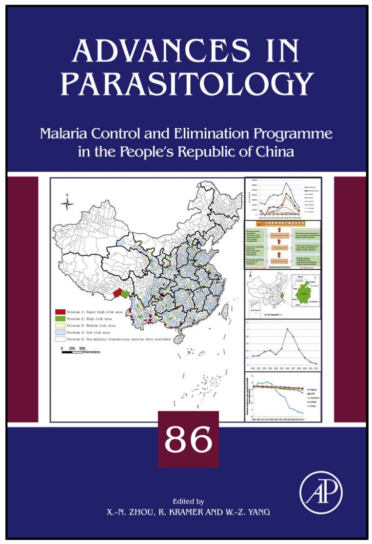

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CHAPTER EIGHT

Preparation of Malaria Resurgence in China: Case Study of Vivax Malaria Re-emergence and Outbreak in Huang-Huai Plain in 2006

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Abstract

This chapter reviews the patterns of malaria re-emergence and outbreak that occurred in the Huang-Huai Plain of China in 2006, and the way of quick response to curtail the outbreak by mass drug administration and case management. The contribution of the each intervention in quick response is discussed. Particularly due to the special ecological characteristics in the Huang-Huai Plain, the intervention of vector control is not implemented. Finally, the challenges in the elimination of malaria in this region are highlighted.

1. INTRODUCTION

Vivax malaria was historically epidemic in the Huang-Huai Plain of China and *Anopheles sinensis* was the main vector. There were two major epidemics in which these malaria cases accounted for 93.1% and 91.2% of total cases of the entire country in 1960 and 1970, respectively. Vivax malaria cases were reduced significantly in the Huang-Huai Plain by the end of the 1980s, and malaria incidence was below 1/10,000 in most areas. However, the incidence of vivax malaria had a resurgence pattern in the early twenty-first century, and malaria outbreaks were found in 2006. This chapter reviews a case study of vivax malaria outbreak in the Huang-Huai Plain in 2006, and the way of quick response to cut down the outbreak by mass drug administration (MDA) and case management.

2. BACKGROUND

Malaria is an important cause of death and illness in children and adults in tropical countries. According to World Malaria Report 2012 (WHO, 2012), there were an estimated 219 million cases of malaria (range 154–289 million) and 660,000 deaths (range 610,000–971,000) in 2010. Of the four human *Plasmodium* species, *Plasmodium vivax* has the widest global distribution and accounts for most malaria infections outside Africa (Mendis et al., 2001).

The greatest proportion of the worldwide vivax malaria burden almost certainly lies in south and southeast Asia (probably more than 80% of infections), with perhaps underappreciated numbers of infection in Africa (Mueller et al., 2009). Despite significant reductions in the overall burden of malaria in the twentieth century, the disease still represents a significant public health problem in China. Vivax malaria was historically epidemic in the Huang-Huai Plain, and there were two major epidemics in which the number of malaria cases accounted for 93.1% and 91.2% of total cases of the entire country in 1960 and 1970, respectively.

Huang-Huai Plain (also called Huang-Huai River region) is located 32°–36° N and 112°–122° E in central China, between south of Yellow River and north of Huai River. The average altitude of this area is 50 m above sea level. The climate of the region is temperate. The area receives about 700 mm of rainfall per annum with 50–80% occurring during the summer from June to September. The average annual temperature is 14–15 °C, ranging from −1 °C to −4 °C in January and from 25 °C to 27 °C in July. The frost-free period is 200–240 days. The main crops are wheat, rice, corn, potato, soybean, cotton and rapeseed. The population of these areas is above 50 million, which covers 116 counties in four provinces of Henan, Anhui, Shandong and Jiangsu (Figure 8.1).

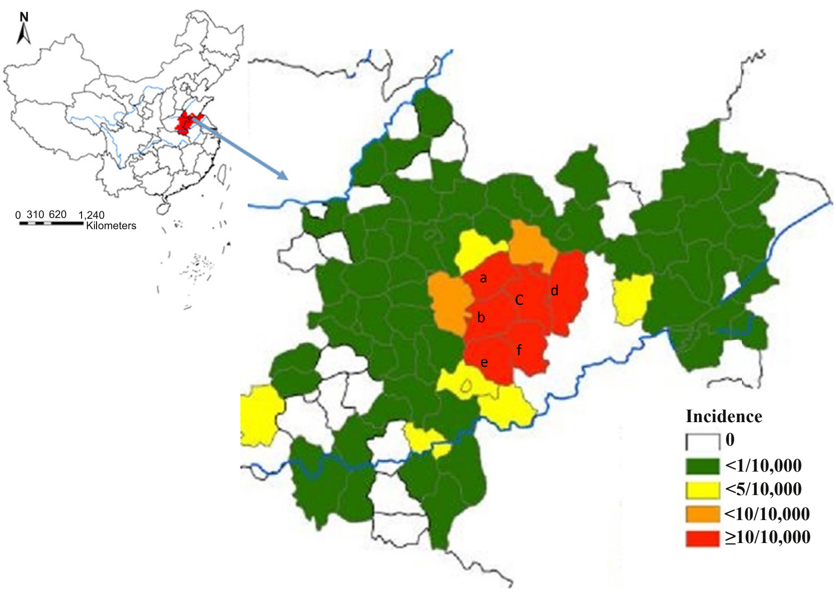

Figure 8.1 Geographic distribution of malaria incidence in the Huang-Huai Plain in 2006 (Different color represents the various malaria incidences at county level. a. Yongcheng; b. Woyang; c. Suixi; d. Yongqiao; e. Lixin; f. Mengcheng).

Malaria in the Huang-Huai Plain can be classified as seasonally unstable and epidemic which means malaria transmission in this region is still existed with a higher incidence. Poor farming communities bear the greatest burden of disease. A major epidemic of *P. vivax* occurred in the 1960s and at the beginning of the 1970s. The total malaria cases in these areas were 9.5 million, accounting for 93.1% of the total reported cases in the country in 1960 (Zhou, 1991). There may be three main reasons that caused the malaria epidemic in 1960. The first and the main reason was a considerable amount of the wheat fields (dry land) changing into rice fields (wet land) in the late 1950s. New irrigating projects were set up; a lot of irrigation channels and a reservoir were built. As a result, the ground water area expanded considerably, stagnant water areas remained constant. The population of *An. sinensis* increased dramatically. An investigation in Suyang County of Jiangsu Province showed that density of *An. sinensis* was dozens to a hundred times higher than that both in house and cattle shelf before changing the dry land to wet land. At that time, local houses were generally simple and crude. It was hot and muggy indoors in summer and autumn, and local residents had the habit of sleeping outside during the summer. This increased the chance of mosquitoes biting residents and strengthened malaria transmission. The second reason may have been a decreasing animal barrier. Animals such as cattle and buffalo play a zooprophylactic role for malaria transmission due to attracting larger numbers of mosquitoes and thus decreasing human vector contact (Manh et al., 2010). Most households have dogs and chickens in this region. Cattle and buffalo free range during the day, when not used for work, but at night are penned or tethered near the owner's house. When People's Community was organized after 1957, the model of livestock feed was changed to feeding together from separate feed, and no cattle were fed near the residents' houses. The chance of local people being exposed to mosquitoes increased significantly due to this decreasing animal barrier. The third reason was that China did not have the ability to produce a large amount of chloroquine and primaquine in 1960, so most MDA of pyrimethamine and proguanil were used to treat patients and give chemoprophylaxis at that time, in which malaria epidemics could be controlled to a low prevalent level, but plasmodium parasites could not be clearly eliminated.

Another major vivax malaria epidemic occurred in 1970. The main reason was the epidemic occurred in the special event of the Cultural Revolution (beginning 1965–1968), during which time civil disturbances resulted in the abandonment of antimalarial activities. Malaria prevalence was controlled by MDA of using chloroquine and primaquine after 1970.

With active implementation of malaria control measures (integrated vector control measures and appropriate treatment of malaria cases) for more than

30 years, considerable success had been achieved and human cases infected with *P. vivax* have been reduced significantly in the Huang-Huai Plain of China in the new millennium. Malaria incidence in the areas where *An. sinensis* was the only vector had been reduced significantly to a low level, for example, a total of 1321 counties reached the standard of the basic malaria elimination (the incidence is less than 1/10,000) in 1999 (Xu et al., 1994, 2006; Tang and Gao, 2013). According to the national data on malaria transmission, the average annual incidences of vivax malaria in 1998 in Anhui and Henan provinces were below 1 per 100,000 and 0.03 per 100,000, respectively (Qian and Shang, 1999).

However, the incidence of vivax malaria had a resurgence in the Huang-Huai Plain in the early part of this century, and malaria outbreaks were found in Anhui and Henan provinces in 2006. About 66.4% of malaria cases in the country were located in the Huang-Huai Plain, especially in Anhui and Henan Provinces (Zhou et al., 2007b).

