



Epidemiological Characteristics of Re-emerging Vivax Malaria in the Republic of Korea (1993-2017)

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Abstract: Historically, *Plasmodium vivax* malaria has been one of the most highly endemic parasitic diseases in the Korean Peninsula. Until the 1970s, vivax malaria was rarely directly lethal and was controlled through the Korean Government Program administered by the National Malaria Eradication Service in association with the World Health Organization's Global Malaria Eradication Program. Vivax malaria has re-emerged in 1993 near the Demilitarized Zone between South and North Korea and has since become an endemic infectious disease that now poses a serious public health threat through local transmission in the Republic of Korea. This review presents major lessons learned from past and current malaria research, including epidemiological and biological characteristics of the re-emergent disease, and considers some interesting patterns of diversity. Among other features, this review highlights temporal changes in the genetic make-up of the parasitic population, patient demographic features, and spatial distribution of cases, which all provide insight into the factors contributing to local transmission. The data indicate that vivax malaria in Korea is not expanding exponentially. However, continued surveillance is needed to prevent future resurgence.

Key words: *Plasmodium vivax*, re-emerging malaria, control, mosquito, vector

INTRODUCTION

Malaria is one of the oldest known and most prevalent parasitic diseases in the world, with an estimated 3.2 billion people being at risk of infection [1]. The incidence of malaria has decreased in recent years. In 2016, there were an estimated 216 million cases of malaria, about 5 million more cases than in 2015, and the number of deaths reached 445,000, a similar number to the previous year [2]. Among the protozoa that cause malaria, *Plasmodium falciparum* is the greatest menace because of its high mortality rate. Malaria caused by *P. vivax* is less lethal but is a huge burden on public health, greatly affecting the quality of life for many people in tropical, subtropical, and temperate countries [3,4]. Previous eradication programs

have shown that *P. vivax* can persist long after *P. falciparum* is eliminated [5]. Unlike *P. falciparum*, *P. vivax* infections include dormant hypnozoites that can survive in the liver without the onset of disease and cause clinical relapses. These relapses manifest as blood infections that are clinically indistinguishable from primary infections. They constitute a substantial, but geographically variable, proportion of the total infections and disease risk within populations [6,7]. Moreover, parasitemia in a *P. vivax* infection is usually of a lower density than that in a *P. falciparum* infection, making diagnostic tools less effective.

Vivax malaria has been an endemic infectious disease in the Korean Peninsula for a long time (Fig. 1). Indigenous falciparum malaria has not been reported. Vivax malaria was eliminated in Korea in the late 1970s but re-emerged in the early 1990s and has continued to prevail despite the ongoing national eradication program [8,9].

The aim of this brief review is to provide key information on the epidemiological and biological characteristics of re-emerging vivax malaria in Korea. The review focuses on the

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characterization of the transmission of vivax malaria in Korea after its re-emergence in 1993.

MALARIA CONTROL UP TO 1993

In Korea, malaria is classified as a group III infectious disease and malaria control efforts started in the middle of the 20th century. From the early 1970s to 1993, Korea was considered to be a malaria-free region. Historically, however, *P. vivax* malaria was highly endemic in the Korean Peninsula for centuries and caused unstable malaria transmission [8,9].

Malaria is popularly known as Hah-roo-geo-ri (meaning “every-other-day fever”) or Hahk-geel (Korean disease name) [10]. Medical characteristics of vivax malaria in Korea include few previous clinical malaria episodes prior to the current infection, no association with concurrent bacteremia, and extremely rare occurrences of severe anemia, hypoglycemia, and acute kidney injury complications. Mortality is rare. Relatively common and notable characteristics include cerebral and pulmonary manifestations, spontaneous bleeding, shock, and metabolic acidosis [11]. Many medical books published in the Joseon Dynasty described the main symptoms and treatments for the disease. The first systematic and scientific descriptions of malaria in the Korean Peninsula were published in 1913 [12]. The article described *P. vivax* cases confirmed by micros-

copy in the general population and stationed Japanese army soldiers. The same article also provided information on the prevalence of vivax malaria in the Korean Peninsula during the Japanese colonial era. During the Korean War (1950-1953), vivax malaria became a serious problem. Treatment of American troops infected with vivax malaria and the recurrence of the infection after repatriation were important medical issues [13,14]. Malaria control was consolidated in 1959 with the inauguration of the National Malaria Eradication Service (NMES) under the control of Korean Government with the assistance of the Global Malaria Eradication Program of the World Health Organization (WHO), which included regions of the globe other than Africa. As a part of these efforts, a nationwide survey was performed to gauge the prevalence of the protozoan parasite [15]. The use of effective insecticides and anti-malarial drugs, as well as an improved standard of living and easy access to medical clinics facilitated the effective treatment of malaria. As a consequence, the national prevalence of malaria was markedly diminished by the late 1970s (Fig. 2) [16-19]. Extensive use of agricultural pesticides also contributed greatly to the decrease in malaria incidence through the eradication of the mosquito vector of the disease. In 1979, the WHO officially certified that Korea was a malaria-free country. The country was the first nation to receive this WHO certification [20]. With the exception of a memoir citing 2 cases of

