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REEMERGENCE, PERSISTENCE, AND SURVEILLANCE OF VIVAX MALARIA AND ITS VECTORS IN THE REPUBLIC OF KOREA

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Abstract *Plasmodium vivax* reemerged in 1993 after a hiatus of 14 years and increased exponentially among South Korean military and civilian populations through 1998. With increased use of chemoprophylaxis by the South Korean military, malaria stabilized and then sharply decreased through 2004. Malaria cases sharply increased in 2005 through 2007 to 2001 levels even though the Korean military chemoprophylaxis program was expanded to approximately 200,000 soldiers. Malaria among US service members demonstrated similar trends and the sites of infections were identified as training areas near the heavily fortified demilitarized zone (DMZ). Similarly, Korean data show that nearly all malaria transmission occurred in the northernmost two provinces bordering the DMZ. In 2005, it was reported that members of the *Anopheles sinensis* Group could not be identified using morphological techniques. Extensive larval and adult surveillance showed that *An. kleini* and *An. pullus* population densities were highest in malaria high-risk areas, while malaria transmission was extremely low where *An. sinensis* predominated. These and other data identify *An. kleini* and *An. pullus* as the primary vectors of malaria in Korea. The number of vivax malaria cases in the US military doesn't warrant the widespread use of chemoprophylaxis, but instead, warrants an increased emphasis on preventive medicine measures (including permethrin impregnated uniforms and approved repellents). This is especially important since the Korean military experienced a large number of chemoprophylaxis breakthroughs during 2007, indicating a potential for drug resistance.
Key Words *Anopheles*, Geographical distribution, Korea

INTRODUCTION

Plasmodium vivax has a worldwide distribution and is well adapted to temperate zone environments and prior to extensive malaria eradication programs extended as far north as Moscow, Russia, and throughout Korea within the 16-20^{O}C northern isotherms (Shute et al., 1976). In Korea, malaria transmission occurs from April through October when temperatures are sufficient to promote mosquito and parasite development. As mosquitoes overwinter as nulliparous females and/or eggs, transmission is initiated annually by patients infected with latent forms of malaria that emerge from the liver the following year after transmission and by asymptomatic carriers.

In 1993, vivax malaria reemerged with the first autochthonous malaria case identified in a South Korean Soldier assigned to the southern boundary of the demilitarized zone (DMZ), a 248 km long X 4 km wide heavily fortified zone that divides the Korean peninsula into North and South at an acute angle across the 38th parallel (Kim, 1997). Malaria cases subsequently increased exponentially to >4,000 in South Korean civilian, veteran, and military populations by 2000 (Chai et al., 1994; Chai, 1999; Lee et al., 2002; Park et al., 2003). While Shin and Kim (1999) found that anopheline species generally have a flight range of <5 Km, Cho et al. (2002) found that 12.4% of recaptured females of members of the *An. sinensis* Group (not identified to species) traveled 6-12 kilometers and Ree (2000) reported distances of 20 Km from their release site, showing that some members of this species Group were capable of crossing the 4-kilometer DMZ from North Korea where the reintroduction most likely occurred (Chai, 1999; Kho et al., 1999; WHO, 2002; Cho et al., 2002; Service and Townson, 2002).

It was assumed that malaria would rapidly spread from along the DMZ to the southern tip of the peninsula (Park et al., 2000, 2003; Lee et al., 1998; Han et al., 2006). However, since its reintroduction, nearly all transmission resulted from exposure near the DMZ where it remains a notable public health concern (Lee et al., 2001; Moon and Cho, 2001; Lee et al., 2002; Lum, 2003; KCDC, 2007; Gustave, 2006). A review of the taxonomic status and surveillance of *Anopheles* spp. throughout Korea provides relative densities, geographical distributions and implicates *An. pullus* and *An. kleini* as the primary malaria vectors, while *An. sinensis* is a secondary vector (Rueda, 2005; Lee et al., 2007).

MATERIALS AND METHODS

Epidemiological investigations were conducted for US and Korean Augmentees to the US Army (KATUSA) soldiers from 1994-2007, as part of the US Forces Korea (USFK) malaria reporting policy, to identify the most likely site and date of transmission and form (latent versus non-latent) of malaria. The second source of vivax malaria cases were reported by Army Medical Surveillance Activity (AMSA) (Forest Glen, Maryland) reports for US soldiers previously deployed to Korea (DoD, 1999; Ciminera and Brundage, 2006). Malaria data for all US military personnel diagnosed with malaria outside of Korea were reviewed to determine the most likely location (country) where malaria was acquired and to identify incubation forms (latent or non-latent).