3. VIVAX MALARIA RE-EMERGENCE AND OUTBREAK IN HUANG-HUAI PLAIN

From 2000 to 2006, there was a substantial increase in malaria cases due to re-emerging vivax malaria in the Huang-Huai Plain. The total number of annual malaria cases was 18,762 and 40,991 in four provinces of Anhui, Henan, Jiangsu and Shandong in 2005 and 2006, respectively, with 118.48% of an increase rate between two years. In 2006, the number of malaria cases in Anhui and Henan provinces accounted for 62.45% of the total cases in the country (Zhou et al., 2007b), and malaria incidence increased by 123.10% and 120.92% compared to that in 2005 in Anhui and Henan provinces, respectively (Table 8.1).

Dramatic resurgence appeared in Yongcheng and Xiayi counties in the east of Henan Province, where malaria incidences in 2006 were increased by

Table 8.1 Malaria situation in the Huang-Huai Plain in 2006 and 2005

	No. of malaria cases			Malaria incidence (1/10,000)		
Province	**Year 2006**	**Year 2005**	**Increase/ decrease (±%)**	**Year 2006**	**Year 2005**	**Increase/ decrease (±%)**
Anhui	34,984	15,681	+123.10	6.40	2.45	+161.22
Henan	5090	2304	+120.92	0.52	0.24	+116.67
Jiangsu	767	651	+17.82	0.11	0.10	+10.00
Shandong	150	126	+19.05	0.02	0.02	+0
Huang-Huai plain	40,991	18,762	+118.48	1.38	0.65	+111.74

307.04% and 360.94% compared to that in 2005, respectively. In Yongcheng County, malaria incidence was 1.23 per 10,000 in 2004 and 5.19 per 10,000 in 2005, so that the malaria incidence of the county in 2006 were 13 and 3.22 times higher than that of the previous year, respectively (Zhang et al., 2007). In Jiangsu Province, malaria cases in 2006 were mainly in the three cities of Xuzhou, Suqian and Huai'an, where a total of 422 malaria cases reported, which accounted for 55.02% of all cases in Jiangsu Province (Wang et al., 2007). There were 150 malaria cases reported in Shandong Province in 2006, a 19% increase over 2005 (Zhou et al., 2007b).

3.1 Distribution by district of malaria outbreaks in the Huang-Huai Plain in 2006

According to the 'Malaria emergency preparedness plan of action in China' published by the Ministry of Heath, a malaria emergency event is defined as described herein: in township level where a malaria case was reported in past three years, 10 or more local malaria cases are found in the same administrative village within one month (MOH, 2006). In this chapter, the definition of the malaria outbreak is the same as the malaria emergency event.

In 2006, a total of 302 outbreaks occurred in 63 townships of 11 counties in the Huang-Huai Plain. All outbreaks were at the administrative village level, of which 275 outbreaks were found in 10 counties of Anhui Province and 36 were reported in 1 county of Henan Province (Zhou et al., 2007b; Su et al., 2008). Totally 280 outbreaks were found in four counties of Guoyang, Lixin, Yongcheng and Mengcheng counties, accounting for 92.72% of total outbreaks (Figure 8.1; Table 8.2).

In Yongcheng County, 36 malaria outbreaks and 1825 cases were found in four townships, accounting for 63.1% of total malaria cases in the county in 2006. Average malaria incidence of four townships was 106.73 per 10,000 and 4.8 times higher than that of Yongcheng County in 2005. In 36 outbreak spots located at administrative villages, 1265 cases were found and the average malaria incidence was 1.8%. The highest malaria incidence was up to 4.0% in a village with 43 malaria cases (Zhou et al., 2008).

3.2 Distributions by sex, age and occupation of malaria cases in outbreak spots in 2006

There were 9678 malaria cases reported in 302 outbreak spots, accounting for 31.27% of total cases (30,951 cases) in 11 counties with outbreaks and 23.85% of total cases (40,574 cases) in the Huang-Huai Plain. It was found that there were 582 patients less than 5 years old, accounting for 4.82% of 9678 malaria cases reported in 302 outbreak spots; 17.67% were

Table 8.2 Malaria situation in 11 counties with outbreaks in the Huang-Huai Plain in 2006

Name of county	Number of cases	Malaria incidence (1/10,000)	Number of townships with outbreak	Number of outbreaks
Lixin	5422	38.86	17	69
Lieshan	728	47.16	1	1
Lingbi	802	7.36	1	2
Mengcheng	3539	30.54	8	30
Jiaocheng	790	5.60	3	3
Suixi	5456	46.05	5	12
Guoyang	7950	58.38	20	145
Xiangshan	163	5.19	1	1
Xiaoxian	996	8.01	2	2
Yongqiao	2214	13.27	1	1
Yongcheng	2891	22.29	4	36

Table 8.3 Distribution of malaria cases by age, sex and occupation in 302 outbreak spots in the Huang-Huai Plain in 2006

Age				Sex		Occupation				
<5	5–15	15–65	≥65	Male	Female	Farmer	Student	Children	Labor	Others
466	1710	6047	1455	5524	4124	6654	2073	725	172	54

between 5 and 15 years old; 62.48% were between 15 and 65 years old; and 15.34% were over 65 years old (Table 8.3). In contrast to holo-endemic and hyperendemic regions in Africa where greater morbidity and mortality occur in children and infants, only a limited proportion of the cases presented in children <5 years of age. But 22.49% of cases occurred in children <15 years old, which may indicate transmission in the household and school neighborhood. The ratio of male to female population was 1.33:1. Farmers were the main portion of patients, accounting for 68.75%, followed by students at 21.42%.

3.3 Distribution by month of malaria cases in outbreak spots in 2006

There were significant seasonal characteristics of malaria transmission in the Huang-Huai Plain. Normally, malaria transmission was from the mid-May to late October. No malaria transmission occurred from early November to next late April, although here were a few reported malaria cases during January to March. Malaria cases increased in April and there was a small pick-up from May to June, malaria cases increased significantly after July, and a high peak can be found from August to September (Figure 8.2).

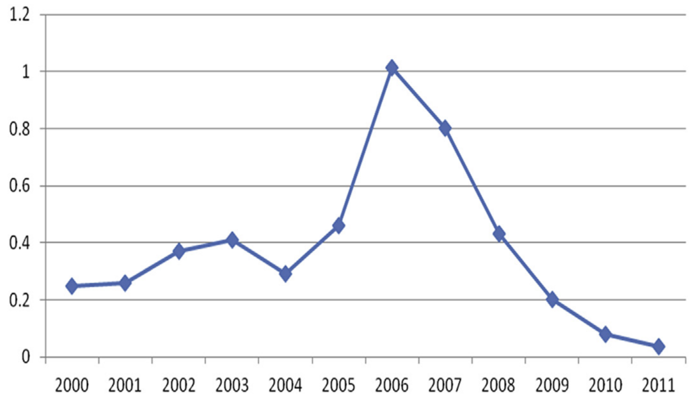

Figure 8.2 Malaria incidence (1/10,000) in the Huang-Huai Plain from 2000 to 2011.

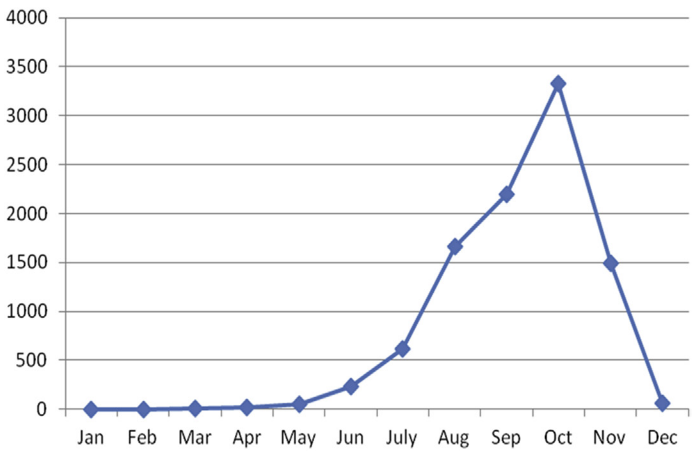

Figure 8.3 Distribution of malaria cases by month in 302 outbreak spots in the Huang-Huai Plain in 2006.

Malaria cases decreased quickly after October. More than 85% of malaria cases were reported from June to October (Su et al., 1995).