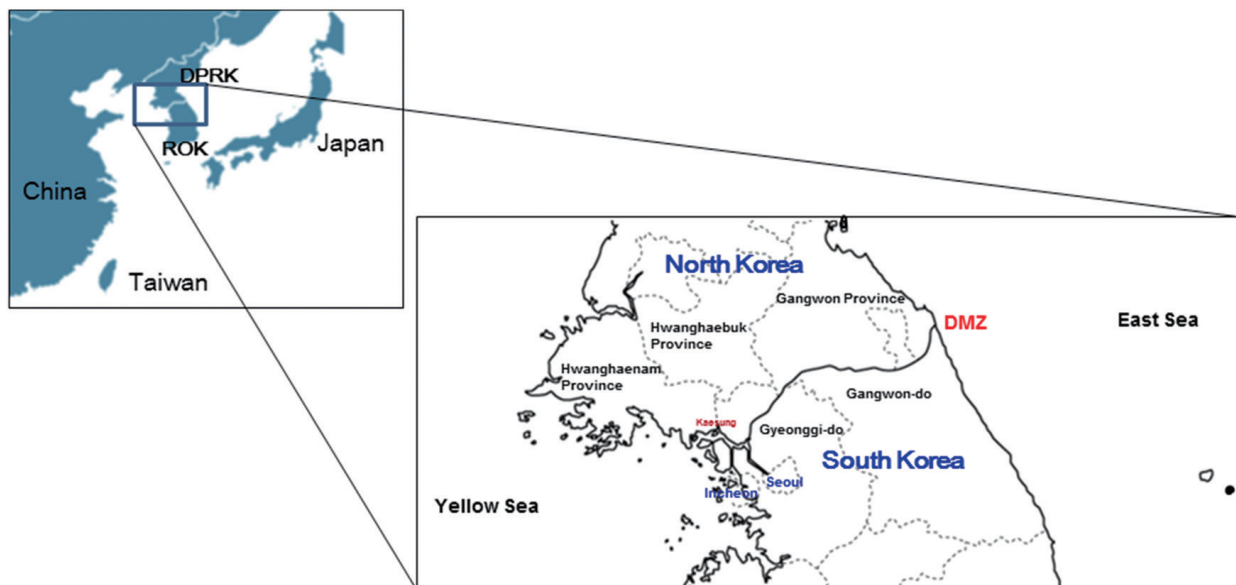


Fig. 1. Map of the Korean Peninsula. The DMZ divides Korea and North Korea. Malaria in Korea occurs mainly in the northern area close to the DMZ of Incheon-si, Gyeonggi-do, and Gangwon-do, and malaria in North Korea occurs in Gaeseong City, North and South Hwanghae provinces, and Gangwon province.

malaria in 1985 [18], no official malaria cases were reported in Korea until 1993. At that time, one case was reported along

the western edge of the Demilitarized Zone (DMZ), a fortified zone 4 km wide and 248 km long that incorporates territory

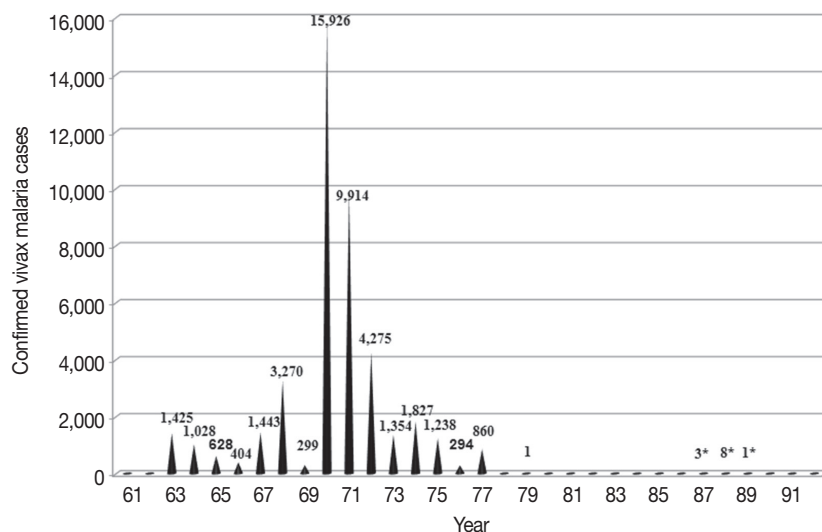


Fig. 2. Indigenous malaria cases in Korea before re-emergence. Indigenous vivax malaria was highly prevalent in Korea, but it was successfully eradicated from the region in the early 1970s [13-16]. The asterisk indicates the number of imported cases of malaria.

Table 1. Number and percentage of vivax malaria cases confirmed in Korea from 1993 through 2017, and the distribution of the confirmed cases according to the month

