CHAPTER ONE

Evolution of the National Schistosomiasis Control Programmes in The People's Republic of China

J. Xu[*,§,¶], P. Steinman[‖,#], D. Maybe[**], X.-N. Zhou[*,§,¶,1], S. Lv[*,§,¶], S.-Z. Li[*,§,¶], R. Peeling[**,1]

[*]National Institute of Parasitic Diseases, Chinese Center for Disease Control and Prevention, Shanghai, The People's Republic of China
[§]Key Laboratory of Parasite and Vector Biology, Ministry of Health, Shanghai, The People's Republic of China
[¶]WHO Collaborating Center for Tropical Diseases, Shanghai, The People's Republic of China
[‖]Swiss Tropical and Public Health Institute, Basel, Switzerland
[#]Basel Universities, Basel, Switzerland
[**]London School of Hygiene and Tropical Medicine, London, United Kingdom
[1]Corresponding authors: E-mail: zhouxn1@chinacdc.cn; Rosanna.Peeling@lshtm.ac.uk

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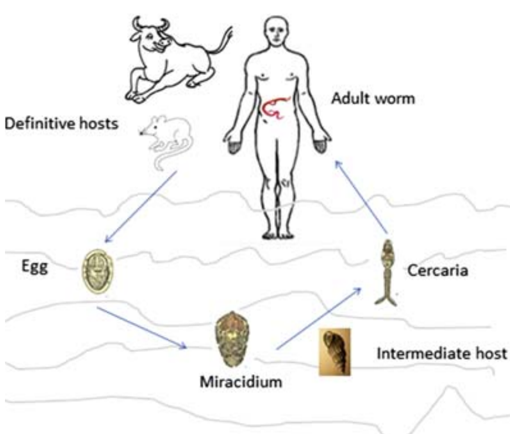
Abstract

Schistosomiasis japonica is caused by the parasitic trematode *Schistosoma japonicum*. It is endemic in The People's Republic of China and has significant impact on human health and socioeconomic development in certain regions. Over the last six decades, the national control programmes evolved in remarkable ways and brought schistosomiasis japonica largely under control. We describe the history and evolution of schistosomiasis control in The People's Republic of China, with an emphasis on shifts in control strategies that evolved with new insights into the biology of the parasite and its intermediate hosts, and the epidemiology of the disease in the country. We also highlight the achievements in controlling the disease in different socioecological settings, and identify persisting challenges to fully eliminate schistosomiasis japonica from the country. To reach the goal of schistosomiasis elimination, further integration of interventions, multisector collaboration, sensitive and effective surveillance are needed to strengthen.

1. INTRODUCTION

Intestinal schistosomiasis japonica is caused by *Schistosoma japonicum* infection and occurs in Indonesia, the Philippines and The People's Republic of China (Gryseels et al., 2006; Ross et al., 2002). The amphibious freshwater snail *Oncomelania hupensis* is the only intermediate host of *S. japonicum* but besides humans (Li et al., 2016), more than 40 mammals can serve as definitive hosts (Cao et al., 2016; McManus et al., 2009; Wang et al., 2008). People are infected during water contact due to economic, leisure and domestic activities. *Schistosoma japonicum* infections often cause more severe morbidity than infections with other schistosomes due to the high number of ova produced by the female worms. People from nonendemic areas and those infected with a large number of cercariae can have particularly acute manifestations such as cercarial dermatitis and Katayama fever (Chen, 2014; Ross et al., 2007). Bloody diarrhoea, abdominal pain, liver cirrhosis and portal hypertension are typical symptoms. Chronic schistosomiasis develops in inhabitants of endemic areas frequently exposed to cercariae. Chronic cases present without symptoms or with nonspecific intermittent abdominal pain, diarrhoea and rectal bleeding, with the frequency of symptoms related to the intensity of infection. If they are not treated promptly and adequately, cases may present as advanced schistosomiasis with symptoms such as splenomegaly, ascites, colonic tumouroid proliferations or growth retardation (Fig. 1) (Colley et al., 2014; Gryseels et al., 2006; Li, 2006).

Symptoms resembling early schistosomiasis or Katayama syndrome have been described in ancient Chinese medical publications where the disease was called water poison disease. Studies in the 1970s on two exhumed 2100-year-old corpses from the western Han dynasty identified schistosome



Disease Progression
Acute schistosomiasis Cercarial dermatitis Katayama fever bloody diarrhea, abdominal pain portal hypertension liver cirrhosis
Chronic schistosomiasis No symptoms or Intermittent abdominal pain Diarrhea Rectal bleeding
Advanced schistosomiasis Splenomegaly Ascites Colonic tumoroid proliferation Growth retardation

Figure 1 Life cycle of *Schistosoma japonicum* and disease progression.