In 2006, malaria cases were mainly reported during August and November; 8681 cases were reported, accounting for 89.7% of total cases found in outbreak spots (Figure 8.3). The peak of the epidemic occurred in October with 3334 cases reported. Transmission season was longer than that of before. There is a continuously increasing trend of malaria cases from June to October, forming a straight rising line (Table 8.4). This shows that malaria transmission was strengthened in the Huang-Huai Plain. Monthly *P. vivax* malaria incidence showed a seasonal pattern, whose peak period

Table 8.4 Distribution of malaria cases by month in 302 outbreaks in the Huang-Huai Plain in 2006

Month	No. of cases
January	3
February	2
March	5
April	22
May	52
June	235
July	618
August	1665
September	2192
October	3334
November	1490
December	60

was from July to November, when nearly 86.58% of total malaria cases were reported in Yongcheng County.

4. CHARACTERISTICS OF MALARIA RE-EMERGENCE AND OUTBREAK IN HUANG-HUAI PLAIN

4.1 Aggregation of malaria cases

From Figure 8.1, we can find that there was an aggregation of malaria cases distributed at the boundary of north Anhui Province and Henan Province, including Guoyang, Mengcheng, Suixi, Yongqiao, Lixin and Yongcheng counties. The center of malaria aggregation was Guoyang County with the highest malaria incidence of 58.38 per 10,000. Zhou et al., (2007a) studied the spatial distribution of malaria in the Huang-Huai Plain based on the kriging method, showed that the distribution of malaria was auto-correlated in space, and the range of the malaria cluster area was 98,928 m. It means that re-emerging malaria will appear in the areas within nearly 100 km around high incidence of malaria areas.

4.2 Sole vector of *An. sinensis*

As a vector-borne disease, malaria transmission has a close relationship with the biological and natural factors due to the anopheles vector distribution features. There are four major vectors of malaria transmission in China, *An. minimus* and *An. dirus* are mostly distributed in Yunnan, Hainan Guangxi and Guizhou provinces of southern China. *An. sinensis* and *An. anthropophagus* are relatively more widely distributed in China.

An. sinensis is the most widely distributed, found in over 29 provinces and regions in China. This species has a large population in most regions, and is the predominant vector (Tang and Gao, 2013). *An. sinensis* is campestral and its blood feeding habit is on cattle and pigs, and its larval habitats are the small water bodies such as ponds, paddy fields, gullies, and so on (Hu et al., 1988; Gou et al., 1998). Since the development of the economy and popularity of agricultural mechanization, the farmers no longer keep pigs in their houses, and the number of farm cattle has also been greatly reduced. Currently, *An. sinensis* is the sole or major vector in the Huang-Huai Plain (Zhou et al., 2010; Liu et al., 2011). One hundred fifty-four *An. sinensis* were captured and no *An. anthropophagus* were found in vector surveillance in Yongcheng County in 2005 (Zhang et al., 2007). The vector species that transmitted malaria in Yongcheng County was morphologically identified as *An. sinensis*, with PCR results of a random sample of 30 mosquitoes confirmed as *An. sinensis* (Zhang et al., 2012b).

4.3 Main cases located around water bodies

The term *water bodies* refers to the paddy fields, gullies and little streams that are suitable breeding sites for *An. sinensis*. Distribution of water bodies may be an important factor influencing the occurrence and distribution of malaria cases in the *An. sinensis* distributed areas. Three hundred fifty-seven malaria cases and their georefereсing data recorded by geographic position system (GPS) as well as surrounding water bodies were collected and analyzed in Anhui Province. The distances from households of cases to the nearest water bodies had a positive-skew distribution, the median of the distrance was 60.9 m, 74.28% (182/246) of cases were distributed at a distance ≤60 m, 16.34% (40/246) of them were located at a distance of 60–120 m, and 9.38% (182/246) were scattered over 120 m. The risk rate of people living within the extent of 60-m proximity to the water bodies and presenting with malaria was significantly higher than others. The results imply that the scope and population within 60 m around water bodies are at risk and could be a targeted population for case management of malaria (Zhou et al., 2012). Other research about relationship between mosquitoes and malaria distributions had similar results, with 80% and 90% of the marked *An. sinensis* recaptured within a radius of 100 m from the release point in study sites I and II, respectively, with a maximum dispersal range of 400 m within the period of the study. The results indicate that local *An. sinensis* may have limited dispersal ranges. Therefore, control efforts should target breeding and resting sites in proximity to the villages (Liu et al., 2012a).

5. FACTORS OF MALARIA RE-EMERGENCE AND OUTBREAK IN HUANG-HUAI PLAIN

5.1 Land use has nothing to do with re-emergance and outbreak in the Huang-Huai Plain

According to historical records, there was malaria outbreak in the Huang-Huai Plain in the early 1960s. One factor related to the outbreak was due to the increased temperatures and rainfall. Another factor was the change of land use status. In the late 1960s, large areas of wheat fields were changed to paddy fields, which changed the local ecological environment, and then induced a malaria outbreak in the region (Zhou, 1991). But the data on changes of land use and land cover of the Huaiyuan and Yongcheng counties in 1996–2000 showed no significant relationship with malaria re-emergence and outbreak (Zhang et al., 2012a).

5.2 Climate warming and increasing rainfall extending malaria transmission

Climate warming can affact the geographic distribution and intensity of the transmission of vector-borne diseases such as malaria. The transmitted parasites usually benefit from increased temperatures as both their reproduction and development are accelerated. It has been investigated that temperature and rainfall played the determinant role of environmental factors in the transmission of malaria. It has been demonstrated that temperature increase would improve the survival chances of anopheles mosquitos and thus contribute to malaria transmission (Bai et al., 2013). Rainfall often leads to small puddles that serve as mosquito breeding sites and it increases humidity, which enhances mosquito survival (Bi et al., 2003). Temperature and rainfall may not influence the transmission of malaria in a linear and direct way (Gou et al., 1998; Qu et al., 2000). Typically, temperatures lower than 16 °C or higher than 30 °C have a negative impact on the development and activities of mosquitoes. Excessive rainfall often leads to small puddles serving as mosquito breeding sites, therefore increasing malaria transmission. But heavy rain may destroy existing breeding places and flush the eggs or larvae out, leading to reduced transmission (Bi et al., 2003; Hui et al., 2009). A negative effect of rainfall on malaria spread was detected in Anhui Province; the results showed that every 1 mm of annual rainfall increase corresponded to a 27% decrease of malaria cases (Wang et al., 2009).

A study in Anhui Province showed that the average monthly temperature and rainfall may be the key factors of malaria transmission; 75.3% changes of monthly malaria incidence contributed to the average monthly temperature, the average temperature of last two months and the average rainfall of current month (Zhou et al., 2010). Another study in Yongcheng County showed that monthly *An. sinensis* density, temperature, humidity, and rainfall had significant positive correlations with malaria incidence with delays of 0 to 3 months, while wind velocity showed negative correlations with delays of 0 and 1 month. There was not a significant association observed between duration of sunshine and malaria incidence (Zhang et al., 2012). A study conducted in Jinan, which is a temperate city in northern China, showed that a 1 °C rise in maximum temperature may be related to a 7.7–12.7% increase in the number of malaria cases, while a 1 °C rise in minimum temperature may result in approximately 11.8–12.7% increase in number of malaria cases (Zhang et al., 2010b).

Moreover, the distribution of mosquitoes is also dependent on relative humidity, and then determines the extent of malaria transmission. Relative humidity exerted an influence on the survival of mosquito eggs and adults and the moderate increase in malaria risk associated with average humidity. No malaria transmission will occur where the monthly average relative humidity is lower than 60%. Conversely, in regions with relative humidity >60%, temperature is the major driver of malaria transmission intensity (Yang et al., 2010).

5.3 Increasing vectorial capacity of *An. sinensis* strengthens malaria transmission

While the level of *P. vivax* transmission is significantly related to two main factors, one is vector capacity and the other one is the number of infectious sources or human cases (Cohuet et al., 2010). It is believed that transmission intensity of human malaria is highly dependent on the vector capacity and competence of local mosquitoes. Vector capacity is a good indicator to assess the transmission level of vivax malaria (Garrett-Jones, 1964). The vector capacity was estimated from the calculation of three indicators: mosquito biting rate (MBR), human blood index (HBIs), and the parous rate (M) (Ree et al., 2001).

Pan et al. (2012) investigated vectorial capacities of *An. sinensis* in 2007; the vectorial capacities of *An. sinensis* in Huaiyuan and Yongcheng counties were 0.7740 and 0.5502, respectively. The results showed that the vector capacity was about 2.3 and 1.7 times higher than 0.331 in the 1990s (Qian et al., 1996), and were 4.6 and 3.3 times higher than 0.1686 in Henan in 1996–1998 (Qu et al., 2000), respectively. Another study got the same results. The vectorial capacities of *An. sinensis* of Huaiyuan and Yongcheng counties were 0.6969 and 0.4689, which were 4.12 and 2.78 times higher compared to that of the 1990s (Zhou et al., 2010). The results demonstrated that the ability of *An. sinensis* to transmit *P. vivax* had been obviously enhanced.