Year	No.	Jan.	Feb.	Mar.	Apr.	May	Jun.	Jul.	Aug.	Sep.	Oct.	Nov.	Dec.
1993	3		1	1			1						
1994	25			1		1	2	1			20		
1995	107			1			13	22	44	22	5		
1996	356				2	10	20	57	138	102	24	3	
1997	1,724	3	1	4	12	35	163	337	465	519	144	36	5
1998	3,932	6	8	9	40	164	509	1,182	1,199	553	219	34	9
1999	3,621	13	12	22	80	257	516	798	978	602	273	59	11
2000	4,142	16	14	30	62	285	516	842	1,076	862	272	115	52
2001	2,556	14	19	34	45	176	369	681	624	378	173	30	12
2002	1,799	11	4	5	34	102	192	407	561	297	145	36	5
2003	1,171	10	8	9	25	73	176	275	295	186	85	22	7
2004	864	6	7	4	19	42	141	211	214	126	76	13	5
2005	1,369	6	5	12	21	49	133	295	398	256	154	34	6
2006	2,051	9	3	19	29	109	301	432	516	384	193	40	16
2007	2,227	15	8	10	20	110	239	605	639	329	173	65	14
2008	1,052	22	8	8	37	85	148	235	228	172	85	14	10
2009	1,345	3	3	9	48	121	213	313	269	211	99	45	11
2010	1,772	1	8	8	36	171	358	454	401	211	93	21	10
2011	838	8	10	12	25	82	171	209	166	95	44	12	4
2012	555	3	3	6	10	45	89	147	116	81	36	10	9
2013	445	4	6	8	15	53	77	95	69	58	49	10	1
2014	638	4	10	5	15	28	107	163	142	92	47	10	15
2015	699	8	5	8	37	84	129	151	146	79	36	7	9
2016	681	9	4	6	30	75	149	166	113	91	35	3	0
2017	515	7	7	2	9	37	86	133	112	76	35	4	7
Total	34,487	178	154	233	651	2,194	4,818	8,211	8,909	5,782	2,515	623	218
(%)	(100)	(0.52)	(0.45)	(0.68)	(1.89)	(6.36)	(13.97)	(23.81)	(25.83)	(16.77)	(7.29)	(1.81)	(0.63)

on both South and North Korea. The DMZ was established following the end of the Korean War by pulling back the respective forces 2 km from each side of the border (Fig. 1) [21,22].

RE-EMERGENCE OF VIVAX MALARIA

In July 1993, a Korean Army soldier stationed near the western edge of the DMZ in northern Gyeonggi-do (do= province) developed a fever with a periodic pattern of occurrence and was admitted to the Capital Armed Forces General Hospital. He was diagnosed with vivax malaria based on the blood smear method [21], which revealed the typical ring, trophozoite, and gametocyte forms of *P. vivax*. After this first case of recurrence, there was an exponential increase in vivax malaria cases in Korea with epidemic outbreaks from 1995-2000 (Table 1; Fig. 3). Since then, vivax malaria has been recognized as a notable public health problem [23-25].

Almost all (>90%) of malaria cases at the beginning of the outbreak occurred among Korean and American soldiers stationed near the DMZ in the northern part of Gyeonggi and Gangwon-do, and among veterans who had been repatriated to their hometowns where they subsequently developed vivax malaria [26]. Prior to 1996, over 80% of vivax malaria patients were military personnel. However, the prevalence gradually

decreased from 65% in the period of 1997-2000 (8,786 of the 13,419 total cases; [27,28]) to approximately 40% in 2007 (908 of the 2,227 total cases) [29]. Correspondingly, the prevalence grew among the civilian population residing in nearby areas. Malaria has once again become endemic and a serious public health burden in Korea. The Korean Army introduced a strategy of mass chemoprophylaxis with chloroquine during the malaria transmission season and primaquine after the transmission season to reduce the number of vivax malaria cases in both the military and civilian populations. Chemoprophylaxis with chloroquine and primaquine began with about 16,000 soldiers in 1997 and was expanded to more than 200,000 military personnel in zones with a high risk for vivax malaria [30].

The increased risk of malaria infection among people near the DMZ suggested that North Korea might be a major reservoir of vivax malaria. The infection would spread across the border to Korea via sporozoite-bearing mosquitoes (Fig. 2) [31]. North Korea had a restricted capacity to eliminate malaria until 1998 and experienced its highest reported incidence of malaria in 2001, peaking at 296,540 microscopically confirmed and indigenous cases (43.4 cases per a population of 1,000), according to the 2010 WHO World Malaria Report. Malaria control efforts by North Korea for at-risk populations focused on mass primaquine preventive treatment (MPPT) as

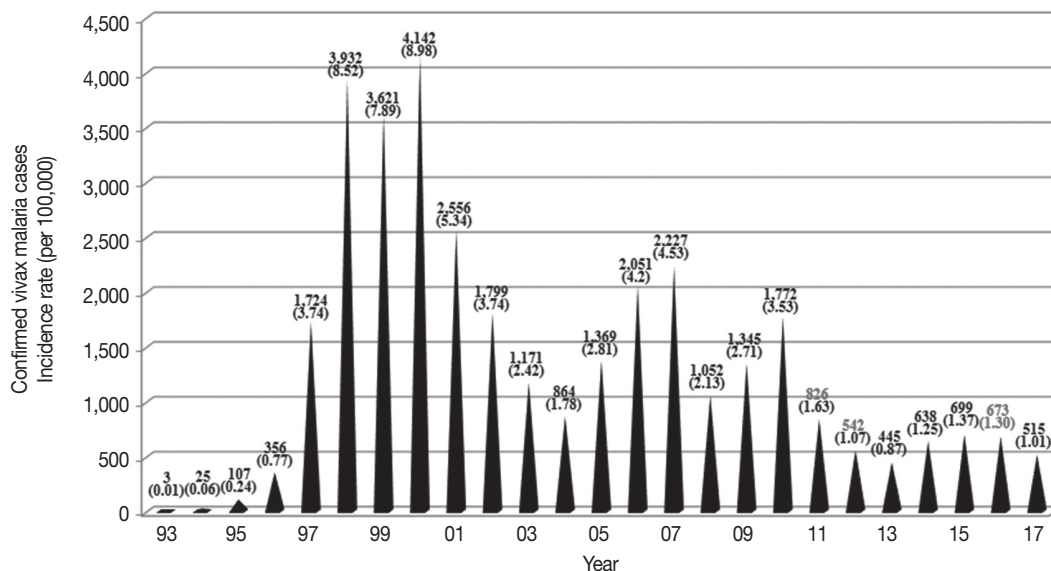


Fig. 3. Indigenous malaria cases in Korea after re-emergence. Since its re-emerging in 1993, the highest patient outbreak occurred in 2000. Since 2000, there has been a mixed pattern of repeated increases and decreases in the incidence of malaria, but the overall trend shows a plateau.

