vivax* are becoming more tolerant/resistant to chloroquine. These are important issues that need further investigation.

The number of cases among soldiers and veterans decreased for the first time in 1999 since the beginning of the malaria epidemic. The decrease among soldiers occurred primarily in Paju, Yeoncheon, and Cheolwon Counties where chloroquine prophylaxis was increasingly emphasized. In con-

TABLE 3
Annual chemoprophylaxis among Republic of Korea (ROK) and 8th U.S. Army personnel*

	1997	1998	1999	2000
ROK Army	15,981	37,529	61,772	90,000
Date started†	June 19	June 8	June 7	June 5
Eighth Army	35	2,485	8,510	1,159
Date started†	ND	June 15	June 1	June 1

* ND = not determined.
† Newly assigned soldiers were placed on chemoprophylaxis upon arrival at their duty station.

trast, malaria cases among civilians residing in the same counties, to whom chemoprophylaxis was not given, continued to increase. In addition, chemoprophylaxis was not provided to soldiers in Pocheon and Hwacheon Counties, where the number of cases in 1999 was five times greater than during 1997.

In 1999 and in 2000, a decrease in the monthly incidence of malaria was noted in June, when the chemoprophylaxis schedule was initiated (Figure 2). Meanwhile, in the military, the number of cases during the prophylactic period (June 7 through October 17, 1999 and June 5 through October 15, 2000) comprised 71.1% of the annual incidence in 1999 and 74.5% in 2000, respectively. In contrast, the number of cases in civilians during the same period comprised 86.8% of the annual incidence in 1999 and 88.0% in 2000. These findings suggest that chemoprophylaxis contributed to the decrease in malaria occurrence in military personnel in 1999 and 2000. However, the impact of chemoprophylaxis was rather modest. Possible explanations for such low efficacy include low compliance, especially during field training.

Initially, observed compliance with chloroquine prophylaxis was not enforced, and this resulted in malaria cases among the prophylaxis population. Therefore, during 1999 and 2000, strictly observed compliance for chloroquine chemoprophylaxis was enforced for U.S. soldiers. However, compliance for terminal prophylaxis with primaquine was not observed, resulting in at least three cases of malaria in soldiers stationed north of the Imjin River and later diagnosed with malaria in the United States. During 2000, primaquine prophylaxis included observed compliance during the last 14 days stationed or at the end of the malaria season, rather than simply giving the soldiers 14 tablets of primaquine as they were leaving the Republic of Korea.

Based on our studies of populations of Republic of Korea Army soldiers who had entered military service after November 1 of the preceding year, the first occurrence of short incubation transmission of malaria due to transmission by mosquitoes normally occurs in June (Figure 3). These short incubation infections are attributed to mosquitoes that become infected from patients expressing their illness in April of the current year and with exposure and transmission in the previous year. Malaria parasite (sporogonic) development ceases in the mosquito at temperatures below 16°C. Therefore, with mean temperatures during April/May between 16°C and 20°C, the expected sporogonic period in the mosquito is more than 20 days.[14] With the short incubation form of vivax malaria, patients become ill 12–17 days after infection.[14] Therefore, the earliest cases would be transmitted from mosquitoes to humans in mid-May of the same year with symptoms being observed in early June. The increases in the number of malaria cases from April through most of May are then largely due to latent malaria cases from the previous year. During April and May, mosquitoes become infected and by mid-May they have developed sporozoites and able to infect humans. Chemoprophylaxis was provided to the Republic of Korea military population from the beginning of June. As shown in Figure 2, there was a subsequent reduction in the number of military malaria patients as a result of institution of chemoprophylaxis. If chemoprophylaxis had been administered to soldiers earlier (i.e., in April), blood stages of the parasite would have been suppressed and latent cases would not have developed to infect mosquitoes, thus reducing the potential for further transmission to humans. Based on these observations, chemoprophylaxis should be administered at the beginning of April.

In conclusion, our study demonstrated that the cases of vivax malaria have rapidly increased annually among counties bordering the DMZ and have spread approximately 40 km south of the DMZ. Mountain terrain may have inhibited the spread of malaria eastward along the DMZ. Decreasing numbers of malaria cases among the Republic of Korea military are attributed to the increased annual use of chemotherapy in certain areas. To reduce the early transmission of malaria from latent malaria infections, chemoprophylaxis should be instituted in early April rather than in June as previously done, thus reducing the number of infected mosquitoes transmitting malaria observed in early June. Extensive intervention and continued surveillance are warranted to eliminate the spread of the disease and once again make the Republic of Korea malaria free.

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