Data, including the location of diagnosis and number of cases, for Korean military, veteran, and civilian populations were provided by the Korea Center for Disease Control and Prevention (K-CDC). Reported herein are only malaria case numerator data. We were not aware of any substantial changes in the Korean civilian and military populations during the period we observed. US military populations were similar from 1993 through the fall of 2004, after which one brigade and several other components were redeployed.

Adult mosquito collections were conducted using New Jersey light traps at selected US military installations located throughout Korea and members of the *An. sinensis* Group identified by polymerase chain reaction (PCR) techniques using species-specific fragments based on published rDNA ITS2 sequence. In addition, larval surveys were conducted at sites throughout Korea and identified similarly by PCR to species to determine the general habitat and geographical distributions.

RESULTS AND DISCUSSION

Vivax malaria reemerged as a primary public health threat in Korea when the first autochthonous vivax malaria case was reported in 1993 in a South Korean soldier stationed near the DMZ, with a total of 25,596 malaria cases reported for South Korean civilian, active duty military and veteran populations through 2007 (Chai et al., 1994; KCDC, 2007) (Figure 1). Malaria predominated in the South Korean military (active duty) through 1998. Malaria was first reported in the civilian population in 1994 and by 1999 the number of cases surpassed the military. To reduce the "spillover" effect from the military population, the military instituted a chemoprophylaxis policy in 1997, placing approximately 16,000 soldiers on hydroxychloroquine sulfate (400 mg) and terminal primaquine prophylaxis (Figure 1). As malaria increased, more soldiers were placed on chemoprophylaxis and by 2000; approximately 90,000 soldiers were placed on hydroxychloroquine, which may have lead to lower numbers in the military while cases in the civilian population continued to increase. The increased use of chemoprophylaxis to approximately 165,000 by 2003, as well as other public health actions resulted in a rapid decline of malaria to a low of 826 cases by 2004. However, the number of cases increased in 2005 to 1,324. Malaria cases continued to increase in 2006 among all populations to 2,021, partially as a result of a very late fall, with abundant larvae and adults through the first week of November, and subsequently with latent cases contributing to a small increase in cases observed during 2007 (Figure 2). While the number of malaria cases in the civilian population decreased, it is alarming that there were a large number of breakthroughs among South Korean soldiers on chemoprophylaxis that accounted for large increases observed in the military population (Park IH, personal communication). At present, it is unknown whether these breakthroughs are due to non-compliance, hydroxychloroquine failure, or both.

From 1993 through 2007 there were a total of 405 malaria cases attributed to exposure in the Korea among US (361) and KATUSA (43) soldiers and USFK civilians (1) (Figure 3). The first cases of malaria were diagnosed in 1994 in two US Soldiers stationed near the DMZ in Korea. However, a US soldier assigned to Korea during 1992 with no history of travel to other malaria areas developed malaria in 1993, suggesting that malaria transmission may have occurred as early as 1992 (AMSA, 2007). Since 1993, malaria increased exponentially in the ROK populations through 1999 with US Forces demonstrating a similar pattern to South Korean population trends (Strickman et al. 2000, Park et al. 2003, Yeom et al. 2005) (Figure 3). The Joint Security Area (JSA), Panmunjom, within the DMZ, accounted for much of the malaria prior to 1998 when US soldiers were placed on chemoprophylaxis. Only 4 cases of cases of malaria were reported in soldiers assigned to JSA after 1998, and epidemiology investigations determined that these occurred as a result of non-compliance. Based on the lack of “true” chemoprophylaxis failures among US personnel, it is assumed that nearly all the Korean breakthroughs are due to non-compliance. However, since the Korean military uses hydroxychloroquine (400 mg) rather than the higher dose of chloroquine phosphate (500 mg) that US soldiers take weekly, chemoprophylaxis failure can not be ruled out (Kim et al., 2006).