Table 2. Number and percentage of vivax malaria cases confirmed in Korea from 1993 through 2017 according to the Province

	Total	Seoul	Busan	Daegu	Incheon	Gwang-ju	Dae-jeon	Ulsan	Gyeong-gi	Gang-won	Chung-buk	Chun-gam	Jeon-buk	Jeon-nam	Gyeong-nam	Jeju	Sejong	Unkon-wn	Import-ed case	Men	Women	
	3	1	1	1	1	1	1	1	1	4	1	1	2	8	1	2	2	2	2	2	2	
1993	3	1	1	1	1	1	1	1	1	4	1	1	2	8	1	2	2	2	2	2	2	
1994	25	1	1	2	2	20			20						1						N.D.	
1995	107	5	1	1	1	93			93	4	1				1						N.D.	
1996	356	9	1	1	5	1	8		290	40		1	2	4	2						N.D.	
1997	1,724	99	17	14	52	6	8		1,277	177	5	14	8	14	20	2					N.D.	
1998	3,932	449	108	55	212	29	24	13	2,197	519	32	63	25	59	99	6					N.D.	
1999	3,621	487	81	41	328	25	40	36	1,760	514	26	40	43	59	60	9					N.D.	
2000	4,142	494	92	82	461	47	43	37	1,649	825	41	60	58	73	71	18		13			N.D.	
2001	2,556	346	65	30	271	30	31	32	898	544	23	34	39	36	61	6		12	67	2,190	366	
2002	1,799	285	49	25	267	17	18	10	756	216	22	22	27	19	32	2		3	36	1,487	312	
2003	1,171	170	27	13	166	17	9	18	518	132	9	16	12	20	13	2		5	64	948	223	
2004	864	136	16	13	107	16	12	13	399	65	12	17	17	11	12	1		1	38	709	155	
2005	1,369	213	28	16	222	8	12	13	660	78	10	11	25	20	22	4		1	45	1,126	243	
2006	2,051	272	62	25	465	15	14	23	869	123	25	23	30	29	40	4			30	1,671	380	
2007	2,227	314	41	36	484	7	23	16	1,007	125	30	23	23	20	41	2			35	1,834	393	
2008	1,052	126	27	15	164	8	10	7	490	109	11	21	14	11	17	5			29	901	151	
2009	1,345	178	33	25	164	10	21	16	611	154	18	27	18	11	26	1			26	1,183	162	
2010	1,772	290	43	19	256	9	15	8	818	184	23	14	22	21	24	7			51	1,476	296	
2011	838	94	24	16	124	6	9	7	389	94	11	12	12	11	13	4			64	744	94	
2012	555	67	7	4	143	1	4	3	263	13	8	7	5	4	16	2			53	446	109	
2013	445	45	8	8	84	3	4	1	228	27	7	3	2	4	8	2			60	369	76	
2014	638	96	17	8	131	3	2	4	311	16	4	12	10	1	12	2			80	514	124	
2015	699	91	6	5	108	1	6	4	417	20	8	8	7	4	5	2	1		71	600	99	
2016	681	94	9	12	84	2	7	7	393	26	8	5	3	8	10	3	1		71	558	123	
2017	515	68	3	4	80	9	1	3	295	12	2	10	3	3	4	4	1	0	79	400	115	
Total (%)	34,487 (100)	4,430 (12.85)	766 (2.22)	468 (1.36)	4,382 (12.71)	270 (0.78)	313 (0.91)	271 (0.79)	16,609 (48.16)	4,017 (11.65)	336 (0.98)	443 (1.28)	403 (1.17)	440 (1.28)	610 (1.77)	88 (0.26)	3	0	35 (0.1)	901 (2.61)	400	115

Table 3. Incidence rate (per 100,000 population) of vivax malaria from 1993 through 2017 according to the Province