eggs in their inner organs (Ross et al., 1997; Wei, 1973). The first modern medical description of schistosomiasis was published by Dr Logan in 1905 based on a case in Changde city of Hunan province (Logan, 1905). Over the subsequent 40 years, many missionary doctors and parasitologists conducted surveys and accumulated valuable information about the epidemiology of schistosomiasis japonica (Faust and Meleney, 1924; Kan and Yao, 1934; Kan and Kung, 1936; Tang, 1939). Mao (1948) reviewed these references and concluded that schistosomiasis japonica was prevalent in 138 counties in the mainland The People's Republic of China where an estimated 5 million people were infected, corresponding to an average infection rate of 21.1%. By 1949, the disease had been recognized in 12 provinces in mainland The People's Republic of China (Ling et al., 1949). The prevalence in some villages even exceeded 70% (Kuo, 1946; Lu et al., 1955; Mao, 1948; Totell, 1924) and many people died due to schistosomiasis as reflected in village names such as 'Big-belly village', 'Widows' village' and 'Village without villagers' (Chen, 1999; Mao and Shao, 1982). Efforts to control the disease were very limited at that time due to poverty, internal strife and a lack of effective tools (Chen et al., 2016).

Schistosomiasis control was a high priority for the leaders of The People's Republic of China soon after its foundation. Chairman Mao issued a slogan of 'Must eliminate schistosomiasis' in 1955 and a vigorous national control programme was established (Zhu et al., 2016). More than 60 years of continuous efforts resulted in the interruption of schistosomiasis japonica transmission in many areas in The People's Republic of China and its control in the remaining endemic areas (Xu et al., 2015; Zhou et al., 2005). By the end of 2014, 98.9% of all endemic counties (448/453) had interrupted or controlled the transmission of schistosomiasis (Lei and Zhou, 2015). In the present article, we review the evolution of the schistosomiasis control programmes in The People's Republic of China, with a focus on a description of the shift in strategies from controlling the intermediate host to preventing morbidity in humans and removing nonhuman end hosts, and finally integrated multisectoral approaches (Cao et al., 2016; Wan et al., 2016; Yang et al., 2016). Existing challenges to completely eliminate schistosomiasis are also explored to provide guidance for policy makers and research scientists.

2. HISTORICAL EVOLUTION OF SCHISTOSOMIASIS CONTROL

Over all of its 60-year history, schistosomiasis japonica control in The People's Republic of China was based on the basic policy of 'Prevention first, comprehensive management, mass control and prevention'. Based on the insight that blocking any step of the schistosome life cycle would interrupt the transmission, control strategies were developed and adapted over time to remain aligned with epidemiological insights, technological advances and the political environment (Fig. 2).

2.1 Preparation stage (1950–55)

In the early stages of the schistosomiasis control programme in The People's Republic of China, the treatment of patients with severe illness was the primary task. An instruction for schistosomiasis control was issued by the Ministry of Health in 1950, followed by the establishment of professional control system, treatment of patients and field surveys, thus providing the basis for future mass campaigns against schistosomiasis.

2.1.1 Set up of control infrastructure

To conduct treatment and control activities on a large scale, a national committee was established to organize the treatment of patients in known endemic regions, and a large number of control teams were formed in a short time (Wang et al., 1989). In 1950, the East Branch of the Central Institute of Health was established. This branch moved to Shanghai in 1957 and become the national agency for research and guiding schistosomiasis control. During 1950–55, schistosomiasis control stations at provincial, city and county levels were set up successively. 16 stations, 78 substations and 420 field units had been established by 1955 (Wang, 2011). The number of

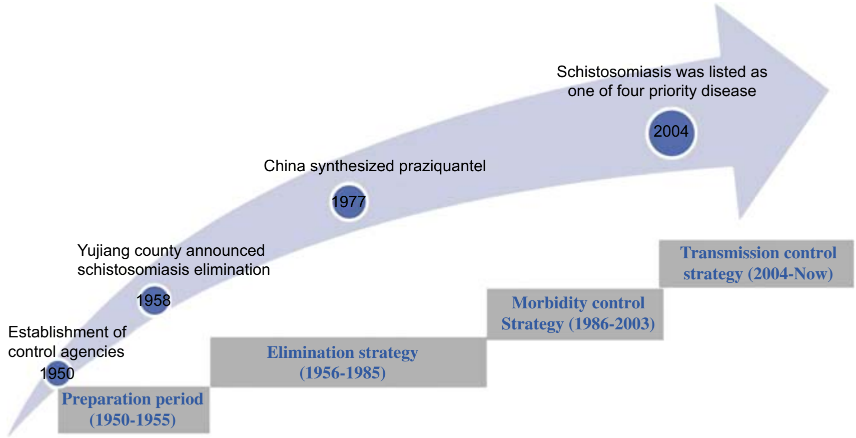


Figure 2 Strategies and key methods for schistosomiasis control in the national control program.

well-trained health workers focussing on schistosomiasis reached 3000 in East China alone (Lu, et al., 1955). Only in 1953, among 55,355 cases who received treatment, 60% of them were cured and health conditions improved in the remaining patients (Lu et al., 1955).