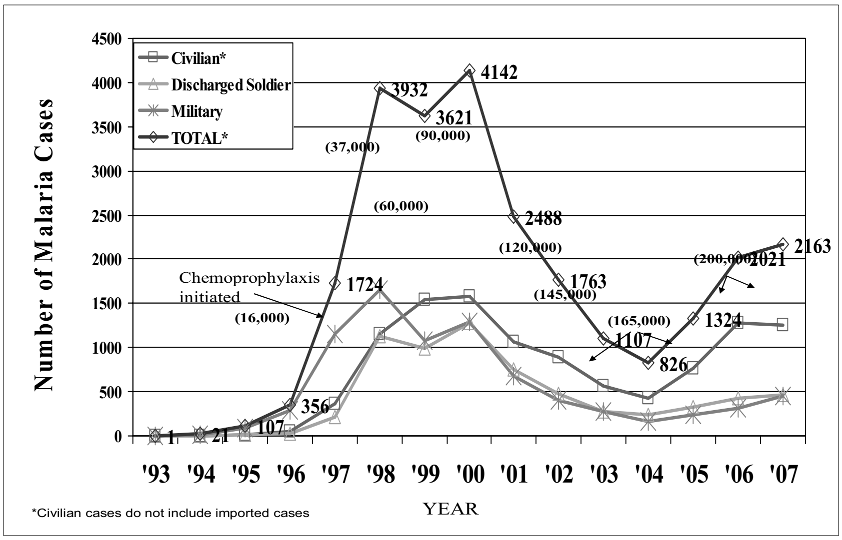

Figure 1. Annual trend of malaria cases diagnosed in South Korean soldiers, veterans (< 2 years after discharge), and civilian populations.

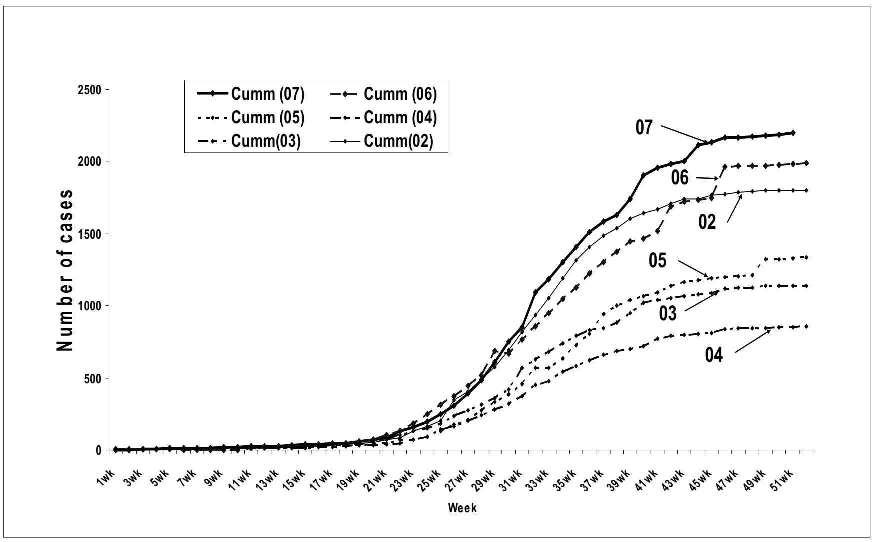

Figure 2. Cumulative annual number of malaria cases among all Korean populations (military, veteran, and civilian) for years 2002-2007.

Malaria in Korea consists of two forms, a non-latent or short incubation form that usually results in disease symptoms within 10-21 days following infection, and a latent or long incubation form with the manifestation of disease symptoms from 6-18 months after infection (Shute et al., 1976). Overall, 27.6% (100) of the malaria cases were identified as non-latent, while 62.7% (227) were latent, and 9.7% (35) of the cases could not be determined as to latency. This resulted in 54.4% of malaria patients developing symptoms following their redeployment from Korea to the US or other countries. Among US soldiers, the first case of latent malaria occurred in March with numbers sharply increasing through August before declining with few cases reported through December (Figure 4). Non-latent cases were first reported in July and sharply increased through September before declining to a low in November. Among South Korean military, latent malaria cases were reported throughout the year, while non-latent malaria cases were reported as early as June with similar trends as those observed among US Forces (Park et al., 2003).

