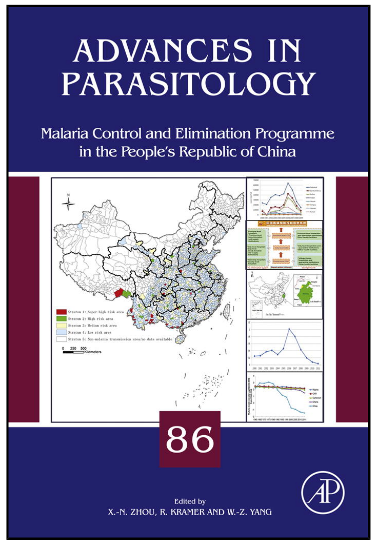

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CHAPTER ONE

Historical Patterns of Malaria Transmission in China

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Contents

Abstract

The historical patterns of malaria transmission in the People's Republic of China from 1949 to 2010 are presented in this chapter to illustrate the changes in epidemiological features and malaria burden during five decades. A significant reduction of malaria incidence has resulted in initiation of a national malaria elimination programme. However, challenges in malaria elimination have been identified. Foci (or hot spots) have occurred in unstable transmission areas, indicating an urgent need for strengthened surveillance and response in the transition stage from control to elimination.

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1. INTRODUCTION

Malaria is one of the most important tropical diseases, mostly affecting poor and vulnerable groups in tropical and subtropical areas of the world. The disease has caused calamity throughout the history of mankind, with records dating back more than 4000 years ago, and it has seriously affected the socioeconomic development in the People's Republic of China (P.R. China). Since 1949, the number of malaria cases, mainly caused by infections of *Plasmodium falciparum* and *P. vivax* in P.R. China, have declined dramatically through years of efforts. These achievements are attributed to the many effective interventions at different malaria transmission phases. A national malaria elimination programme (NMEP) was launched in P.R. China in 2010, with a goal of eliminating malaria by 2020. This chapter presents a comprehensive review of the historic patterns of malaria transmission in P.R. China so that the reader can understand the perspectives of NMEP initiation.

2. BACKGROUND

Great achievements in the global battle against malaria have been made in recent decades, with tremendous funding for malaria research and innovative measures, such as rapid diagnostic tests (RDTs), long-lasting insecticidal nets and artemisinin-based combination therapy (ACT). According to the *World Malaria Report*, in 2013 (WHO, 2013), global malaria mortality and incidence rates were reduced by about 45% and 29% compared to the year 2000, respectively. However, malaria epidemiology changed significantly due to different factors, such as vector control measures and increasing population flows, resulting in several new challenges to meet the terminal goal of malaria eradication (Bhatia et al., 2013; Cotter et al., 2013; Kitua et al., 2011). Thus, malaria is still one of the greatest public health problems around the world, and there is still a long way to go to overcome this ancient foe.

Malaria has been recorded in Chinese traditional medicine books, and the prevalence of the disease dates back about 4000 years ago in the history of P.R. China. The disease spreads widely, especially in rural areas, and outbreaks occurred frequently in the past. Before 1949, it was estimated that more than 30 million cases of malaria occurred nationwide each year, and mortality was around 1% (Zhou, 1985). However, through sustained efforts in different control phases, malaria has declined dramatically, to less than 15,000 cases in 2009 (Zhou et al., 2011a), and the endemic areas have shrunk greatly. Moreover, the transmission of malaria species has changed; no autochthonous malariae malaria and ovale malaria were reported in recent years, and falciparum malaria was only reported in Yunnan (Xia et al., 2012; Xia et al., 2013; Zhou et al., 2011b). Vivax malaria is the predominant species in P.R. China, with a significant reduction compared to the historical data (Tang et al., 2012; Zhou, 1991). The main malaria vector mosquitoes are *Anopheles sinensis*, *An. dirus*, *An. anthropophagus* and *An. minimus* (MOH, 2007), while *An. jeyporiensis candidiensis*, *An. pseudowillmori* and *An. sacharovi* also play roles in malaria transmission in some specific localities (Wu et al., 2009; Wu et al., 2012; Wu et al., 2013; Zhou, 1991). To fulfil Millennium Development Goals and achieve global eradication of malaria, the Chinese government initiated the NMEP in 2010, with the goal of eliminating malaria nationwide by 2020. Although tremendous successes in malaria control have been achieved, challenges still exist in the transition stage from control towards elimination.