HBIs in Huaiyuan and Yongcheng counties in 2007 were 0.6667 and 0.6429, respectively and the HBI values were more than 12 times higher than that in the historical records. The increased probability of *An. sinensis* feeding on human blood indicates that mosquitoes change their behavior caused by changes in number of livestock (Habtewold et al., 2004). The significant changes in man-biting habit reflected that the number of livestock as sources of infection changed, and this change in pattern is closely related to the reduction of livestock numbers. Artificial infection of *P. vivax* to *An. sinensis* and *An. anthropophagus* had been carried out. The results showed that the susceptibility of *An. sinensis* to *P. vivax*-infected blood is similar to *An. anthropophagus* (Zhu et al., 2013c).

Mosquito nets and mosquito-repellent incense were generally used in the local villages, and most families had screened doors, and/or screened windows. An investigation showed that 93.0% of 80 households in Huaiyuan and 89.3% of 192 households in Yongcheng County had anti-mosquito facilities. It was interesting that the most patients in Wuhe County lived in brick or cement buildings without mosquito-proof doors or windows (Wang et al., 2013c). But the villagers had a habit of enjoying cool outdoor fresh air before midnight, and they preferred sleeping outside during summer. These behaviors increased the chance of mosquitos biting residents, which led to being infected by the mosquitoes.

5.4 Low capacity of diagnosis leading to accumulation of infectious sources

Diagnosis is usually based on parasite identification on a thin–thick smear. There were deficiencies in providing timely diagnosis and treatment due to insufficient microscopists in rural areas. Among 9678 cases reported in 302 outbreak spots in 2006, 57.13% (5529 cases) were confirmed by blood smear and 42.87% (4149 cases) were diagnosed by clinical symptoms; 11.2% (1084 cases) were treated within 1 day, 29.62% (2867 cases) were treated within 3 days, and 59.18% (5727 cases) were treated over 3 days, with average treatment within 6 days. Of 767 malaria cases in Jiangsu Province in 2006, only 6% (46) were confirmed with 1 day, 72.10% (553) were confirmed within 10 days, and the longest one needed 113 days to be confirmed (Wang et al., 2007). Of 710 malaria cases in Yongcheng County in 2005, patients needed (6.27 ± 5.58) days to be confirmed (Zhang et al., 2007).

Of the human malaria parasites, only *P. vivax* and *P. ovale* have the ability to delay the development of a fraction of the infectious load of sporozoites in the liver. The activation of dormant hypnozoites results in the relapse of the disease after the primary infection is cleared from the bloodstream. Low patient compliance for the full primaquine treatment poses a serious challenge to eliminating the disease, with relapses known to occur for up to 5 years (Roy et al., 2013). An investigation of 703 malaria patients in Anhui Province in 2001 showed a relapse rate of 10.67% (Xu et al., 2003). Of 767 malaria cases in Jiangsu Province in 2006, the relapse rate was 9.00% (Wang et al., 2007).

Parasitaemia surveys were carried among 22,500 and 4518 residents in Henan and Anhui provinces, and the parasitaemia rate was 0.47% and 0.58%, respectively, in 2006 (Liu et al., 2008); 87.8% of the antibody positive cases were asymptomatic, indicating that there were potential infection sources with symptomatic parasitaemia in the Huang-Huai Plain (Zheng et al., 2008). The underreporting rate was 5% in outbreak spots, and 417 suspect cases were found in Yongcheng County in 2006 (Zhou et al., 2008).

6. RESPONSE TO RE-EMERGENCE AND OUTBREAK IN HUANG-HUAI PLAIN

6.1 Mass drug administration

MDA has been a key strategy for controlling or eliminating highly prevalent neglected tropical diseases (NTDs) such as lymphatic filariasis (Mwakitalu et al., 2013), soil-transmitted helminthes (Parikh et al., 2013), onchocerciasis (Tekle et al., 2012), and schistosomiasis (Omedo et al., 2012; Wu and Huang, 2013). The simultaneous administration of essential medicines to target high-prevalence NTDs has two main functions: to treat prevalent infection and subsequently to reduce further transmission within the population.

The administration of antimalarial drugs to whole populations, termed MDA, was one of the measures for malaria elimination programmes in the 1950s, and was once again attracting interest as a malaria elimination tool. Mass antimalarial drug administration, defined as the empiric administration of a therapeutic course of an antimalarial regimen to an entire population at the same time without screening or diagnostic testing prior to administration, has been used for malaria control since the early 1930s; it was advocated by the World Health Organization (WHO) in the 1950s as a tool in situations where other more conventional control measures had

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failed (Poirot et al., 2013). MDA of chloroquine could reduce parasitaemia prevalence and potentially reduce malaria transmission by inhibiting asexual intraerythrocytic stages of the parasite, thereby reducing the number of parasites that can progress to form gametocytes. In addition, MDA of primaquine could have a direct effect on gametocytes and the liver stages of the parasite to inhibit the sporogonic cycle in the mosquito. If every member of a given population is treated by antimalarial MDA, then one would expect an immediate reduction in asexual parasite prevalence in the population, and possibly a sustained reduction in the population parasitaemia prevalence if there was a concomitant reduction in transmission.

China had extensive experience with MDA for malaria control in the 1970s and 1980s. Large-scale MDA was implemented and associated with declines in high *P. vivax* malaria transmission in Jiangsu province (Hsiang et al., 2013); About 148.17 million residents were given chloroquine and primaquine before or at the start of the malaria transmission season that typically begins in April, and 202.75 million were given chloroquine in transmission season in the Huang-Huai Plain in 1974–1986. The number of malaria cases was 231,000 in 1986 with a decrease of 98.2% compared with that in 1973 (Zhou, 1991). The main antimalaria measures included health education in at-risk villages, MDAs in at-risk populations staying overnight in the mountains, following up malaria cases for implementing radical cure, but without using traditional residual spraying or impregnating bed-nets with insecticides in the mountainous areas of Hainan Province. The annual parasite incidence (API) of malaria declined from 3.5% in 1994 to 1.1% in 1996 and 0.8% in 1997, and the API of falciparum malaria declined from 1.0% to 0.3% and 0.3%, respectively (Chen et al., 1999).

6.1.1 MDA-'spring treatment'

P. vivax places dormant forms in the liver (hypnozoites) that cause repeated attacks called relapses. Primaquine, an 8-aminoquinoline, has been in widespread clinical use for over 60 years and remains the only treatment option for eradication of liver hypnozoites, or the prevention of relapses. High doses of primaquine are associated with lower rates of relapse of *P. vivax* infection (Townell et al., 2012). An effective relapse treatment level can have a bigger impact when transmission in the previous year is low (e.g. cumulative cases below 1000 between August and November), with the prevention of 10% of relapses reducing cases in the following transmission season by as much as 70% (Roy et al., 2013).

The goal of seasonal MDA with primaquine was to treat potential reservoirs of *P. vivax* blood and liver stage infection before the start of the malaria transmission season. MDA was administered before or at the start of the malaria transmission season that typically begins in April, so that it is called as 'spring treatment'. From 2006 to 2010, 3.9 million residents were given the 'spring treatment' of chloroquine plus primaquine in the Huang-Huai Plain. In Yongcheng County, all the residents in four townships with the highest malaria incidence and outbreaks were targeted; 80,438 residents received MDA in 2006 and 59,457 in 2007; 1.71 million of residents in 15,459 natural villages received MDA for the spring treatment in Anhui Province in 2008. In other areas, people with a history of infection during the past year and their families and neighbors were given pretransmission season treatment with chloroquine and primaquine for the radical cure, or 'spring treatment' of *P. vivax* malaria (Hsiang et al., 2013).

Community health workers and/or local public health doctors administered medications daily by directly observed therapy and documented this by collecting patient signatures. Informed consent was conducted verbally and through a handout. Villagers were instructed to have food before taking the medication. The administration of drugs was by directly observed therapy and documented by collecting patient signatures. Exclusion criteria for MDA targets included: age <1 year, pregnancy, serious heart, liver or kidney disease, fever, and history of cyanosis, systemic bleeding, or dark-colored urine. Medication was stopped if serious adverse effects such as dark urine, cyanosis or haemolysis occurred.