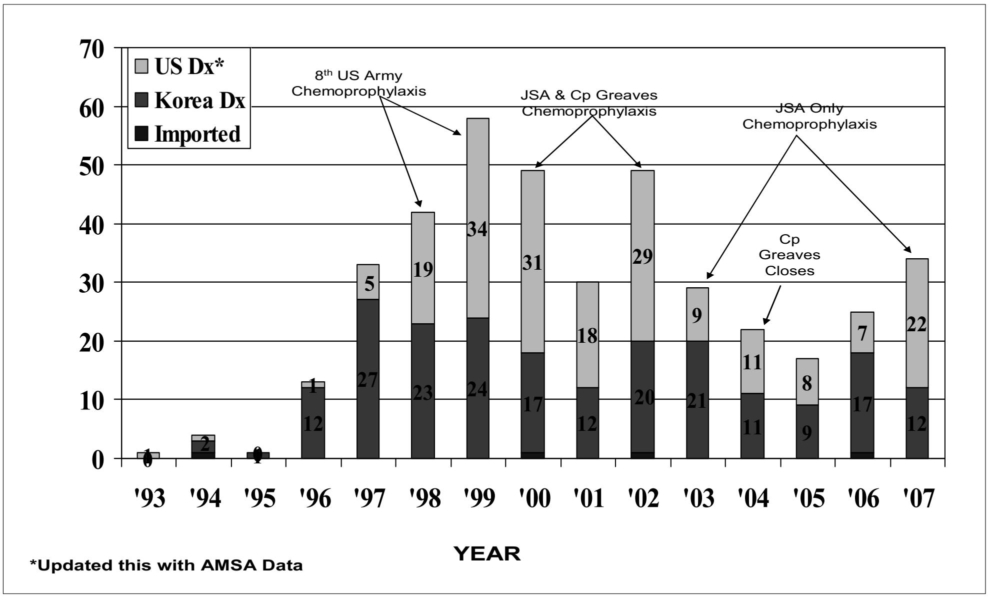

Figure 3. Annual trend of malaria cases among US Forces Korea personnel attributed to exposure in South Korea from 1993 through 2007.

Epidemiology investigations of malaria cases among US military showed that nearly all the malaria was contracted while they were training at US and Korean operated training sites located near the DMZ (Figure 5). Nearly all the malaria cases contracted at the JSA and Camp Greaves (closed in 2004) occurred prior to 1998 when US soldiers were not on chloroquine/primaquine chemoprophylaxis. Only one malaria case was reported in a US civilian (2007), and the patient resided near Twin Bridges Training Area, a malaria high-risk area, and reported numerous mosquito bites during 2006-7. The paucity of cases among US civilians (1) and family members (0) throughout Korea indicates that malaria transmission is primarily the result of exposure of military personnel while training near the DMZ.

Data from 2001-2007 demonstrate that the primary source of malaria infections (based on area of diagnosis) among all three ROK populations are northern Gyeonggi and Gangwon Provinces (Figure 6). South of Gyeonggi and Gangwon Provinces, mean annual malaria cases were attributed mostly to veterans (discharged <2 yrs) that were previously assigned to malaria high-risk areas near the DMZ and subsequently returned to their hometowns (0-35 cases), while mean annual cases among military and civilian populations in these same provinces ranged from <1-5 and 0-1, respectively. Additionally, Lee et al. (1998) noted that of 107 civilian patients that resided outside the malaria risk areas of northern Gyeonggi and Gangwon Provinces, 70.1% had previous exposure near the DMZ. These data demonstrates that malaria transmission occurs primarily near the DMZ at military training sites and bases and associated civilian villages.