The main objective of this chapter is to comprehensively review malaria transmission patterns, including malaria cases, vector mosquitoes and specific strategies, in the different malaria transmission phases in P.R. China, to synthesize the experiences and lessons worthy to be learnt by other malaria endemic areas. We also identify the potential challenges that need to be addressed in order to reach the goal of malaria elimination nationally and eradication globally.

3. HISTORICAL PATTERNS OF MALARIA IN CHINA

From the foundation of P.R. China in 1949 to the launch of NMEP in 2010, the malaria transmission in the country can be principally divided into four phases, according to the transmission profiles, namely: (1) indeterminacy of malaria transmission (1949–1959), (2) outbreak and pandemic transmission (1960–1979), (3) decline with sporadic case distribution (1980–1999), and (4) low transmission with a re-emergence in central China (2000–2009) (Figure 1.1).

3.1 First phase: indeterminacy of malaria transmission (1949–1959)

Although malaria was highly prevalent nationwide, the information on parasite species, vectors, epidemiology, and geographic/demographic distributions were not well addressed in this time period because of the country's poor economy and low capacity. However, many professional institutes were established in succession at national and provincial levels, and malaria prevalence was investigated in some endemic areas for professional training and pilot studies. The first five-year National Malaria Control Programme (NMCP) was issued with two epoch-making events: malaria was designated as a notifiable disease and a malaria-reporting mechanism was implemented nationwide (MOH, 1956).

Many investigations and surveys were carried out to understand the malaria profile and to determine epidemiological factors. Baseline data on *Plasmodium* species and vectors were collected from trials (Tang et al., 2012; Zhou, 1981). The country was divided into four different zones on the basis of the extensive epidemiological surveys (Tang et al., 2012; Zhou, 1981; Zhou, 1991). Zone 1 was the tropical and subtropical areas covering the southern parts of Yunnan, most parts of Guangdong (including Hainan Island), Guangxi, and southeastern Fujian. In Zone 1, *P. falciparum* was the predominant species; *P. vivax* was common, while *P. malariae* was scattered and *P. ovale* was also suspected in the southwestern Yunnan. The season of malaria transmission was from March to December. Zone 2 included Guizhou, Hunan, Jiangxi, Hubei, Zhejiang and Shanghai, northern Yunnan, parts of Tibet, Guangxi, Guangdong, Gansu, Shanxi and Henan. *P. vivax* was the main species, and the season of malaria transmission was from May to November, with a peak from August to October. Zone 3 covered Shandong, Liaoning, Jilin, Heilongjiang, Beijing and Tianjin, most parts of Hebei and Shaanxi, parts of Shanxi, Henan, Jiangsu, Anhui and Xinjiang. Only vivax malaria was prevalent in this zone, with the transmission season lasting from June to November (with the peak from August to October). Zone 4 consisted of malaria-free areas including the cold high-altitude areas, dry desert, plateau, etc.

An. sinensis was found to be widely distributed in most parts of the country; it was the only malaria vector or the preponderant one in many provinces, such as Gansu, Liaoning, Shanxi, Shaanxi, Shandong, Henan, Shanghai, Jiangsu and Zhejiang Provinces. It was also the main vector in Anhui, Hubei, Fujian, Hunan and Sichuan provinces, with *An. minimus* also playing an important role in malaria transmission in these areas. *An. minimus* was the main vector in the mountainous areas of Guangxi and the high or hyper-high transmission areas in Guizhou. *A. sinensis* was the main vector in the plains of Guangxi and the northwestern and southern of Guizhou. Also, *An. minimus* was the preponderant vector in Guangdong, Hainan, Yunnan and Jiangxi provinces. Other mosquitoes such as *An. dirus* in Hainan island (a part of Guangdong province then) and *An. jeyporiensis candidiensis* in several southern provinces and *An. sacharovi* in Xinjiang also played a part role in malaria transmission in local areas (Tang et al., 2012; Zhou, 1991).

3.2 Second phase: outbreak and pandemic transmission (1960–1979)

The transmission of malaria in this period was unstable and hyperendemic (Figure 1.1(a)). A pandemic transmission of vivax malaria occurred in the Huang-huai plain (Sang et al., 2011) and central China, including Jiangsu, Shandong, Henan, Anhui and Hubei provinces, because of the interruption of malaria control activities attributed by a natural disaster in the beginning of 1960s and political unrest in 1967. In addition, malarial outbreaks caused by population movements were recorded in Hainan, Zhejiang, Fujian and Yunnan, etc. (Tang et al., 2012; Zhou, 1991). During the 20 years, more than 18,000,000 malaria cases were accumulatively reported from each of five central parts of China, including Henan, Jiangsu, Shandong, Anhui and Hubei provinces. More than 1,000,000 cases were individually reported from the other 10 provinces including Jiangxi, Zhejiang, Sichuan, Hunan, Fujian, Guangdong, Hebei, Guangxi, Shanghai and Yunnan, and approximately 1,000,000 cases were form other endemic areas (Tang et al., 2012). Annual deaths suffered from malaria numbered in the hundreds, with the highest total of approximately 2050 in 1963 (Figure 1.2(a)). The country was stratified into four transmission areas according to malaria prevalence (Figure 1.3(a)).