2.1.2 Understanding the epidemiology

During this period, field surveys on the distribution of intermediate host snails and human stool examinations were conducted to understand the endemic areas and epidemiology of schistosomiasis in The People's Republic of China (Chen, 1956; Sleigh et al., 1998; Tang, 1951; Wen and Tao, 2008; Zhuang, 1992). Knowledge about the schistosome life cycle, morbidity and prevention was disseminated through meetings, newspapers, leaflets, etc., providing peasants the basis for reporting the presence of snails or illnesses indicative of schistosomiasis to village leaders in their areas. Pilot studies in different endemic areas were implemented to explore effective approaches for controlling schistosomiasis. However, the achievements did not alter significantly the number of cases due to limited manpower and resources as well as lack of relevant tools and overall planning.

2.2 Mass campaign stage focussed on snail control (1956–85)

During this stage, the first national plan for schistosomiasis control was drafted and an elimination strategy based on snails control was implemented nationwide following the fully understanding of the endemic status of schistosomiasis across The People's Republic of China.

2.2.1 Understanding the endemic status and characteristics of schistosomiasis across The People's Republic of China

The first national schistosomiasis survey was initiated in 1956 and lasted 2 years. Its aim was to identify the true extent of schistosomiasis in The People's Republic of China. The results of the survey showed that schistosomiasis japonica was endemic in 373 counties in 12 provinces south of the Yangtze River. The endemic area was between 33°25′ N and 22°42′N and between 121°45′ E and 99°5′ E. Endemic areas were found from 0 to 3000 m above sea level (Chen and Feng, 1999). It was estimated that more than 10 million individuals were infected with *S. japonicum* and more than 100 million people were at risk of infection (Wang et al., 1989; Xia and Wang, 1989). The number of infected bovines was calculated at 1.2 million while the total area of *O. hupensis* habitat reached 14.5 billion m^2 (Chen, 1999). The most seriously affected areas were located in the delta of the Yangtze River including parts of Jiangsu, Shanghai and Zhejiang provinces, and in the marshland and lake regions along the Yangtze River including the Poyang and Dongting Lakes (Mao and Shao, 1982). The endemic areas were then classified according to eco-geographical characteristics into three categories: plain regions with waterway networks, mountainous and hilly regions, and marshland and lake regions (Fig. 3) (Mao and Shao, 1982).

2.2.2 Strengthening control agencies and guidance on control activities

In 1957, a bureau of schistosomiasis control was set up in the Ministry of Health, merging with the national leading group of schistosomiasis. By August 1957, there were 19 institutes, 236 stations and 1346 substations nationwide for schistosomiasis control, and the number of well-trained staff for schistosomiasis control reached over 17,000 (Daily, 1958). To strengthen the management of the national control programme, the national leading group was rebuilt up in 1970 and a national conference on schistosomiasis

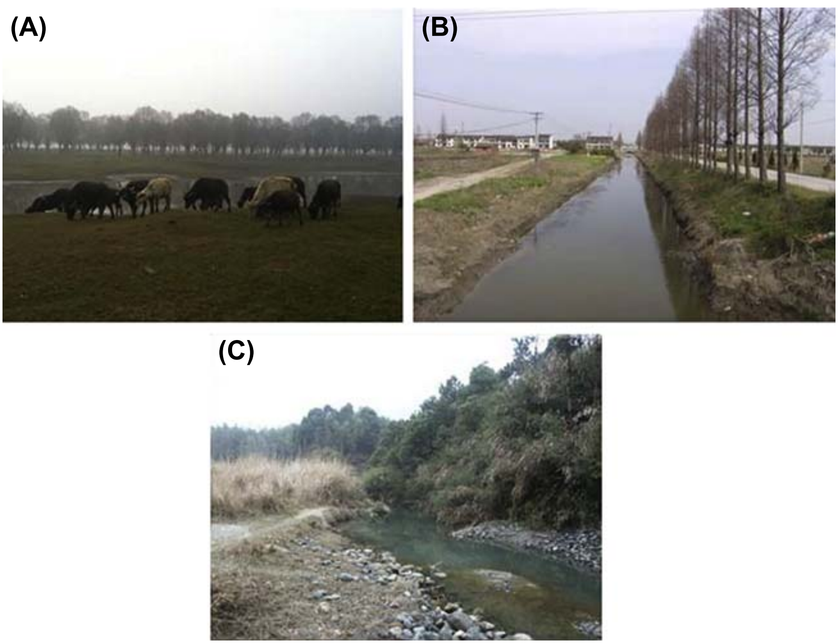


Figure 3 Categories of schistosomiasis japonica endemic areas in The People's Republic of China. (A) Marshland and lake region; (B) Plain region with waterway network; (C) Mountainous and hilly region.

control was organized each year. Furthermore, a national schistosomiasis research committee was established in 1956 to conduct studies on technologies and strategies for schistosomiasis control. The first version of the manual for schistosomiasis control was compiled and published in 1956 to guide the control of schistosomiasis. Criteria of schistosomiasis elimination were issued in 1958 and updated in 1980 by the Ministry of Health (Zhu et al., 2016).