	Total	Seoul	Busan	Daegu	Incheon	Gwang-ju	Daejeon	Ulsan	Gyeong-gi	Gang-won	Chung-buk	Chung-nam	Jeon-buk	Jeon-nam	Gyeong-buk	Gyeong-nam	Jeju	Sejong	Unkonwn
1993	0.01	0.01			0.04				0.01										
1994	0.06	0.01	0.03		0.09				0.26							0.03			
1995	0.24	0.05	0.03	0.04	0.04				1.22	0.27	0.07					0.03			
1996	0.77	0.09	0.03	0.04	0.20	0.07			3.22	2.69	0.05			0.10	0.15	0.07			
1997	3.74	1.00	0.46	0.56	2.10	0.44	0.58		14.20	11.90	0.34	0.76	0.42	0.70	0.40	0.67	0.39		
1998	8.52	4.54	2.94	2.22	8.57	2.14	1.75	1.28	24.45	34.90	2.18	3.41	1.32	2.96	1.54	3.32	1.17		
1999	7.89	4.92	2.21	1.65	13.25	1.85	2.92	3.55	19.59	34.57	1.77	2.17	2.27	2.96	2.64	2.01	1.75		
2000	8.98	4.99	2.51	3.31	18.63	3.47	2.92	3.65	18.35	55.48	2.80	3.25	3.07	3.66	2.86	2.38	3.51		
2001	5.34	3.40	1.79	1.20	10.37	2.14	2.12	2.94	8.31	36.04	1.54	1.73	1.92	1.99	1.56	1.93	1.08	0	0
2002	3.74	2.80	1.35	1.00	10.22	1.21	1.23	0.92	7.00	14.31	1.47	1.12	1.01	1.38	1.08	1.01	0.36	0	0
2003	2.42	1.67	0.74	0.52	6.35	1.21	0.62	1.65	4.80	8.75	0.60	0.81	1.07	0.61	0.89	0.41	0.36	0	0
2004	1.78	1.34	0.44	0.52	4.10	1.14	0.82	1.19	3.69	4.31	0.80	0.86	0.59	0.87	0.60	0.38	0.18	0	0
2005	2.81	2.09	0.77	0.64	8.50	0.57	0.82	1.19	6.11	5.17	0.67	0.56	1.07	1.28	0.97	0.69	0.72	0	0
2006	4.20	2.67	1.71	1.00	17.80	1.07	0.96	2.11	8.05	8.15	1.68	1.17	1.60	1.48	1.19	1.26	0.72	0	0
2007	4.53	3.08	1.14	1.44	18.30	0.50	1.56	1.46	9.15	8.31	2.00	1.16	1.23	1.03	1.30	1.19	0.36	0	0
2008	2.13	1.24	0.76	0.60	6.12	0.56	0.68	0.63	4.38	7.24	0.73	1.05	0.75	0.57	0.63	0.53	0.89	0	0
2009	2.71	1.74	0.93	1.00	6.07	0.70	1.42	1.44	5.37	10.19	1.18	1.33	0.97	0.57	1.20	0.80	0.18	0	0
2010	3.53	2.83	1.21	0.76	9.36	0.62	1.00	0.71	7.04	12.09	1.49	0.68	1.18	1.10	0.71	0.73	1.23	0	0
2011	1.63	0.91	0.67	0.64	4.46	0.41	0.60	0.62	3.28	6.13	0.71	0.57	0.64	0.57	0.45	0.39	0.70	0	0
2012	1.07	0.66	0.20	0.16	5.07	0.07	0.26	0.26	2.19	0.85	0.51	0.34	0.27	0.21	0.30	0.48	0.34	0	0
2013	0.87	0.44	0.23	0.32	2.94	0.20	0.26	0.09	1.87	1.75	0.45	0.15	0.11	0.21	0.41	0.24	0.34	0	0
2014	1.25	0.95	0.48	0.32	4.53	0.20	0.13	0.34	2.53	1.04	0.25	0.58	0.53	0.05	0.33	0.36	0.33	0	0
2015	1.37	0.92	0.17	0.20	3.74	0.07	0.39	0.34	3.34	1.32	0.50	0.38	0.38	0.22	0.22	0.15	0.30	0.49	0
2016	1.33	0.95	0.26	0.49	2.91	0.13	0.46	0.60	3.15	1.71	0.50	0.24	0.16	0.44	0.34	0.30	0.46	0.49	0
2017	1.01	0.67	0.09	0.16	2.71	0.61	0.07	0.26	2.29	0.78	0.13	0.47	0.16	0.16	0.48	0.12	0.61	0.35	0

a means of chemoprophylaxis directed towards relapse, and the introduction of a National Malaria Control Program (NMCP) in 1999. Both strategies have been fully operational since 2001 [32,33]. The majority of cases in North Korea occurred in Gangwon and Hwanghae Province, which border the DMZ. Korea had over 4,000 cases reported in the 2010 WHO World Malaria Report (Table 1) [34]. High-risk areas in Korea were adjacent to those in North Korea, including Incheon-si (si = city) and northern Gyeonggi and Gangwon-do. Perhaps exacerbating the transmission, travelers from Korea were allowed to visit certain regions of North Korea, including Gaeseong City and Geumgang-san (san = mountain) (Fig. 1). The influx of mosquitoes (*Anopheles sinensis*) infected with *P. vivax* from North Korea could be one of the possible routes of re-emergence. *An. sinensis*, the major anopheline vector for vivax malaria in Korea, travels up to 12 km in a single night, theoretically permitting traversal of the DMZ [35]. Meanwhile, a haplotype network analysis of the parasite's mitochondrial genome suggested that the genealogical origin of the re-emerged *P. vivax* in Korea was Southern China [36]. Further complex analyses of the genotypes of the Korean *P. vivax* population are necessary to conclusively trace the path of re-emerged *P. vivax* in Korea.

PREVALENCE OF THE MALARIA PARASITE

The published articles included in this review chronicle the prevalence of vivax malaria between 1993 and 2017 in Korea. We incorporated data from several sources, including [1] national-level data including guidelines, reports, documents, and maps from the Korea Centers for Disease Control & Prevention (KCDC), [2] related data from outside the Ministry of Health and Welfare, [3] scientific articles on malaria in Korea, and [4] WHO reports of technical missions, records, and reports of the WHO Regional Office for Asia meetings. In Korea, reports to the local Public Health Center (PHC) for malaria cases in hospitals or clinics are required by law. PHCs must periodically report cases to the KCDC using the infectious diseases surveillance system [37]. Since the re-emergence of vivax malaria in Korea (1993-2017), 33,972 cases have been diagnosed and reported (Table 1).