The pandemic transmission in the central parts was caused by *An. Sinensis,* with its wide distribution, large population, and outdoor-biting behaviour. Nevertheless, malaria prevalence in Hainan and the southeastern coastal areas decreased because of the shrinking distribution of *An. minimus*. During this phase, *An. anthropophagus* was identified as an important malaria vector in the some southern and central areas with a high transmission capacity. Meanwhile, *An. dirus* become the main vector in Hainan with the elimination of *An. minimus* (Tang et al., 2012).

Specific strategies were formulated to control outbreaks and pandemics, mainly based on the species of vector in particular areas. Vector control interventions, such as insecticide treated net (ITN), combined with case management were the primary strategies implemented in the southern areas, where *An. minimus* was the predominant vector (MOH, 1964; Tang et al., 2012). The northern parts of China, where *An. sinensis* was the key vector, adopted integrated measures, including environment improvement, a radical treatment that administration with primaquine plus pyrimethamine/quinine, and prophylactic chemotherapy with pyrimethamine in high-transmission settings.

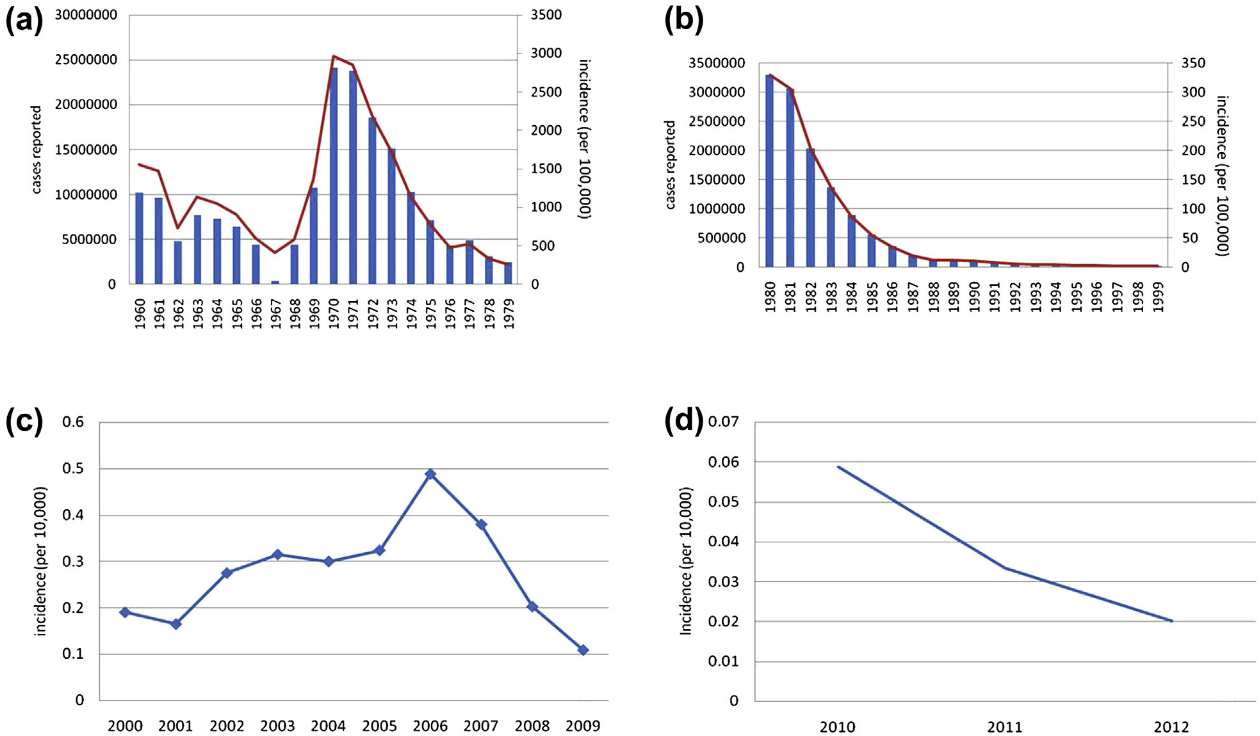

Figure 1.1 The reported cases and incidence in P.R. China. (a) 1960–1979; (b) 1980–1999; (c) 2000–2009; (d) 2010–2012.