2.2.3 Mass campaign focussed on snail control

In 1956, schistosomiasis was listed as one of five major parasitic diseases in the national programme for agricultural development (1956–67). The objective was set to eliminate schistosomiasis in any possible endemic areas within 12 years but the complexity of schistosomiasis transmission and its control had been neglected. The systematic control activities were affected 1966–69 by the culture revolution. Under the concerns of Chairman Mao and Prime Minister Zhou, several national conferences on schistosomiasis control were organized and control activities were implemented in subsequent years (Wang et al., 1989). The key tools to eliminate schistosomiasis were snail control through environmental modification and mollusciciding (Li et al., 2016). The basic principle of snail control was implementing activities from the upper to the lower reaches of a drainage system, with snail treatment strategies mainly determined by the environment, available resources and cost-effectiveness considerations (Yang et al., 2010, 2012; Yuan et al., 2005). A large number of people were mobilized to participate in the snail elimination campaign. As the most effective drugs at the time, potassium and sodium antimony tartrate was used to treat patients before the 1980s. The clinical use of praziquantel with its low toxicity and high cure rates started in 1978 and decreased the mortality and prevalence of late-stage schistosomiasis. By the end of 1984, a total of 11 million patients had received treatment (Zheng, 1986). Other control measures such as self-protection with chemical repellents or niclosamide impregnated clothes, safe water and sanitary toilets were also provided as complementary interventions (Wen and Tao, 2008).

2.2.4 Achievements and lessons learnt

Following three decades of intensive efforts, the schistosomiasis japonica prevalence and the number of patients with severe illness as well as the snail-infested area had decreased significantly. By 1981, 11 billion m^2 snail habitats were free of snails (Guo and Zheng, 1999). Guangdong Province and Shanghai Municipality had reached the criteria of schistosomiasis elimination in 1985 while Fujian Province and Guangxi Zhuang Autonomous Region eliminated schistosomiasis in 1987 and 1989, respectively (Pan et al., 2002; Sleigh et al., 1998; Wu et al., 2005). The experience showed that elimination of schistosomiasis with snail control could be achieved in areas where the water level was controlled and the economy was relatively developed. However, in 1986–88 the number of acute cases remained high (Xia and Wang, 1989) and the snail-infested area increased from 2.75 billion m^2 in 1980 to 3.47 billion m^2 in 1988 (Yuan, 1999) as an elimination strategy focused on snail control did not work well in places characterized by unstable water levels, a complicated environment or comparatively retarded economic development as it is found in the middle and lower reaches of the Yangtze River as well as in the mountainous areas of Sichuan and Yunnan provinces.

2.3 Morbidity control stage boosted by international cooperation (1986–2003)

2.3.1 Morbidity control strategy and pilot studies

Realizing elimination of schistosomiasis was difficult in poor countries, the WHO expert consultation committee adjusted its strategy and objective from transmission interruption or elimination to morbidity control in 1984 (WHO, 1985). This strategy focused on people and their behaviour rather than the snail and the environment, and had as its objective to reduce morbidity and mortality caused by schistosomiasis rather than focussing on halting transmission. Since 1980, The People's Republic of China carried out pilot studies on this new strategy in heavy endemic areas (Yuan et al., 1990; Zheng et al., 1996). In 1986, new policies were formulated that consisted of four items: to actively prevent and treat cases; to consider local and seasonal conditions; to integrate scientific techniques into mass campaign against schistosomiasis; to fight against schistosomiasis repeatedly (Mao, 1987). Since 1987, the morbidity control strategy intended to reduce the prevalence and intensities among local residents and livestock had been inaugurated in Hunan, Hubei, Jiangxi and Anhui provinces (Yuan et al., 2002).

2.3.2 World Bank loan project

The nationwide implementation of morbidity control was boosted by the World Bank Loan Project (WBLP) on schistosomiasis control which was initiated in 1992 in eight provinces, and ended in 1998 in five provinces and in 2001 in Hubei, Hunan and Yunnan provinces. The key aims of the project were to reduce morbidity caused by schistosomiasis and interrupt transmission in some regions were considered possible. Mass chemotherapy was used in endemic areas with a high prevalence (prevalence >15%) while selective chemotherapy was given to those with positive stool examinations or serological tests in areas with moderate (15% > prevalence > 3%) and low endemicity (prevalence < 3%). Praziquantel treatment of infected cattle along with chemotherapy for humans was also tested. In the frame of the project, almost 19 million treatments were given to humans while 1.7 million cattle and buffaloes were screened and those infected were treated (Chen et al., 2005).