The high-risk areas in Korea adjacent to the malaria-risk areas in North Korea, which include Incheon-si, Gyeonggi-do, and Gangwon-do, account for over 70% of all vivax malaria cases in Korea (Table 2). Each malaria case in Korea is reported

in the metropolitan area/province where the diagnosis is made, which may differ from the area where the infection occurred. In addition, it is particularly difficult to ascertain the transmission sites, since approximately 60% of vivax malaria in Korea is latent, with symptoms occurring 1-24 months after infection [38]. The issue of latency of vivax malaria will be discussed in later sections. Thus, despite the recent progress to reduce malaria cases, these efforts will likely not be sufficient to eliminate malaria from Korea.

The temporal frequency of cases includes 3 major peaks in 2000 (4,142 cases), 2007 (2,227 cases), and 2010 (1,772 cases) (Table 1). The overall decline in cases may reflect the dedicated anti-malarial chemoprophylaxis that has been carried out on military bases since 1997 and the anti-malarial efforts of the government. The current vivax malaria incidence indicates that exponential growth is not occurring. However, the annual volatility of the pattern of sharp decline since 2000 may also correlate to changes in the environment of the parasite and the mosquito in the endemic areas of Korea.

Although the incidence of malaria is directly affected by the malaria parasites and individuals bitten by infected mosquitoes, climate factors such as temperature, precipitation, humidity, rainfall, and flooding also play critical roles [39]. The correlation between climate change and increased malaria risk in Korea is under investigating. However, there are concerns that changing climate determinants will have an impact on the incidence of malaria. For example, climate change might potentially lead to increased locally-acquired autochthonous transmission by enhancing the growth, survival, and distribution of mosquitoes that can mediate malaria and by changing human activities [39-41]. Thus, efforts to suppress vivax malaria cases should be maintained so that no intrinsic potential for transmission remains.

CASE DISTRIBUTION AND SEASONAL TRENDS

Cases of vivax malaria were limited and sporadic from 1993-1996 but endemic thereafter (Table 1). The incidence of malaria rapidly increased from 0.01/100,000 population in 1993 to 8.52/100,000 population in 1998, peaking at 8.98/100,000 population in 2000 (Table 3). A total of 34,487 indigenous vivax malaria cases were officially reported in Korea from 1993-2017. Although a substantial decrease in the annual number of malaria cases was observed in recent years, vivax malaria still remains endemic in Korea.

Table 4. Number and percentage of vivax malaria cases confirmed in Korea from 2001 through 2017 according to the age groups and gender. Because of unavailability of number of vivax malaria according to age groups, this table presents the vivax malaria cases in Korea from 2001 through 2017

	0-9		10-19		20-29		30-39		40-49		50-59		60-69		70-		Total								
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female		Total							
2001	13	7	20	66	35	101	1,530	36	1,566	190	56	246	222	76	298	86	50	136	58	67	125	25	39	64	2,556
2002	15	7	22	38	18	56	969	41	1,010	166	52	218	145	74	219	82	48	130	53	47	100	19	25	44	1,799
2003	9	9	18	28	17	45	602	28	630	119	35	154	116	51	167	38	29	67	22	32	54	14	22	36	1,171
2004	3	3	6	30	17	47	444	18	462	64	29	93	81	29	110	45	23	68	28	19	47	14	17	31	864
2005	9	3	12	32	14	46	590	26	616	156	34	190	184	60	244	80	41	121	55	41	96	20	24	44	1,369
2006	17	11	28	68	28	96	843	45	888	257	47	304	241	87	328	130	65	195	80	55	135	35	42	77	2,015
2007	10	9	19	60	33	93	989	43	1,032	217	46	263	282	80	362	161	80	241	73	60	133	42	42	84	2,227
2008	1	2	3	34	8	42	498	22	520	87	26	113	146	35	181	74	27	101	37	17	54	24	14	38	1,052
2009	5	3	8	43	13	56	738	27	765	86	14	100	156	39	195	104	31	135	35	17	52	16	18	34	1,345
2010	7	5	12	55	23	78	813	36	849	145	52	197	223	67	290	147	48	195	62	37	99	24	28	52	1,772
2011	2	1	3	29	7	36	484	14	498	53	6	59	64	24	88	67	17	84	26	12	38	9	11	20	826
2012	3	1	4	17	8	25	197	14	211	47	15	62	77	20	97	58	18	76	19	12	31	16	20	36	542
2013	3	1	4	16	8	24	181	8	189	49	12	61	51	13	64	45	13	58	15	12	27	9	9	18	445
2014	1	1	2	20	9	29	195	10	205	77	22	99	100	24	124	85	29	114	27	13	40	9	16	25	638
2015	4	6	10	24	6	30	309	13	322	80	12	92	85	20	105	66	22	88	23	9	32	9	11	20	699
2016	3	1	4	12	4	16	326	21	347	69	7	76	71	23	94	52	28	80	22	12	34	9	13	22	673
2017	0	5	5	15	5	20	188	19	207	47	11	58	57	28	85	64	19	83	24	19	43	5	9	14	515
Total	105	75	180	587	253	840	9,896	421	10,317	1,909	476	2,385	2,301	750	3,051	1,384	588	1,972	659	481	1,140	299	360	659	20,544
(%)	(0.51)	(0.37)	(0.88)	(2.86)	(1.23)	(4.09)	(48.17)	(2.05)	(50.22)	(9.29)	(2.32)	(11.61)	(11.20)	(3.65)	(14.85)	(6.74)	(2.86)	(9.60)	(3.21)	(2.34)	(5.55)	(1.46)	(1.75)	(3.21)	(100)