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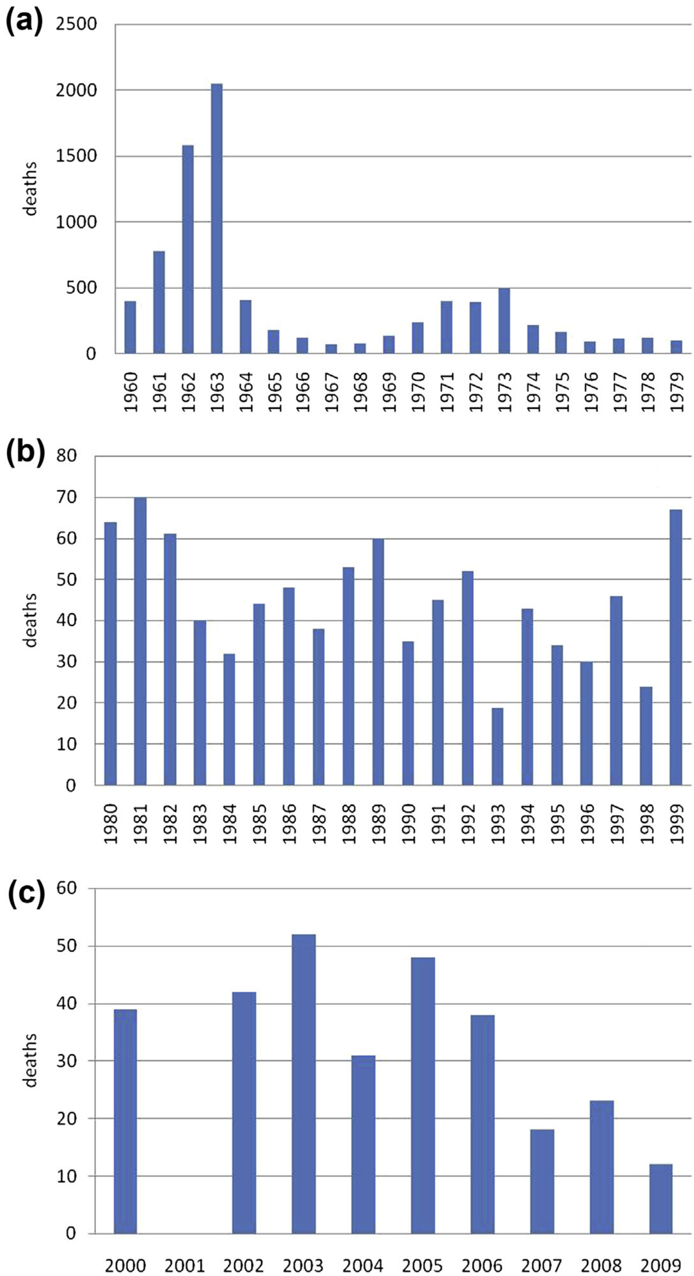

Figure 1.2 The number of death due to malaria in P.R. China. (a) 1960–1979; (b) 1980–1999; (c) 2000–2009.