Control through mollusciciding and/or environmental modification was reinforced as supplementary methods. Areas with infected snails were treated annually with niclosomide. Environmental modification was mainly conducted in low endemic areas with the goal to reach transmission interruption (Chen et al., 2005; Yuan et al., 2002). Health education aiming to change the behaviour of people at high risk was an important intervention measure in this strategy. By the end of 1995, there were more than 4000 full or part time staff conducting health education (Guo, 2006).

2.3.3 Achievements and lessons

Among the 219 counties covered by the WBLP, 47 had met the criteria of transmission control and 82 had met the criteria of transmission interruption by 2001. Zhejiang Province with 44 formerly endemic counties had reached the target of elimination in 1995 (Chen et al., 2005). Three national sampling surveys on schistosomiasis conducted before, during and after the WBLP in 1989, 1995 and 2004 demonstrated the impact of the WBLP but also showed the shortcomings of this morbidity control strategy (Fig. 4). The number of cases decreased from an estimated 1,638,103 in 1989 to 865,084 in 1995 while the average prevalence decreased from 9.7% to 4.9%. The prevalence

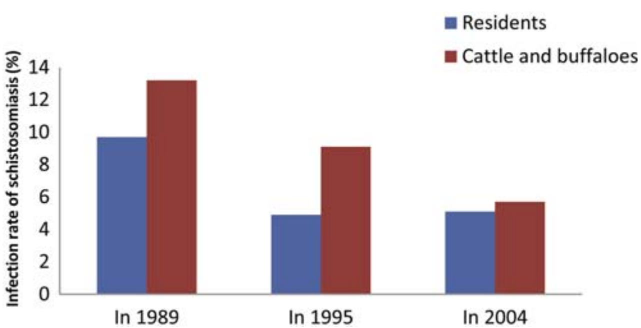


Figure 4 Prevalence of schistosomiasis in human beings and bovines in The People's Republic of China according to the three national sampling surveys.

in cattle and buffalos was reduced from 13.2% to 9.1% (Ministry of Health, 1993, 1998). However, the third national sampling survey conducted in 2004 after the termination of WBLP indicated that 726,112 individuals were estimated to be infected with schistosomes, and that the prevalence was 3.8% in the marshland and lake region (Zhou et al., 2007). Schistosomiasis had re-emerged in The People's Republic of China due to a shortage of financial support following the completion of the WBLP, devastating floods in 1998, important ecological changes caused by water conservancy projects, reforms in the economic and health systems, etc. (Bian et al., 2004; Liang et al., 2006; Xu et al., 2000; Yang et al., 2005; Zhou et al., 2002). The chemotherapy-based strategy could quickly decrease the prevalence of schistosomiasis but failed to interrupt transmission in the hyperendemic areas as it did not prevent reinfection.

2.4 Comprehensive strategy to block schistosomiasis transmission (2004–present)

2.4.1 Formulation of comprehensive strategy to block schistosomiasis transmission

Livestock, especially buffaloes, accounted for 70–90% of all new schistosomiasis cases in the marshland regions along the Yangtze River (Gray et al., 2007, 2008; Guo et al., 2001; Wang et al., 2005a,b). Pilot studies of a new strategy emphasizing health education, removing cattle from snail-infested grasslands, providing farmers with mechanized farm equipment, access to clean water and adequate sanitation and thus aiming to stop the contamination of the environment with schistosome eggs were conducted (Wang et al., 2009a,b; Zhou et al., 2009). While the human prevalence fluctuated in control villages, the infection rate decreased to less than 1% in two intervention villages after three transmission seasons. The prevalence of soil-transmitted helminthiases also gradually decreased (Wang et al., 2009a,b), supporting the public health relevance of this new strategy (Chen et al., 2014; Hong et al., 2013; Sun et al., 2011).

2.4.2 National control programme implementing comprehensive strategy

To curb the rebound of schistosomiasis in the new millennium and realize the final goal of eliminating schistosomiasis in The People's Republic of China, a national strategic plan for schistosomiasis control was issued in 2004. It aimed to reduce the prevalence in humans and livestock in all endemic counties to less than 5% by 2008 and then to below 1% by 2015 (Wang et al., 2009a,b). Two comprehensive multisectoral control projects adopting the comprehensive strategy to block the contamination of water bodies with schistosome eggs and thus prevent snail from being infected were conducted, covering 164 counties during 2004–08 and 189 counties during 2009–15, respectively.

The intervention approaches varied between counties according to the local conditions: (1) In endemic counties targeting infection control, interventions focused on infection resource control, including simultaneous chemotherapy of humans and livestock, snail control in high risk regions, agriculture mechanization to replace buffaloes with tractors, prohibiting pasturing animals in grasslands where infested snails exist, raising livestock in stables or on grasslands free of snails, etc. Environmental modification to destroy snail habitats was conducted in combination with farmland rehabilitation projects and forestry projects where possible (Yang et al., 2016). (2) In regions aiming to reach transmission control or transmission interruption, in addition to strengthening control interventions as described above and surveillance of remaining infection resources, snail control focussed on eliminating snail breeding areas through agriculture, water conservancy and forestry projects (Feng et al., 2016; Li et al., 2016).