A major challenge of primaquine use for MDA is the risk of haemolysis in patients with underlying glucose-6-phosphate dehydrogenase (G6PD) deficiency. The most comparable MDA was conducted in 300,000 U.S. soldiers returning from Korea on troopships in 1952–1954 who received 210 mg of primaquine over 2 weeks. The severe haemolytic reaction rate was estimated at 4 per 100,000 (Alving, 1954). Fok et al., (1985) screened G6PD deficiency by fluorescent spot test on cord blood samples of 1228 Chinese neonates, revealing an incidence of 4.4% in males and 0.35% in females. G6PD deficiency is common in Guangdong, Taiwan, Guangxi and other parts of South China. Yan et al., (2006) investigated 4704 individuals in Guangxi, the mutation frequency of male G6PD-deficient individuals was observed to be 7.43% in population. For ethnic Han Chinese, the detection rate was 0.7%, which was lower than the majority of ethnic minorities. In Henan Province, 500 adults were investigated in 1977, and no G6PD deficiency was found (Su et al., 1995). The reported prevalence of G6PD deficiency among Han, the predominant ethic group in Jiangsu, is low, <5% among males (Jiang et al., 2006). Five reports documenting G6PD deficiency-related severe adverse events from primaquine treatment were identified in Jiangsu Province when they carried out MDA of spring treatment in 1973–1983 (Hsiang et al., 2013). No irreversible adverse events were reported in the Huang-Huai Plain in 2006–2010.

6.1.2 MDA-'chemoprophylaxis on transmission season'

The aim of chemoprophylaxis on transmission season was to interrupt transmission, where antimalarial drugs are administered throughout transmission season. Chemoprophylaxis has been found to be highly effective at reducing mortality and morbidity from malaria in highly endemic areas (Greenwood, 2004). Residents who lived near water bodies and patients were targeted for chemoprophylaxis on transmission season in Anhui Province (Zhu et al., 2013a). From August to October in 2007, piperquine (600 mg) was given once a month to residents who lived near a water body in 24 counties of Anhui Province; 4.43 million population in 15,740 natural villages received the administration, covering 98.69% of the population. Compared to that in the last month, malaria incidence of these areas decreased by 2.0%, 46.3%, and 60.2% from August to October in 2007, respectively. Malaria incidence in 2007 decreased by 21.82% compared to that in 2006.

6.2 Case management

Malaria case management is focused on early detection, i.e. diagnosis of malaria cases, prompt and effective treatment of symptomatic patients. Doctors at all levels make malaria diagnosis according to epidemiological history and clinical manifestations, such as fever, chill, rigor, headache and body ache etc. Malaria cases are confirmed by blood smear examination carried out on three kinds of fever cases, including suspected cases, clinically diagnosed cases and patients with fever of unknown origin. A total of 7,756,119 febrile individuals recieved blood smear examination in 2006–2010 in the Huang-Huai Plain. 91,900 local doctors and microscopists were trained for malaria diagnosis in the Huang-Huai Plain from 2006 to 2010. The number and ratio of laboratory-confirmed malaria cases obviously increased as a result of this work, and all malaria cases were laboratory-confirmed in 2012.

Chloroquine and primaquine is still the first-line treatment for vivax malaria. Clinical chloroquine-resistant *P. vivax* was firstly reported from Papua New Guinea in 1989 (Peters, 1990; Schuurkamp et al., 1992;

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Murphy et al., 1993), followed by multiple reports from Indonesia, Myanmar, India, Guyana, Brazil, Colombia, and more recently in Ethiopia and South Korea (Baird et al., 1991; Collignon, 1991; Phillips et al., 1996; Singh, 2000; Soto et al., 2001; de Santana Filho et al., 2007; Guthmann et al., 2008; Teka et al., 2008; Ketema et al., 2009; Lee et al., 2009). Although some hypotheses suggest that the chloroquine–primaquine combination, which has been the first-line of treatment for *P. vivax* for almost 50 years, may not be equally effective nowadays, there is no evidence of this decrease in effectiveness of malaria treatment in China.

In 2005–2006, drug susceptibility in vitro was measured for 42 clinical *P. vivax* isolates by using a schizont maturation inhibition technique. Geometric means of 50% inhibitory concentrations (IC50s) and 95% confidence intervals (CIs) were 10.87 (4.50–26.26) ng/mL for chloroquine. The IC50 for chloroquine was lower than those obtained from isolates from Thailand and South Korea, suggesting that chloroquine remained effective against *P. vivax* malaria in central China (Lu et al., 2011).

Thirty-nine monoinfection vivax malaria patients were enrolled to evaluate efficiency of chloroquine treatment of vivax from 2008 to 2009 in Suixi County, Jiangsu province. No recrudescence or danger signs were observed within the 28-day follow-up, which showed vivax was still susceptible to chloroquine in China (Zhu et al., 2013b).

6.3 Vector control

An. sinensis is slightly exophagic, which means *An. sinensis* tends toward outdoor resting after indoor blood feeding. This behavior has made vector control of this species more difficult. Insecticide-treated nets (ITNs) and indoor residual spraying (IRS) were not useful for vector control of *An. sinensis*. Biologic control measures against mosquito larvae were carried out in 31 administration villages of five townships in Yongcheng County with malaria outbreaks in 2006. 8 mL/m^2 suspending agent of *Bacillus sphaericus* were nebulized on surfaces of ponds in/or around the villages at intervals of 15 days. Density of *An. sinensis* larvae and adults decreased by 75.6–100%, 50–100%, respectively, two days after nebulizing. No outbreak was found in Yongcheng County in 2007. Three hundred twenty-three malaria cases were reported and malaria incidence was 0.48% in villages where carrying biologic control measures in 2007, dropped by 51.3% of malaria incidence compared to 0.98% of previous year. *B. sphaericus* had the effect of decreasing density of *An. sinensis* larvae and adult. Biologic control measures against mosquito larvae can effectively decrease malaria incidence (Zhou et al., 2009).

6.4 Training supported by global fund and government

Social and economic status significantly changed since the 1990s in central parts of China, and malaria control interventions also transferred from vectorial control, such as IRS, ITNs combined with case management, to enhancing case detection with health education particularly on risks and vulnerable populations. A total of 91,900 local doctors and microscopists were trained on malaria diagnosis in the Huang-Huai Plain from 2006 to 2010. Residents in epidemic areas received knowledge of malaria through a range of media, such as radio and TV broadcasts, newspaper articles, and posters, especially for the annual Malaria Day Campaign all over the epidemic areas on 26 April every year.

Malaria control was supported by 5 rounds of Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) programmes since 2003. This indicates the great efforts of the country to decrease malaria transmission, and during the last couple of years more timely diagnosis and treatment as well as prevention and control activities are being deployed jointly supported by the government and the GFATM programmes. This approach appears to be producing a beneficial impact. In the context of the GFATM programmes, the malaria control strategy is successfully leading to community participation in prevention and control activities that therefore become more efficient and cost-effective.

Currently, greater efforts are being invested to maintain the decreasing trend of malaria transmission in the Huang-Huai Plain, China, although long-term monitoring to avoid epidemic outbreaks is still required, i.e. by prioritizing critical control activities such as effective vector management and educational activities as well as greater efforts to overcome administrative hurdles that limit a more robust diagnosis and treatment system.

7. EFFECTS ON RESPONSE TO RE-EMERGENCE AND OUTBREAK

The re-emergence of malaria was effectively controlled by an extensive control strategy on patient management supported by the central government and GFATM programmes. Malaria incidence dropped dramatically in the Huang-Huai Plain after 2007. A total of 769 vivax malaria cases from the Huang-Huai Plain were reported in 2011. Only 30 local vivax malaria cases were reported in Anhui Province, and no local transmission vivax malaria was reported in Henan, Jiangsu, and Shandong provinces in 2012.

8. CHALLENGE OF MALARIA ELIMINATION IN HUANG-HUAI PLAIN

8.1 Imported malaria

Imported malaria has been found in more provinces in China, which requires urgent information to be dispensed in a setting of increasing travel activity and migration. In 2011, 4479 malaria cases were reported in China, of which 66.4% were imported cases that were mainly distributed in Yunnan (36.5%), Jiangsu (12.0%), Henan (6.2%), Sichuan (5.8%) and Hunan (4.8%) provinces. The number of malaria deaths due to falciparum malaria increased to 33 from 19 in 2010 (Xia et al., 2012). A total of 84 imported falciparum malaria cases with one death were reported in Henan Province in 2005–2009. The ratio of males to females was 20:1(80/4). The average age was (34 ± 11) years old. Seventy-five patients returned from Africa, accounting for 89.3% of total number of imported cases. The number of annual imported cases reported in 2008 (24 cases) and 2009 (32 cases) was higher than that in 2005–2007 (9–10 cases). The top three high-risk populations were farmers (34 cases), workers (17 cases) and the cadre (13 cases), which accounted for 76.2% of all cases (Zhang et al., 2010a). A total of 233 overseas imported malaria cases were reported in Jiangsu Province, and 226 cases (97.0%) were back from African countries. A total of 208 cases (89.3%) were falciparum malaria, and 224 cases (96.1%) were laboratory confirmed. The imported malaria cases were young adults who were mainly migrant farmers and skilled male workers (Liu et al., 2013). It was necessary to further strengthen the professional training and multisectoral cooperation, establish the collaborative investigation mechanism for high-risk groups, and take effective prevention and control measures, in order to reduce the risk of malaria resurgence in the Huang-Huai Plain. due to overseas-imported malaria.