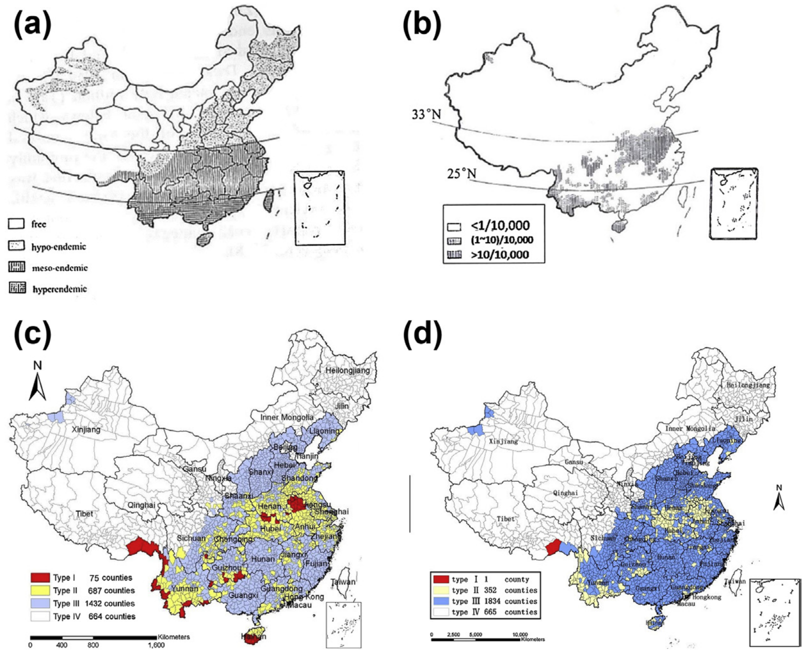

Figure 1.3 The geographical stratification of malaria based on the incidences in P.R. China: (a) 1979 (Tang et al., 1991); (b) 1985 (Tang et al., 2012); (c) 2007–2009 (Yin et al., 2013); (d) 2010–2012 (Yin et al., 2013).

3.3 Third phase: decline with sporadic case distribution (1980–1999)

In this phase, malaria prevalence was declining gradually, with the exception of the year 1989 and 1994 (MoH Expert Advisory Committee on Malaria, 1993; MoH Expert Advisory Committee on Malaria, 1994; MoH Expert Advisory Committee on Malaria, 1995; MoH Expert Advisory Committee on Malaria, 1998; MoH Expert Advisory Committee on Malaria, 1999; MoH Expert Advisory Committee on Malaria, 2000; MoH Expert Advisory Committee on Parasitic Diseases, 1988; MoH Expert Advisory Committee on Parasitic Diseases, 1989; MoH Expert Advisory Committee on Parasitic Diseases, 1990; MoH Expert Advisory Committee on Parasitic Diseases, 1991; MoH Expert Advisory Committee on Parasitic Diseases, 1992; MoH Expert Advisory Committee on Parasitic Diseases, 1996; MoH Expert Advisory Committee on Parasitic Diseases, 1997; CoMS Malaria Commission, 1983; CoMS Malaria Commission, 1984; CoMS Malaria Commission, 1985; CoMS Malaria Commission, 1986; CoMS Malaria

Commission, 1987) (Figure 1.1(b)). The case reduction rates were reported of approximately 30–43% during 1982–1988 and approximately 15–25% during 1990–1996, except for 1994 because of increasing population movement towards southern parts of China with high malaria transmission (MoH Expert Advisory Committee on Malaria, 1995). In the first 10 years of this period, more than 40% of cases were reported from central China including Jiangsu, Shandong, Henan, Anhui and Hubei, while in the latter 10 years more than 40% of cases were from the southern China, including Yunnan, Hainan, Guizhou, Guangxi, Guangdong, Fujian, Sichuan and Chongqing. Vivax malaria was the predominant species and was widely distributed in the endemic areas in the period. Falciparum malaria has been limited to Yunnan and Hainan provinces since 1995, although it also occurred in a few provinces in the past. The number of death due to malaria dramatically decreased, with less than 70 deaths reported annually (Tang et al., 1991) (Figure 1.2(b)). Malaria stratification was also updated along with the changing transmission (Figure 1.3(b)).

No significant variation in the species and distribution of vectors was found, but the malaria situation in the areas with different main vectors underwent a great change. In the areas where *An. sinensis* was the dominant vector, malaria transmission steadily decreased due to the shrinking of breeding grounds. However, the transmission was unstable in the areas where *An. anthropophagus* was the main vector, with a higher vector capacity (Pan et al., 1999; Wang et al., 1986). *An. dirus* was mainly distributed in particular areas in Yunnan and Hainan, which greatly contributed to the high prevalence of falciparum malaria in Hainan.

Control measures were tailored to different malaria profiles and specific vectors. At the beginning of this phase, case management combined with vector control interventions were adopted in the areas where vivax malaria was prevalent by *An. sinensis*. ITNs using DDT or pyrethroid insecticides followed by case management were applied in the areas where *An. anthropophagus* or *An. minimus* was the main vector. Environment modifications for breeding sites reduction were added in the areas with *An. dirus*. Residual foci elimination and case surveillance were carried out in areas with relatively low transmission, where the prevalence was less than 5 per 10,000 population. Especially in this phase, the concept and target of malaria eradication were initially proposed in 1983 (MOH, 1983). Subsequent technical guidelines and protocols related to case management, vector control, surveillance, and training were developed, with a target of basically eradicating malaria in particular localities

(MOH, 1984a,b; MOH, 1986; MOH, 1986; MOH, 1989; MOH, 1990; MOH, 1996; MOH et al., 1985).