Malaria in Korea is unstable and seasonal, with 94% of cases (32,429 of 34,487 cases) occurring between 1993-2017 reported between May and October when malaria vectors exist in the field (Table 1). This seasonal distribution pattern of malaria cases has not changed over time and has not been affected by the decline in malaria transmission. Indigenous malaria cases that occurred in the first 4 months of the calendar year, winter and spring, might comprise *P. vivax* infections contracted in the previous malaria season that had a subsequent prolonged incubation. Such prolonged incubation cases account for approximately 60% of cases annually [38].

Malaria is detected in all age groups, but the most affected group is the 20-29-year-old group (10,317 of 20,544 cases [50.22%] in 2001-2017; Table 4). Malaria incidence in males (17,140 of 20,544 cases [83.43%] in 2001-2017) was markedly higher than that in females (3,404 of 20,544, 16.57%) (Table 4). Although there was a progressive decline in vivax malaria cases in individuals over 17 years of age from 2001-2017, the majority of cases were reported in young men 20-29 years of age (10,317 of 20,544 cases, 50.22%) (Table 4). Males 40-49 years of age comprised the group with the second highest number of cases (3,051 of 20,544, 14.85%) (Table 4). The notably higher case prevalence in 20-29-year-old males suggests an increase in the risk of infection outside their places of residence, as these males are the most mobile members of the population and are most likely to be working in the fields or serving as military personnel in Korea. This is consistent with the fact that human contact with vector mosquitoes and the distance between human residences and mosquito habitats are pivotal conditions determining the incidence of malaria [42].

IMPORTED CASES

The number of imported malaria cases has increased in Korea over the past 20 years (Table 1). Most cases of imported malaria were infections with *P. falciparum* or *P. vivax*. Infections with *P. falciparum* were mainly acquired in Africa, and vivax malaria infections mainly in Southeast Asia, consistent with the typical parasite frequencies of these areas. Imported malaria has a higher incidence in males than in females. Similar demographics have been reported in European countries [43-45]. Males in their 20s are most likely to be infected with imported malaria, likely because they are more likely to travel to areas with a high risk of malaria infection and participate in experiential tourism [43-45].

MOSQUITO VECTOR

A dramatic reduction in the incidence of vivax malaria has been achieved through large-scale national control systems in Korea. Yet, active transmission still persists, particularly in Incheon-si and northern part of the Gyeonggi-do. Control of the mosquito vector is essential for the eradication of malaria. Vector, pathogen, and host controls are the principal strategies of an effective malaria control program. The use of national media to increase the awareness of the need for personal protection against mosquitoes should also aid in transmission reduction.

Malaria is transmitted to humans by the bite of a female anopheline mosquito vector carrying malaria parasites during the acquisition of a blood meal. These vector populations depend on specific climatic and sociodemographic factors. *P. vivax* is transmitted in Korea by 6 *Anopheles* species (the Hyrcanus Group): *An. sinensis* sensu stricto, *An. belerae*, *An. pullus*, *An. kleini*, *An. sineroides*, and *An. lesteri* [46,47]. The Hyrcanus group of *Anopheles* mosquitoes typically dwells near irrigation ditches, ponds, ground pools, and uncultivated fields [48]. Studies of the infection capacity of *An. sinensis*, the most dominant Hyrcanus species in August, September, and October, and the primary vector of malaria in Korea, have been conducted [48-50]. However, an understanding of the other 5 species remains elusive [51]. The frequency of contact of *An. sinensis* with humans is very low because this vector is highly zoophilic [52,53]. Other factors reducing the contact are the widespread application of personal protection against mosquito bites [54] and the low to moderate longevity of *An. sinensis* in Korea [19,49]. Thus, the opportunity for malaria transmission by mosquitoes appears limited. In addition to the 6 major *Anopheles* species, *An. koreicus* and *An. lindesayi japonicus* (from the Barbirostris and Lindesayi group, respectively) have been reported in Korea [55-58]. However, the incidence of malaria due to these 2 vectors has not been studied. It is presumed that these 2 species live mainly in swamps and stream margins, including stream inlets and pools [48,59], with low human-vector contact preventing human blood meals and *P. vivax* infection. However, there is no evidence that these species cannot develop or propagate malaria parasites. Additionally, no systematic reports have focused on the densities of the malaria vector mosquitoes as active disease vectors from 1993-2017. The only related report was issued by the KCDC, which chronicled the monitoring of malaria vector mosquito density and *P. vivax* malaria infections since 2009 [60]. From 2013-2014, the density of *An. sinensis* in-

creased at most collection sites with the same high tendency of annual mean temperature and precipitation [61]. More research on malaria vectors in Korea is needed to provide detailed information about *P. vivax* transmission capacity. The hypnozoites that cause relapse may be activated weeks or months after the initial infection. Little is known about the biology and determinants of this latency [62].