8.2 Long incubation time of *P. vivax*

P. vivax was endemic in temperate areas in historic times up to the middle of the last century. *P. vivax* has a long incubation time of up to 8–10 months, which partly explains how it can be endemic in temperate areas in the cold winter season. Lately *P. vivax* has been seen along the demilitarized zone in South Korea, replicating a high endemicity in North Korea. The potential for transmission of *P. vivax* still exists in temperate zones, but reintroduction of a larger scale of *P. vivax* to areas without present transmission requires large population movements of *P. vivax*-infected people. The highest threat at present is from refugees from *P. vivax* endemic North Korea entering China and South Korea in large numbers (Petersen et al., 2013).

8.3 Insecticide resistance

Insecticide resistance in malaria vectors is a growing concern in many countries and requires immediate attention because of the limited chemical arsenal available for vector control. Bioassays were performed on F1 progeny of *An. sinensis* reared from wild-caught females using the standard WHO susceptibility test with diagnostic concentrations of 0.25% deltamethrin and 4% DDT. The results indicated that *An. sinensis* was completely resistant to both deltamethrin and DDT, and resistance to pyrethroid has risen strikingly compared to that recorded during 1990s. The results highlight the importance of longitudinal insecticide resistance monitoring and the urgent need for a better understanding of the status of insecticide resistance in this region (Wang et al., 2013). The same results were found in Henan, Jiangsu and Anhui provinces (Li et al., 2011; Wu et al., 2011; Liu et al., 2012b; Zhang et al., 2012; Chang et al., 2013).

9. CONCLUSIONS

Unlike *P. falciparum*, *P. vivax* rarely causes severe disease in healthy travelers or in temperate endemic regions, and has been regarded as readily treatable with chloroquine in the Huang-Huai Plain. However, in tropical areas, recent reports have highlighted severe and fatal disease associated with *P. vivax* infection. Studies from Indonesia, Papua New Guinea, Thailand and India have shown that 21–27% of patients with severe malaria have *P. vivax* mono-infection. The clinical spectrum of these cases is broad with an overall mortality of 0.8–1.6%. Major manifestations include severe anaemia and respiratory distress, with infants being particularly vulnerable. Severe, fatal and multidrug-resistant vivax malaria challenges our perception of *P. vivax* as a benign disease. Strategies to understand and address these phenomena are urgently needed if the global elimination of malaria is to succeed (Price et al., 2009).

In order to avoid death from the imported malaria cases and reduce the risk of secondary transmission, malaria screening and health education for those returned from malaria-endemic countries should be strengthened, and the diagnosis and treatment capabilities must be improved at county medical units (Chen et al., 2012).

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REFERENCES

Alving, A., 1954. Clinical treatment of malaria. U.S. Army Med. Sci. 22, 210–218.

Bai, L., Morton, L.C., Liu, Q., 2013. Climate change and mosquito-borne diseases in China: a review. Global Health 9, 10.

Baird, J.K., Basri, H., Purnomo, Bangs, M.J., Subianto, B., Patchen, L.C., Hoffman, S.L., 1991. Resistance to chloroquine by *Plasmodium vivax* in Irian Jaya, Indonesia. Am. J. Trop. Med. Hyg. 44 (5), 547–552.

Bi, P., Tong, S., Donald, K., Parton, K.A., Ni, J., 2003. Climatic variables and transmission of malaria: a 12-year data analysis in Shuchen County, China. Public Health Rep. 118 (1), 65–71.

Chang, X.L., Xue, Y.Q., Zhang, A.D., Zhu, G.D., Fang, Q., 2013. Deltamethrin resistance, metabolic detoxification enzyme and kdr mutation in *Anopheles sinensis* in region along Huaihe River in Anhui Province. Chin. J. Epi. 25 (3), 263–267 (in Chinese).

Chen, W.Q., Su, Y.P., Deng, Y., Zhang, H.W., 1999. A pilot study on malaria control by using a new strategy of combining strengthening infection source treatment and health education in mountainous areas of Hainan province. Chin. J. Parasitol. Parasit. Dis. 17 (1), 1–4 (in Chinese).

Chen, W., Wu, K., Lin, M., Tang, L., Gu, Z., Wang, S., Lan, C., Lan, X., Li, H., Huang, M., Chen, X., Sheng, H., 2012. Epidemiological analysis of imported malaria in Henan Province in 2011. Chin. J. Parasitol. Parasit. Dis. 30 (5), 387–390 (in Chinese).

Cohuet, A., Harris, C., Robert, V., Fontenille, D., 2010. Evolutionary forces on *Anopheles*: what makes a malaria vector? Trends Parasitol. 26 (3), 130–136.

Collignon, P., 1991. Chloroquine resistance in *Plasmodium vivax*. J. Infect. Dis. 164 (1), 222–223.

Fok, T.F., Lau, S.P., Fung, K.P., 1985. Cord blood G-6-PD activity by quantitative enzyme assay and fluorescent spot test in Chinese neonates. Aust. Paediatr. J. 21 (1), 23–25.

Garrett-Jones, C., 1964. Prognosis for interruption of malaria transmission through assessment of the mosquito's vectorial capacity. Nature 204, 1173–1175.

Gou, G.X., Li, D.F., Shang, L.Y., Guo, X.S., 1998. The study on ecological habits of *Anopheles sinensis* in Guantang, Luyi county from 1971 to 1996. Chin. J. Vector Bio. Con. 9 (2), 133–134 (in Chinese).

Greenwood, B., 2004. The use of anti-malarial drugs to prevent malaria in the population of malaria-endemic areas. Am. J. Trop. Med. Hyg. 70 (1), 1–7.

Guthmann, J.P., Pittet, A., Lesage,, A., Imwong, M., Lindegardh, N., Min Lwin, M., Zaw, T., Annerberg, A., de Radigues, X., Nosten, F., 2008. *Plasmodium vivax* resistance to chloroquine in Dawei, southern Myanmar. Trop. Med. Int. Health 13 (1), 91–98.

Habtewold, T., Prior, A., Torr, S.J., Gibson, G., 2004. Could insecticide-treated cattle reduce Afrotropical malaria transmission? Effects of deltamethrin-treated Zebu on *Anopheles arabiensis* behaviour and survival in Ethiopia. Med. Vet. Entomol. 18 (4), 408–417.

Hsiang, M.S., Hwang, J., Tao, A.R., Liu, Y., Bennett, A., Shanks, G.D., Cao, J., Kachur, S.P., Feachem, R.G., Gosling, R.D., Gao, Q., 2013. Mass drug administration for the control and elimination of *Plasmodium vivax* malaria: an ecological study from Jiangsu province, China. Malar. J. 12 (1), 383.

Hu, Y.X., Miao, Y.G., Fan, TB, 1988. The further study on ecological habits of *Anopheles sinensis* in the area along Yellow River and Huai River. Chin. J. Parasitol. Parasit. Dis. S1, 135 (in Chinese).

Hui, F.M., Xu, B., Chen, Z.W., Cheng, X., Liang, L., Huang, H.B., Fang, L.Q., Yang, H., Zhou, H.N., Yang, H.L., Zhou, X.N., Cao, W.C., Gong, P., 2009. Spatio-temporal distribution of malaria in Yunnan Province, China. Am. J. Trop. Med. Hyg. 81 (3), 503–509.

Jiang, W., Yu, G., Liu, P., Geng, Q., 2006. Structure and function of glucose-6-phosphate dehydrogenasedeficient variants in Chinese population. Hum. Genet. 119, 463–478.

Ketema, T., Bacha, K., Birhanu, T., Petros, B., 2009. Chloroquine-resistant *Plasmodium vivax* malaria in Serbo town, Jimma zone, south-west Ethiopia. Malar. J. 8, 177.

Lee, K.S., Kim, T.H., Kim, E.S., Lim, H.S., Yeom, J.S., Jun, G., Park, J.W., 2009. Short report: chloroquine-resistant *Plasmodium vivax* in the Republic of Korea. Am. J. Trop. Med. Hyg. 80 (2), 215–217.

Li, J.L., Zhou, H.Y., Cao, J., Zhu, G.D., Wang, W.M., Gu, Y., Liu, Y., Cao, Y., Zhang, C., Gao, Q., 2011. Sensitivity of *Anopheles sinensis* to insecticides in Jiangsu Province. Chin. J. Schisto. Control, 23 (3), 296–300 (in Chinese).