2.4.3 Achievements and lessons learnt

After 10 years of implementing the comprehensive control strategy, the medium term goal of reaching infection control nationwide was achieved on schedule. Five provinces which had reached transmission interruption by 1995 consolidated their achievements and no new cases or infected snails had been found during this period. Hubei, Hunan, Anhui and Jiangxi provinces reached the criteria of infection control by 2008 simultaneously while Sichuan, Yunnan, Jiangsu and Hubei provinces reached the criteria of transmission control in 2008, 2009, 2010 and 2013, respectively (Fig. 5.). The estimated number of infected people decreased from 842,525 in 2004 to 184,943 in 2013, a reduction of 78.1%. The number of reported acute cases was nine in 2013 (Fig. 6) (Hao et al., 2005; Lei et al., 2014). These achievements suggested that the long-term target of the national programme drafted in 2004 could be achieved by the end of 2015.

3. DEVELOPMENT OF MAJOR CONTROL TOOLS AND TECHNIQUES

3.1 Drugs

3.1.1 Chemical drugs

In the 1950s, potassium and sodium antimony tartrate were considered the most effective drugs to treat schistosomiasis. However, they were toxic and

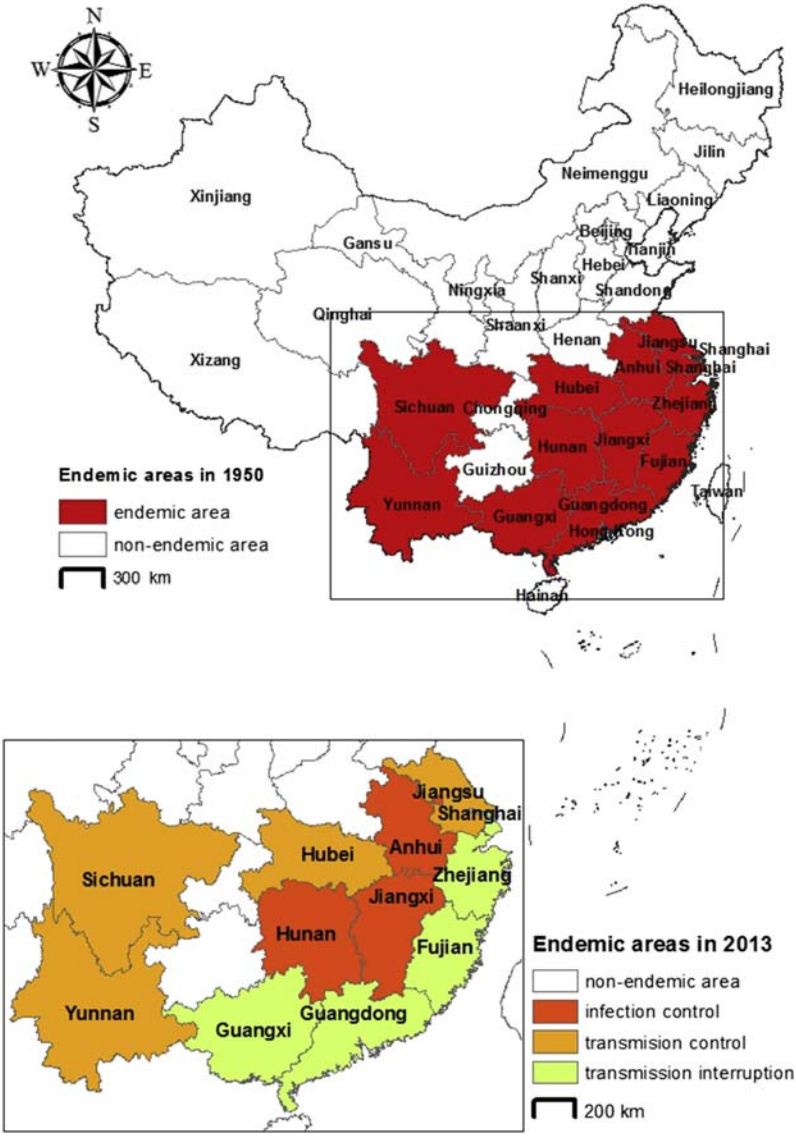


Figure 5 Distribution of schistosomiasis japonica in The People's Republic of China in the 1950s and in 2013.

could have serious side effects (Le et al., 1957; Lu et al., 1955). Furapromidum, the first nonantimonial oral drug against schistosomiasis japonica, was synthesized in The People's Republic of China in 1962 and used for acute cases (Hsiao et al., 1975; Lei et al., 1963). Treatment was only given to cases