INCUBATION PERIOD OF *P. vivax* MALARIA

In Korea, tertian malaria consists of 2 sub-groups. A non-latent group displays symptoms 10-21 days after infection (a short incubation period) [63]. A latent group displays symptoms 6-18 months after infection (a longer incubation period) with unusual biological characteristics and the presence of hypnozoites. In addition, the observed distribution of latent and non-latent infection reflects the adaptation of the parasite to the seasonal population dynamics of the *An. sinensis* vector, ensuring continued transmission of vivax malaria in this temperate zone despite a long winter period [63]. The occurrence of this long-term latency in vivax malaria in Korea over all four seasons impedes disease management at the national level.

In Korea, vivax malaria transmission is largely limited to the DMZ. Sixty to seventy percent of patients, including those diagnosed in the summer, are classified as long-term latency patients [38]. By monitoring travel routes of people living in non-endemic areas from 2000-2003, the mean duration of long-term latency was identified as 48.2 weeks (337.4 days), which was 12.7 times longer than that of short-term latency (26.6 days) [63]. The factors affecting long-term latency remain unclear, but it is presumed that temperature, infection time, and number of sporozoites play a role. It has also been hypothesized that differences in latency periods among populations may involve parasite genetics and/or the vector's capacity for sporozoites. It was recently reported by Goo et al. [64] that the genotype of *PvMSP-1* is related to the duration of the latent period. The *PvMSP-1* recombinant type was predominant in the long latent period samples, while the *PvMSP-1* Sal-1 type was most prevalent in the short latent period.

FUTURE STRATEGIES FOR THE ELIMINATION OF VIVAX MALARIA IN KOREA

Malaria has been an endemic disease in Korea for 25 years since its re-emergence in 1993, with a rapidly increasing trend

up until 2000. Since then, there has been a mixed pattern of repeated increases and decreases in malaria outbreaks but a steadily declining trend in overall incidence. Academia, central government, local governments, and the military are carrying out various projects that include rapid patient discovery and treatment, and vector control with the basic goal of malaria elimination through treatment, intervention, and pathogen management. Korea is now reaching the pre-phase of malaria elimination, but outbreaks still continue. Additional efforts are needed for the complete elimination of malaria within the next few years and ongoing prevention.

Microscopic examination as a method to diagnose malaria has some limitations, but this method is regarded as the gold standard. Microscopic examination requires skilled specialists to prepare and examine blood smears. Furthermore, sample preparation and inspection are time-consuming. Polymerase chain reaction (PCR)-based diagnostic protocols have been recognized as powerful tools to detect malaria infection and differentiate the infected species with high specificity and sensitivity [65,66]. Nevertheless, PCR methods also have limitations, such as high cost and low applicability without adequate laboratory equipment. The rapid diagnostic test (RDT) has replaced microscopic examination in many malaria endemic countries worldwide because of its relatively reliable diagnostic performance and easy applicability. However, the RDT also has several drawbacks including its low sensitivity against low parasitemia blood samples. To overcome these shortcomings, a new tool that can detect very small amounts of antigen and antibody is needed. As shown in Table 1 and Fig. 3, similar numbers of vivax malaria cases were reported from 2014-2017, implying that a steady state of malaria transmission in Korea has been maintained in recent years. Therefore, efforts toward more intensive and systematic malaria surveillance, especially in Incheon-si and the northern part of Gyeonggi-do, are necessary to reduce the potential for future increases in malaria cases in endemic areas. The re-emergence of malaria at the DMZ in 1993 is regarded as an unstable malaria transmission that spontaneously appeared and disappeared within a short period of time without a clear reason [31]. To achieve the goal of complete malaria eradication in Korea, it is necessary to consider re-introduction of active case detection, as employed in the 1960s and 1970s.

In general, the circumsporozoite protein (CSP) antibody is produced by sensitization to the antigen presenting cell (APC) when the sporozoite circulates in the human body for 30 to

60 minutes. The CSP antibody has a short half-life that disappears before the next epidemic [67]. In the winter season, a survey for the presence of the CSP antibodies among the residents of high malaria risk areas in Paju-si, Gyeonggi-do, Cheolwon-gun, Gangwon-do, and Gangwha-gun, Incheon-si, might be useful for providing valuable and indirect data with other malarial antibodies for the certification of complete elimination of vivax malaria in Korea. In addition, new malaria management measures should be carried out in accordance with the situation in 2018.

CONCLUSION

The continued and systematic strengthening of control activities for vivax malaria in Korea is premised on the view that the number of vivax malaria cases has reached a steady-state level after its re-emergence in 1993. In spite of the good prospects for success, elimination has proceeded slowly and has been unsuccessful. The geographic boundary of transmission has not shrunk. These realities provide hints that technical aspects, such as resistance to the vector and drugs, are not primarily important and multiple factors are involved in an effective control system. With the current plateau in the number of malaria cases, more efforts must be made to ensure elimination of vivax malaria in Korea. Thus, the government and private sector have to collaborate in diverse areas including education, agriculture, environment, finance, research, medical inspection, communication, and transportation, and must implement all strategies that feasibly suppress the transmission of the infection. Although, in the past time, vivax malaria were considered to be mostly benign and rarely severe and Korea is one of successfully controlled nations for vivax malaria, the precise pathophysiology of *P. vivax* infection still remain poorly elusive and there is a critical aperture in the current knowledge on vivax malaria in Korea, for examples, drug resistance against chloroquine and primaquine that have been used for the treatment in Korea, genetic alterations in parasite's genomic contents, changes in host responses and incubation times etc. Coordinated multidisciplinary struggles are pivotal to bridge this knowledge aperture.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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