Liu, Q., Liu, X., Zhou, G., Jiang, J., Guo, Y., Ren, D., Zheng, C., Wu, H., Yang, S., Liu, J., Li, H., Li, Q., Yang, W., Chu, C., 2012a. Dispersal range of *Anopheles sinensis* in Yongcheng City, China by mark-release-recapture methods. PLoS One 7 (11), e51209.

Liu, X.B., Liu, Q.Y., Guo, Y.H., Jiang, J.Y., Ren, D.S., Zhou, G.C., Zheng, C.J., Zhang, Y., Liu, J.L., Li, Z.F., Chen, Y., Li, H.S., Morton, L.C., Li, H.Z., Li, Q., Gu, W.D., 2011. The abundance and host-seeking behavior of culicine species (Diptera: Culicidae) and *Anopheles sinensis* in Yongcheng city, People's Republic of China. Parasit. Vectors 4, 221.

Liu, Y., Chen, J.S., Zhou, R.M., Qian, D., Chen, Q.W., Xu, B.L., Zhang, H.W., 2012b. Investigation on the sensitivity of *Anopheles sinensis* to insecticide. Chin. J. Parasitol. Parasit. Dis. 30 (4), 309–311 (in Chinese).

Liu, Y., Su, Y.-P., Zhang, H.-W., 2008. Analysis of malaria situation in five-provinces of Jiangsu, Shandong, Henan, Anhui and Hubei in 2006. Chin. J. Trop. Med. 8 (2), 190–192 (in Chinese).

Liu, Y.B., Cao, J., Zhou, H.Y., Wang, W.M., Cao, Y.Y., Gao, Q., 2013. Analysis of overseas imported malaria situation and implication for control in Jiangsu Province, PR China. Chin. J. Schisto. Control. 25 (1), 44–47 (in Chinese).

Lu, F., Gao, Q., Chotivanich, K., Xia, H., Cao, J., Udomsangpetch, R., Cui, L., Sattabongkot, J., 2011. In vitro anti-malarial drug susceptibility of temperate *Plasmodium vivax* from central China. Am. J. Trop. Med. Hyg. 85 (2), 197–201.

Manh, C.D., Beebe, N.W., Van, V.N., Quang, T.L., Lein, C.T., Nguyen, D.V., Xuan, T.N., Ngoc, A.L., Cooper, R.D., 2010. Vectors and malaria transmission in deforested, rural communities in north-central Vietnam. Malar. J. 9, 259.

Mendis, K., Sina, B.J., Marchesini, P., Carter, R., 2001. The neglected burden of *Plasmodium vivax* malaria. Am. J. Trop. Med. Hyg. 64 (Suppl. 1–2), 97–106.

MOH, 2006. Malaria Emergency Preparedness Plan of Action in China. Ministry of Heath.

Mueller, I., Galinski, M.R., Baird, J.K., Carlton, J.M., Kochar, D.K., Alonso, P.L., del Portillo, H.A., 2009. Key gaps in the knowledge of *Plasmodium vivax*, a neglected human malaria parasite. Lancet Infect. Dis. 9 (9), 555–566.

Murphy, G.S., Basri, H., Purnomo, Andersen, E.M., Bangs, M.J., Mount, D.L., Gorden, J., Lal, A.A., Purwokusumo, A.R., Harjosuwarno, S., 1993. Vivax malaria resistant to treatment and prophylaxis with chloroquine. Lancet 341 (8837), 96–100.

Mwakitalu, M.E., Malecela, M.N., Pedersen, E.M., Mosha, F.W., Simonsen, P.E., 2013. Urban lymphatic filariasis in the metropolis of Dar es Salaam, Tanzania. Parasit. Vectors 6 (1), 286.

Omedo, M.O., Matey, E.J., Awiti, A., Ogutu, M., Alaii, J., Karanja, D.M., Montgomery, S.P., Secor, W.E., Mwinzi, P.N., 2012. Community health workers' experiences and perspectives on mass drug administration for schistosomiasis control in western Kenya: the SCORE Project. Am. J. Trop. Med. Hyg. 87 (6), 1065–1072.

Pan, J.Y., Zhou, S.S., Zheng, X., Huang, F., Wang, D.Q., Shen, Y.Z., Su, Y.P., Zhou, G.C., Liu, F., Jiang, J.J., 2012. Vector capacity of *Anopheles sinensis* in malaria outbreak areas of central China. Parasit. Vectors 5, 136.

Parikh, D.S., Totanes, F.I., Tuliao, A.H., Ciro, R.N., Macatangay, B.J., Belizario, V.Y., 2013. Knowledge, attitudes and practices among parents and teachers about soil-transmitted helminthiasis control programs for school children in Guimaras, Philippines. Southeast Asian J. Trop. Med. Public Health 44 (5), 744–752.

Peters, W., 1990. Plasmodium: resistance to antimalarial drugs. Ann. Parasitol. Hum. Comp. 65 (Suppl. 1), 103–106.

Petersen, E., Severini, C., Picot, S., 2013. *Plasmodium vivax* malaria: a re-emerging threat for temperate climate zones? Travel Med. Infect. Dis. 11 (1), 51–59.

Phillips, E.J., Keystone, J.S., Kain, K.C., 1996. Failure of combined chloroquine and high-dose primaquine therapy for *Plasmodium vivax* malaria acquired in Guyana, South America. Clin. Infect. Dis. 23 (5), 1171–1173.

Poirot, E., Skarbinski, J., Sinclair, D., Kachur, S.P., Slutsker, L., Hwang, J., 2013. Mass drug administration for malaria. Cochrane Database Syst. Rev. 12, CD008846.

Price, R.N., Douglas, N.M., Anstey, N.M., 2009. New developments in *Plasmodium vivax* malaria: severe disease and the rise of chloroquine resistance. Curr. Opin. Infect. Dis. 22 (5), 430–435.

Qian, H., Shang, L., 1999. Malaria situation in the People's Republic of China in 1998. Chin. J. Parasitol. Parasit. Dis. 17 (4), 193–195 (in Chinese).

Qian, H.L., Tang, L.H., Tang, L.Y., 1996. Preliminary estimation on the critical value of man biting rate and vectorial capacity of *Anopheles sinensis*. Practical Preventire Med. 3, 1–2 (in Chinese).

Qu, C.Z., Su, T.Z., Wang, M.Y., 2000. Vectorial capacity of malaria transmission of *Anopheles sinensis* in Zhengzhou in nature. J. Henan Medieal Univ. 35, 394–396 (in Chinese).

Ree, H.I., Hwang, U.W., Lee, I.Y., Kim, T.E., 2001. Daily survival and human blood index of *Anopheles sinensis*, the vector species of malaria in Korea. J. Am. Mosq. Control Assoc. 17 (1), 67–72.

Roy, M., Bouma, M.J., Ionides, E.L., Dhiman, R.C., Pascual, M., 2013. The potential elimination of *Plasmodium vivax* malaria by relapse treatment: insights from a transmission model and surveillance data from NW India. PLoS Negl. Trop. Dis. 7 (1), e1979.

de Santana Filho, F.S., Arcanjo, A.R., Chehuan, Y.M., Costa, M.R., Martinez-Espinosa, F.E., Vieira, J.L., Barbosa, M.D., Alecrim, W.D., Alecrim, M.D., 2007. Chloroquine-resistant *Plasmodium vivax*, Brazilian Amazon. Emerg. Infect. Dis. 13 (7), 1125–1126.

Schuurkamp, G.J., Spicer, P.E., Kereu, R.K., Bulungol, P.K., Rieckmann, K.H., 1992. Chloroquine-resistant *Plasmodium vivax* in Papua New Guinea. Trans. R. Soc. Trop. Med. Hyg. 86 (2), 121–122.

Singh, R.K., 2000. Emergence of chloroquine-resistant vivax malaria in south Bihar (India). Trans. R. Soc. Trop. Med. Hyg. 94 (3), 327.

Soto, J., Toledo, J., Gutierrez, P., Luzz, M., Llinas, N., Cedeno, N., Dunne, M., Berman, J., 2001. *Plasmodium vivax* clinically resistant to chloroquine in Colombia. Am. J. Trop. Med. Hyg. 65 (2), 90–93.

Su, S.Z., Ma, Y.X., Wang, Z. (Eds.), 1995. Malaria Study and Control in Henan Province. Zhongyuan Nongmin Press, Zhengzhou (in Chinese).

Su, Y.P., Zhang, H.W., Liu, Y., 2008. Evaluation on malaria control and malaria situation in Henan province in 2006. J. Pathogen Bio. 3 (9), 670–672 (in Chinese).

Tang, L.H., Gao, Q., 2013. Malaria Control and Eliminate in China. Shanghai Scientific & Technical Publishers, Shanghai. 42 (in Chinese).