3.4 Fourth phase: low transmission with a re-emergence in Central China (2000–2009)

Malaria transmission presented an unstable pattern from 2000 to 2009, with the highest incidence of 0.49 per 10,000 in 2006 and the lowest incidence of 0.11 per 10,000 in 2009 (MoH Expert Advisory Committee on Malaria, 2001; Sheng et al., 2003; Zhou et al., 2005; Zhou et al., 2006a; Zhou et al., 2006b; Zhou et al., 2007; Zhou et al., 2008; Zhou et al., 2009; Zhou et al., 2011) (Figure 1.1(c)). Moreover, there still existed a large number of suspected malaria cases nationwide, with no data available for the suspected cases in 2000 and 2001. Less than 100 deaths due to malaria were reported in each year (Figure 1.2(c)). A new malaria transmission map was drawn for further stratification leading to malaria control and elimination (Figure 1.3(c)).

In particular, since 2001, a re-emergence unpredictably occurred in central parts of China along the Huang-Huai River, including Anhui, Henan, Hubei and Jiangsu provinces. Anhui Province alone accounted for more than 50% of the country's total cases. Even so, Yunnan Province maintained its rank in the top three for numbers and incidence rates (Figure 1.4). Vivax malaria accounted for a majority of cases. Locally-transmitted falciparum malaria declined significantly and was limited to Yunnan and Hainan provinces (Figure 1.5).

An. sinensis, *An. dirus*, *An. anthropophagus,* and *An. minimus* were still the main malaria vectors in this period (MOH, 2007), while *An. pseudowillmori* was identified as the key malaria transmiting vector in Motuo County of Tibet (Wu et al., 2009). The intensity of *An. anthropophagus* and *An. minimus* were much lower, so it was difficult to capture in the most endemic areas (Wang et al., 2013). New geographic distributions of *An. anthropophagus* were identified in three provinces of Henan, Shandong and Liaoning (Gao et al., 2002; Ma et al., 2000; Shang et al., 2007).

Specific strategies were adopted in particular malaria transmission areas and for the control of re-emergence. Comprehensive measures were intensively implemented in the high-transmission areas of borders of Yunnan and the central southern mountainous counties of Hainan to control or eliminate falciparum malaria, supported by the first round of the Global Fund to Fight AIDS, Tuberculosis and Malaria programme (GFATM).

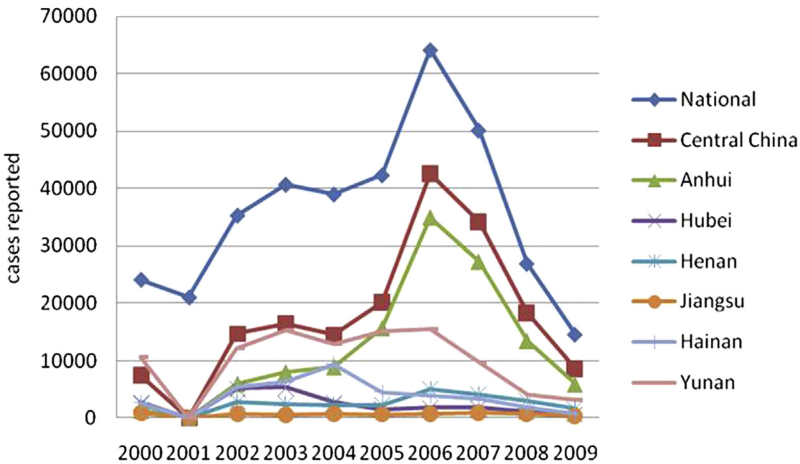

Figure 1.4 The changes of the number of reported malaria cases in P.R. China, 2000–2009.

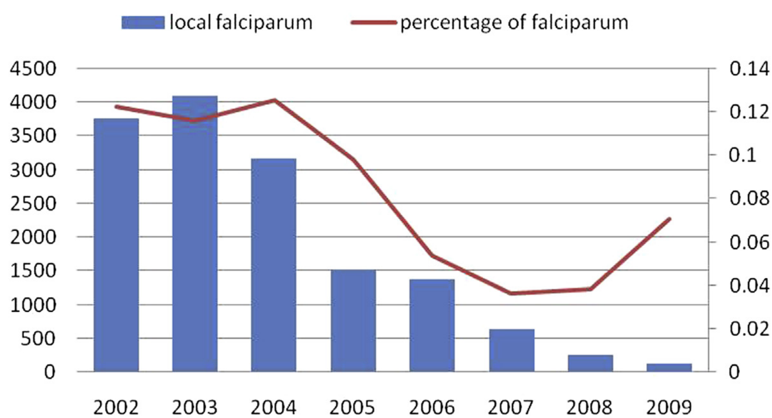

Figure 1.5 The changes in number and proportion of falciparum malaria cases reported in P.R. China, 2002–2009.