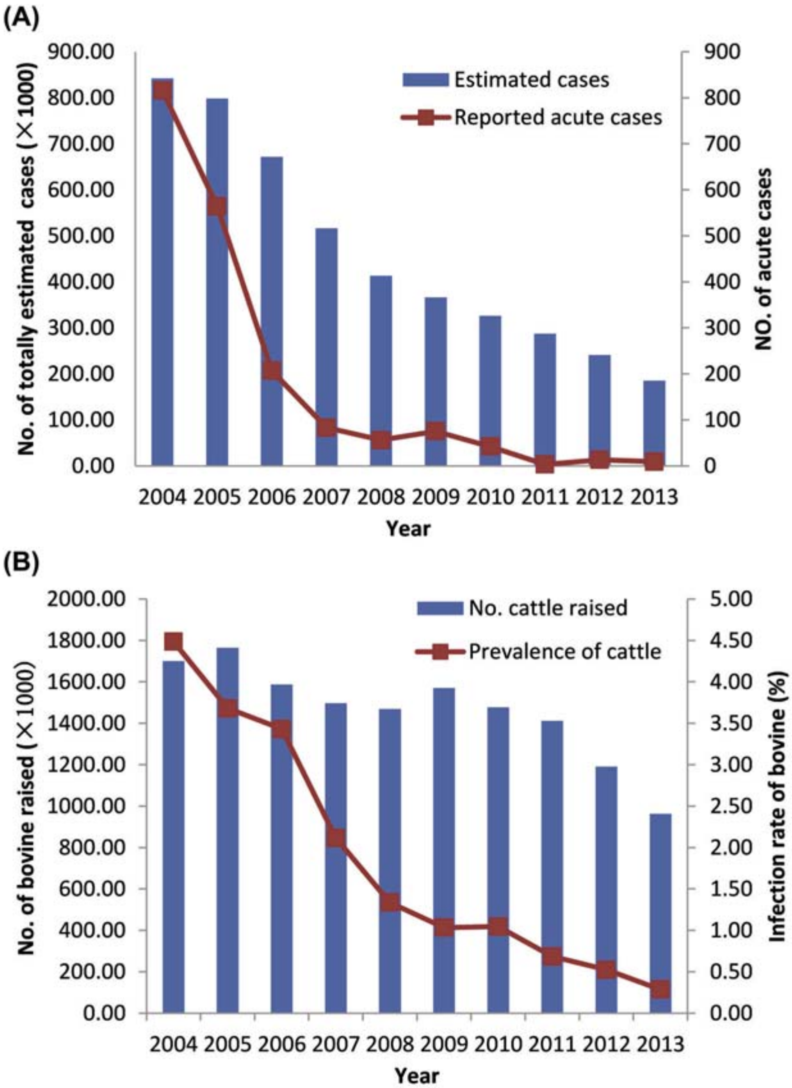


Figure 6 Changes in the prevalence of schistosomiasis japonica in humans and livestock during 2004–2013.

confirmed by direct stool parasitological tests (Maegraith, 1958). The first clinical trial with praziquantel conducted in the late 1970s in The People's Republic of China proved that the drug had a high efficacy against *S. japonicum* (Tambo et al., 2015; Yang et al., 1981). In 1977, praziquantel was synthesized in The People's Republic of China and later released for clinical use

(Fu et al., 1988). The significantly lower price compared to other drugs, high efficacy against acute and chronic schistosomiasis, and good safety profile of a single oral dose of usually 40–50 mg/kg body weight made praziquantel an ideal drug for large-scale use (Fu et al., 1988; Ojurongbe et al., 2014; Zhou et al., 2005). Chemotherapy with praziquantel became the backbone of the WBLP for schistosomiasis control in The People's Republic of China and also plays an important role in the current national control programme (Chen et al., 2005; Zhou et al., 2005).

3.1.2 Alternative treatments

Different antischistosomal drugs were developed based on traditional Chinese herbal medicine during the past six decades (Li et al., 2015). Pumpkin seeds exhibited antischistosomal activity especially against schistosomula (Chou et al.,1958; Shiao et al., 1959). Other herbs, although they showed activity against schistosomes, were finally abandoned due to toxic effects (Chen et al., 1962; Shiao et al., 1962; Wang et al., 1979; Shen et al., 1981; Yue et al., 1985). Herbs such as astragalus, angelica, paeoniflorin, salvia or their extracts were found to have high activity against liver fibrosis caused by chronic schistosomiasis when used alone or combined with other herbs (Li et al., 2009; Wang, 1984; Wu and Sun, 2014; Xie et al., 2002). In 1980, Chinese scientists first described the antischistosomal properties of artemisinin (Chen et al., 1980). Two years later, Le reported the antischistosomal activity of the derivatives of artemisinin, such as artemether and artesunate, which were found to be highly active against immature schistosomes (Le et al., 1982, 1983; Xiao et al., 2002; Xiao, 2005). The administration of these drugs effectively prevented the outbreak of schistosomiasis and was found to be especially useful during the unusual flood disaster in 1998 (Dai et al., 1999; Hu et al., 2000; Song et al., 1997). Considering that the derivatives of artemisinin and praziquantel exhibit high activity against schistosomula and adult worms, respectively, a combined treatment has been proposed to enhance the worm burden reduction and thus benefit the elimination of schistosomiasis but limited in use due to the high cost of the derivatives of artemisinin and afraid of the drug resistance against malaria (Hou et al., 2008; Liu et al., 2014; Villar et al., 2012; Xiao et al., 2000, 2010).