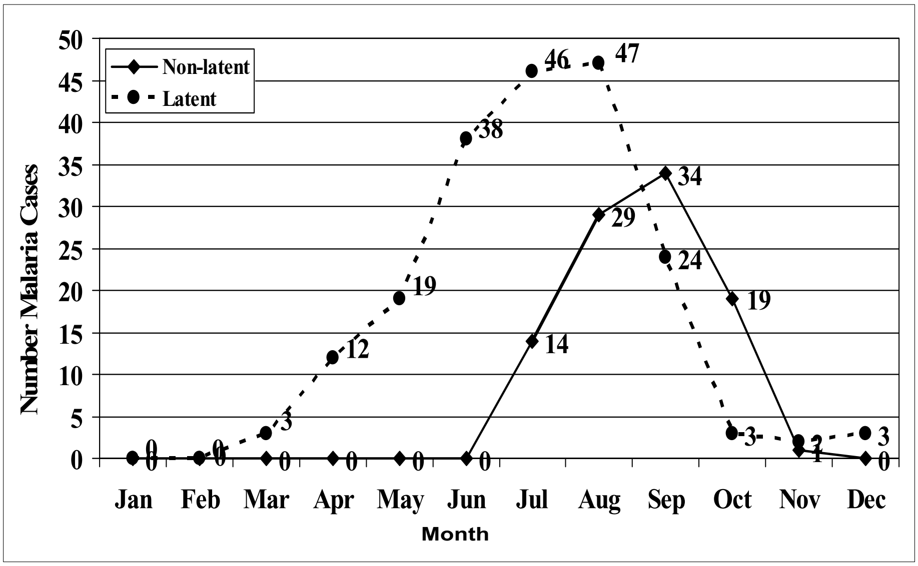

Figure 4. Non-latent and latent malaria cases attributed to exposure in Korea, 1993-2007.

Prior to 2005, there were only six *Anopheles* spp. reported from Korea and it was assumed that all these species could be identified by morphological techniques. In 2005 two additional species were identified and it was determined that none of the now five members of the *An. sinensis* Group could be identified by morphological techniques. This has and continues to create much confusion in the literature concerning population densities and vector status as many authors continue to use only morphological techniques to identify these species. A study of *Anopheles* spp. relative abundance using PCR species-specific primers to identify members of the *An. sinensis* Group captured by New Jersey light traps at selected US military installation showed that *An. kleini* and *An. pullus* populations densities were high near the DMZ while *An. sinensis* accounted for the majority of mosquitoes collected south of Seoul, except at Camp Long (Figure 7). In addition, larval surveys that were conducted throughout Korea demonstrated high densities of *An. kleini* and *An. pullus* near the DMZ whereas, similar to the adult data, few were collected south of Seoul (Figure 8). These data, in addition to malaria case data for US and Korean populations and recent studies by Lee et al. (2007), support the conclusion that *An. kleini* and *An. pullus* are the primary vectors, while *An. sinensis* is a secondary vector.

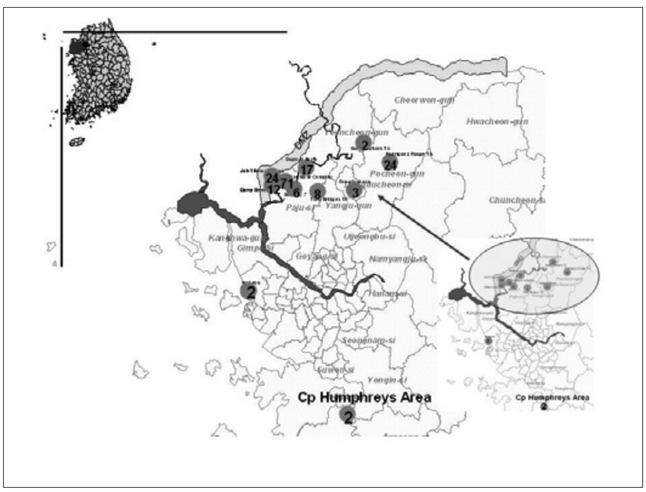

Figure 5. Suspected sites of transmission of vivax malaria among US military in Korea, 1993-2007.

CONCLUSIONS

Vivax malaria is a primary health threat to South Korean and US military and civilian populations near the DMZ. Limited transmission occurs south of Seoul, but a return to hostilities could change that scenario. Malaria trends in US military populations follow those of Korean populations, and careful monitoring of malaria in these populations provides for rapid assessment, modifications, and implementation of malaria plans and regulations to reduce malaria risks among US soldiers. The US military must continue to be vigilant to identify latent malaria and provide educational materials to service members once they have departed Korea, since they may develop malaria when redeployed to non-malarious areas or after discharged from the military. The relatively low numbers of vivax malaria cases does not warrant the mass use of chemoprophylaxis for all US soldiers, thus relying on the use of permethrin-treated uniforms, proper wear of the uniform, and use of approved arthropod repellents to decrease the risk of transmission. Additional studies to better define the geographical distribution (modeling and surveillance) that provides a better understanding of vector relationships (zoophilic/anthropophilic behavior, habitat preferences, susceptibility) of malaria transmission is warranted as part of the USFK health threat analysis.

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