Teka, H., Petros, B., Yamuah, L., Tesfaye, G., Elhassan, I., Muchohi, S., Kokwaro, G., Aseffa, A., Engers, H., 2008. Chloroquine-resistant *Plasmodium vivax* malaria in Debre Zeit, Ethiopia. Malar. J. 7, 220.

Tekle, A.H., Elhassan, E., Isiyaku, S., Amazigo, U.V., Bush, S., Noma, M., Cousens, S., Abiose, A., Remme, J.H., 2012. Impact of long-term treatment of onchocerciasis with ivermectin in Kaduna State, Nigeria: first evidence of the potential for elimination in the operational area of the African Programme for Onchocerciasis Control. Parasit. Vectors 5, 28.

Townell, N., Looke, D., McDougall, D., McCarthy, J.S., 2012. Relapse of imported *Plasmodium vivax* malaria is related to primaquine dose: a retrospective study. Malar. J. 11, 214.

Wang, D.Q., Xia, Z.G., Zhou, S.S., Zhou, X.N., Wang, R.B., Zhang, Q.F., 2013a. A potential threat to malaria elimination: extensive deltamethrin and DDT resistance to *Anopheles sinensis* from the malaria-endemic areas in China. Malar. J. 12, 164.

Wang, L.P., Fang, L.Q., Xu, X., Wang, J.J., Ma, J.Q., Cao, W.C., Jin, S.G., 2009. Study on the determinants regarding malaria epidemics in Anhui province during 2004-26. Chin. J. Epi. 30 (1), 38–41 (in Chinese).

Wang, W.M., Gao, Q., Jin, X.L., Zhou, H.Y., 2007. Malaria epidemic situation in Jiangsu Province in 2006. Chin. J. Parasitol. Parasit. Dis. 25 (3), 258–259 (in Chinese).

Wang, X.M., Xia, L.H., Fang, Q., Tao, Z.Y., Jiao, Y.M., Xia, H., Sun, X., 2013b. Malaria epidemiologic characteristics in Wuhe County of Anhui Province from 2009 to 2011. Chin. J. Schisto. Control 25 (1), 70–72 (in Chinese).

WHO, 2012. World Malaria Report 2012. World Health Organization, Geneva.

Wu, S., Liu, Q., Yang, F.T., 2011. Investigation of *Anopheles sinensis* resistance to deltamethrin in the malaria-endemic northern part of Anhui Province,China. J. Pathog. Biol. 6 (12), 920–921 (in Chinese).

Wu, W., Huang, Y., 2013. Application of praziquantel in schistosomiasis japonica control strategies in China. Parasitol. Res. 112 (3), 909–915.

Xia, Z.G., Yang, M.N., Zhou, S.S., 2012. Malaria situation in the People's Republic of China in 2011. Chin. J. Parasitol. Parasit. Dis. 30 (6), 419–422 (in Chinese).

Xu, B., Li, H., Webber, R.H., 1994. Malaria in Hubei Province, China: approaching eradication. J. Trop. Med. Hyg. 97 (5), 277–281.

Xu, B.L., Su, Y.P., Shang, L.Y., Zhang, H.W., 2006. Malaria control in Henan Province, People's Republic of China. Am. J. Trop. Med. Hyg. 74 (4), 564–567.

Xu, F.N., Shen, Y.Z., Jia, S.Y., 2003. Feature analysis of local malaria re-rise in *Plasmodium vivax* endemic area in anhui province. Chin. J. Parasit. Dis. Control 16 (1), 20–21 (in Chinese).

Yan, T., Cai, R., Mo, O., Zhu, D., Ouyang, H., Huang, L., Zhao, M., Huang, F., Li, L., Liang, X., Xu, X., 2006. Incidence and complete molecular characterization of glucose-6-phosphate dehydrogenase deficiency in the Guangxi Zhuang autonomous region of southern China: description of four novel mutations. Haematologica 91 (10), 1321–1328.

Yang, G.J., Gao, Q., Zhou, S.S., Malone, J.B., McCarroll, J.C., Tanner, M., Vounatsou, P., Bergquist, R., Utzinger, J., Zhou, X.N., 2010. Mapping and predicting malaria transmission in the People's Republic of China, using integrated biology-driven and statistical models. Geospat. Health 5 (1), 11–22.

Zhang, H.W., Su, Y.P., Zhao, X.D., Yan, Q.Y., Liu, Y., Chen, J.S., 2007. Re-emerging malaria in yongcheng city of Henan Province. Chin. J. Vector Bio. Control 18 (1), 42–44 (in Chinese).

Zhang, H.W., Su, Y.P., Zhao, X.D., Yan, Q.Y., Liu, Y., Chen, J.S., 2010a. Imported falciparum malaria situation in Henan Province during 2005–2009. Chin. J. Parasitol. Parasit. Dis. 28 (6), 476–477 (in Chinese).

Zhang, S.S., Zhou, S.S., Tang, L.H., Huang, F., Zheng, X., 2012a. Study on the correlation between land use and cover change and malaria transmission in the areas along the Yellow River and Huai River. Chin. J. Parasitol. Parasit. Dis. 30 (2), 102–108 (in Chinese).

Zhang, Y., Bi, P., Hiller, J.E., 2010b. Meteorological variables and malaria in a Chinese temperate city: a twenty-year time-series data analysis. Environ. Int. 36 (5), 439–445.

Zhang, Y., Liu, Q.Y., Luan, R.S., Liu, X.B., Zhou, G.C., Jiang, J.Y., Li, H.S., Li, Z.F., 2012b. Spatial-temporal analysis of malaria and the effect of environmental factors on its incidence in Yongcheng, China, 2006–2010. BMC Public Health 12, 544.

Zhang, Y.Q., Liu, J.Q., Guo, X.S., Tang, Z.Q., Zhao, X.D., Zhou, R.M., Zhao, Q., 2012c. Resistance of *Anopheles sinensis* to insecticides in Huaibin County of Henan Province. Chin. J. Parasitol. Parasit. Dis. 30 (6), 493–495 (in Chinese).

Zheng, X., Fang, W., Huang, F., Shen, Y.Z., Su, Y.P., Huang, G.Q., Zhou, S.S., 2008. Evaluation on malaria situation in areas along Yellow River and Huaihe River by indirect fluorescent antibody test. Chin. J. Parasitol. Parasit. Dis. 26 (6), 417–421 (in Chinese).

Zhou, G.C., Zhang, H.W., Su, Y.P., 2008. Analysis of malaria outbreak in Yongcheng county of Henan province. J. Trop. Med. 8 (4), 381–383 (in Chinese).

Zhou, G.C., Zhang, H.W., Su, Y.P., 2009. Study on control of malaria outbreak and prevalence by biologic control measures against mosquito larvae in Yongcheng County. Chin. Trop. Med. 9 (2), 103–105 (in Chinese).

Zhou, S.S., Huang, F., Wang, J.J., Zhang, S.S., Su, Y.P., Tang, L.H., 2007a. Study on the spatial distribution of malaria in Yellow River and Huai River areas based on the "kriging"method. J. Pathog. Biol. 2 (3), 204–206.

Zhou, S.S., Huang, F., Wang, J.J., Zhang, S.S., Su, Y.P., Tang, L.H., 2010. Geographical, meteorological and vectorial factors related to malaria re-emergence in Huang-Huai River of central China. Malar. J. 9, 337.

Zhou, S.S., Wang, Y., Tang, L.H., 2007b. Malaria situation in the People's Republic of China in 2006. Chin. J. Parasitol. Parasit. Dis. 25 (6), 439–441 (in Chinese).

Zhou, S.S., Zhang, S.S., Wang, J.J., Zheng, X., Huang, F., Li, W.D., Xu, X., Zhang, H.W., 2012. Spatial correlation between malaria cases and water-bodies in *Anopheles sinensis* dominated areas of Huang-Huai Plain, China. Parasit. Vectors 5, 106.

Zhou, Z.-J., 1991. Malaria Control and Study in China. People Health Press, Beijing (in Chinese).

Zhu, D.S., Wang, J.J., Xu, X., Zhu, J., Li, H.Z., 2013a. Evaluating the effect of preventive medicine for residents living around mosquito breeding water during rest period of malaria. Chin. J. Preventive Med. 47 (1), 44–48 (in Chinese).

Zhu, G., Lu, F., Cao, J., Zhou, H., Liu, Y., Han, E.T., Gao, Q., 2013b. Blood stage of *Plasmodium vivax* in central China is still susceptible to chloroquine plus primaquine combination therapy. Am. J. Trop. Med. Hyg. 89 (1), 184–187.

Zhu, G., Xia, H., Zhou, H., Li, J., Lu, F., Liu, Y., Cao, J., Gao, Q., Sattabongkot, J., 2013c. Susceptibility of *Anopheles sinensis* to *Plasmodium vivax* in malarial outbreak areas of central China. Parasit. Vectors 6 (1), 176.