The main activities involved in various aspects of malaria control which included early diagnosis and appropriate treatment, focal vector control interventions, malaria management among mobile populations, health education and promotion, and surveillance, monitoring and evaluation. The successful application and implementation of the fifth round of the GFATM greatly contributed to the rollback of re-emergence in central China and made a strong base for the NMEP.

Table 1.1 Epidemiological features of four phases of malaria in P.R. China from 1949 to 2009

Phase (period)	Epidemiological features	Control strategy
Indeterminacy of malaria transmission phase (1949–1959)	Seriously prevalent, information about malaria species and vectors unclear nationwide	Notifiable disease enrolment, malaria-reporting mechanism, malaria control trials, baseline surveys of *Plasmodium* and vectors, etc.
Outbreak and pandemic transmission phase (1960–1979)	Unstable and hyperendemic, vivax malaria pandemic in the Huang-huai plain and central China	ITNs combined with case management; integrated measures composed of environment improvements, radical treatment with primaquine plus pyrimethamine/quinine, prophylactic chemotherapy with pyrimethamine, etc.
Decline phase with sporadic case distribution (1980–1999)	Decreasing, sporadic distribution	Case management, vector control with ITNs, environment modification, case surveillance, personnel training, etc.
Low transmission phase with a re-emergence in the central China (2000–2009)	Unstable but low transmission, unpredictable re-emergence in the central China	Early diagnosis and appropriate treatment, focal vector control interventions, malaria management among mobile populations, health education and promotion, and surveillance, monitoring and evaluation, etc.

4. LOOKING FORWARD

With tremendous investments and intensive interventions, malaria has been effectively controlled in China (Figure 1.1(d), Table 1.1), with autochthonous cases being dramatically reduced to limited localities (Xia et al., 2012; Xia et al., 2013; Zhou et al., 2011b) (Figure 1.6). In recent years, locally transmitted malaria was limited to a few counties, from 303 counties in 18 provinces in 2010, to 160 counties in 12 provinces in 2011, down to 41 counties in 5 provinces in 2012 (Yin et al., 2013) (Figure 1.3(d)). However, almost all of counties in the whole country have reported the importation of malaria mainly due to labours back from other countries, covering 651 counties in 23 provinces in 2010, 760 counties in 26 provinces in 2011, and 598 counties in

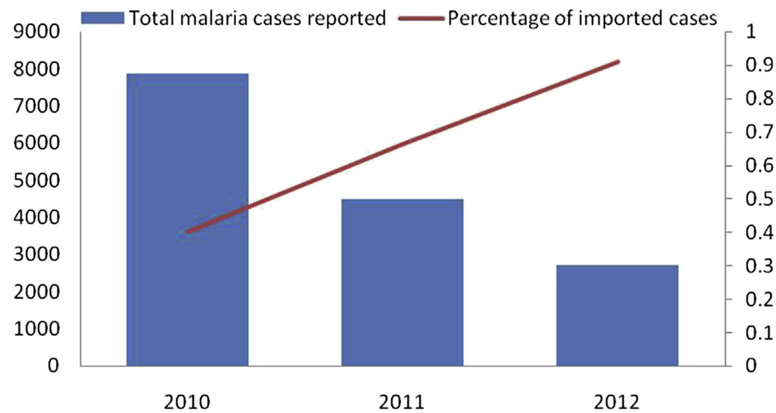

Figure 1.6 The trends of the number and proportion of malaria cases reported in P.R. China, 2010–2012.

29 provinces in 2012. Only 15 counties – 11 counties of Anhui, 3 of Yunnan, and 1 of Tibet – had no imported cases in the years of 2010, 2011 and 2012. Therefore, there still have technical and managerial challenges in the transition from control towards elimination (Zheng et al., 2013; Tambo et al., 2014a).

4.1 Challenges

As efforts toward malaria elimination progress, more and more areas will be investigated by timely experts for surveillance and response after onsets of malaria cases in order to interruption of malaria transmission promptly in the NMEP. This will result in a shortage of human resources and finances for malaria surveillance and response (Yin et al., 2013), including vector surveillance (Tambo et al., 2014b). It is an essential to sustain personnel training and finances, as well as formulate proposals for postelimination malaria surveillance. It must pay much more attention to the following three scenarios, while keeping routine surveillance for malaria cases and mosquito vectors.

4.1.1 Imported malaria

Imported malaria has become an important challenge with an increasing proportion of total cases, accounting for more than 90% in 2012 (Figure 1.6). There has been a remarkable upward trend in recent years, with the increasing movement of labourers returning from Africa and frequent movement cross the borders. Moreover, not only dominant falciparum malaria from African countries and vivax malaria from Asian countries, but also some malariae and ovale malaria, have been reported with an increasing pattern as well (Xia et al., 2012). The transmission settings, especially the distribution of malaria vectors, cannot be changed fundamentally following the reduction of malaria transmission. It is necessary to monitor whether domestic mosquitoes in P.R. China could be infected with the imported *Plasmodium* spp. In addition, current measures on imported cases and foci-related investigation should refer to the diagnosis, treatment, and management of imported malaria cases. In addition, domestic multisectoral cooperation, international multilateral collaboration, and information harmonization should be sustained and strengthened.

4.1.2 Asymptomatic and low-parasitemia infections

Little data about asymptomatic or low-parasitemia individuals in P.R. China can be retrieved. These populations account for most infections from *Anopheles* mosquitoes and are difficult to identify due to low-parasitemia (Ganguly et al., 2013; Harris et al., 2010; Starzengruber et al., 2014; Zoghi et al., 2012). It is also an important challenge related to transmission interruption. China lacked malaria-sensitive diagnostic tools for asymptomatic patients and patients with low levels of parasitemia. Although RDTs, polymerase chain reaction, and other techniques have been used in NMEP, most cases were tested based on the results of microscopy (Zheng et al., 2013). Therefore, development of much more sensitive and cost-effective techniques for malaria diagnosis is essential for the NMEP in P.R. China.

4.1.3 Resistance of **P. falciparum** *to artemisinin*

Although *P. falciparum* resistance to artemisinin is restricted to the Greater Mekong Subregion including Cambodia, Laos, Myanmar, Thailand and Vietnam, different day-3 positivity rates among malaria patients treated with artemether-lumefantrine were reported in South America (Ariey et al., 2014; Liu, 2014; Miotto et al., 2013; WHO, 2014). The consequence of widespread resistance to artemisinin will be catastrophic (Bhatia et al., 2013). Routine monitoring of *P. falciparum* resistance to artemisinin is especially necessary to carry out in Yunnan border areas, although no artemisinin-resistant cases have been found so far (Starzengruber et al., 2012).

4.2 Recommendation

To achieve the final goal of eliminating malaria in China, sustained efforts are essential to transfer from the control stage to the elimination stage. Therefore, efforts to accelerate the transition stage from control to elimination are recommended in the following five fields:

- Improving surveillance technology with more sensitivity of malaria detection as well as modeling transmission patterns supported by the

essential database (ERACGoM mal 2011; malEra Consultative Group on Monitoring et al., 2011; Zhou et al., 2013; Liu et al., 2012; Xia et al., 2013).
- Strengthening the health system through multisectorial cooperation, which enforces the response action to malaria foci (Alonso and Tanner, 2013; ERACGoHS mal, 2011).
- Sustaining the NMEP investments to further improve the quality of the programme activities, such as monitoring and evaluation, health education, etc. (Alonso and Tanner, 2013; Brijnath et al., 2014; Koenker et al., 2014; ERACGoIS mal, 2011; malEra Consultative Group on Monitoring, 2011).
- Enforcing capacity building, with both professional institutions and personnel working in NMEP (Alonso et al., 2011).
- Encouraging more activities in research and development in order to cope with emerging issues, such as artemisinin resistance, identification of parasite origins, G6PD deficiency, community-based interventions, etc. (Alonso and Tanner, 2013; Brijnath et al., 2014; Liu, 2014; ERACGoD mal, 2011).

5. CONCLUSION

Malaria incidence in P.R. China has been reduced to the lowest level in the history. However, the NMEP goal of malaria elimination will not be achieved by 2020 if the efforts of the consistent phase-specific interventions are not intensified enough. Major challenges include malaria surveillance and response, which should be tailored to local settings in the transition stage from control to elimination, particularly for the increasing patterns of imported malaria cases, asymptomatic and low-parasitemia infections, and artemisinin resistance. It is suggested that the activities of the NMEP, including multilateral cooperation, investments in NMEP, health systems, and personnel capacity, research and development, have to be strengthened in both the elimination and postelimination stages to finally win the battle against malaria.

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