3.2 Diagnostic tools

3.2.1 Parasitological methods

The detection of eggs or miracidia in stool samples is the traditional way to confirm an infection with *S. japonicum*. Before the 1980s, direct smears, sedimentation, concentration and hatching tests and rectal biopsy were the main approaches to diagnose schistosome infection (Maegraith, 1958; Mao and Shao, 1982). Following its recommendation as a routine standard method for schistosomiasis diagnosis by WHO, the Kato−Katz thick smear method has been widely used in The People's Republic of China since the 1980s due to its favourable characteristics including a quantitative result, being cheap and technologically undemanding, and easy to use (Katz et al., 1972; WHO, 1985; Wu et al., 1995). The Kato−Katz test was most useful in high endemic areas as its sensitivity increased with the number of slides examined and the infection intensity (Lin et al., 2008; Yu et al., 2007). The miracidium hatching technique is another traditional method used in The People's Republic of China, arguably with a higher sensitivity than Kato−Katz due to the large volume of faeces examined (Ministry of Health, 2000). This technique is limited to use in low infection intensity areas due to its labour-intensive and time-consuming nature (Zhu et al., 2005). In the guidelines for schistosomiasis control and elimination in The People's Republic of China issued in 2006, the Kato−Katz method (three slides from one stool sample) or screening by serological tests followed by Kato−Katz method for antibody-positive individuals is recommended to evaluate whether a community has reached the infection control criteria while the miracidium hatching technique alone (3 hatching tests per stool sample) or in combination with serological tests was used to assess the endemic status where the aim was to achieve transmission control or transmission interruption (Collins et al., 2012; Ministry of Health, 2007).

3.2.2 Immunological assays

Immunological tests have a long history in the national schistosomiasis control programmes of The People's Republic of China due to advantages such as high sensitivity, easy use and rapidity (Chen et al., 2016; Zheng et al., 2013). Intradermal tests (ID) were the first successfully developed immunodiagnostic method. The strategy of screening a population by ID first followed by stool examination only for the ID positives made large-scale screening feasible and allowed understanding the distribution and approximate prevalence of schistosomiasis in a short time during the 1950s (Maegraith, 1958; Mao and Shao, 1982). Antibody-detection immunoassays such as the cercaria huellen reaction (CHR), circumoval precipitin test (COPT), indirect haemagglutination assay (IHA), enzyme-linked immunosorbent assay (ELISA) as well as rapid diagnostic assays such as the Dye Dipstick immunoassay (DDIA) and the Dot immunogold filtration assay (DIGFA) based on immunofiltration or immunochromatography principles were developed and some of them were widely used in The People's Republic of China (Wu, 2002; Zhu, 2005). Comprehensive assessments in the laboratory and in field settings conducted in recent years proved that most serological techniques to detect antibodies developed so far had a sensitivity of about 90% or more while showing only limited cross-reactions with other helminth infections (Xu et al., 2011a,b, Zhou et al., 2011). However, such tests cannot distinguish current from past infections. Still, they proved invaluable for the national control programmes when targeting chemotherapy, in epidemiological surveys, for surveillance and for the assessment of control strategies (Dang et al., 2014; Zhou et al., 2007, 2011). Research on antigen-based immunoassays for the detection of *S. japonicum* started in the late 1970s in The People's Republic of China (Wu, 2002). A number of monoclonal antibodies targeting circulating anodic antigen (CAA), circulating cathodic antigen (CCA) or membrane-associated antigen (MAA) were developed but such assays were not integrated into the national control programmes due to their unsatisfactory specificity and sensitivity in patients with light infections (Guan and Shi, 1996; Yi et al., 1995).

3.3 Snail control

3.3.1 Physical methods

Physical methods for snail control involve the environmental modification of snail habitats to make survival difficult for snails (Li et al., 2016).

3.3.1.1 Agricultural activities

Changing flood plains to farmland through construction of dykes and embankments, changing farmland to fish ponds, raising crawfish and rice alternately in paddy fields, planting rice in the mid-altitude lands and cotton in dry, high-altitude lands have played important roles in snail control by reducing snail habitats (Fan et al., 2009; Lei et al., 2000; Li, 2002; Wang et al., 2005a,b). These approaches have thus contributed to the gradual elimination of *S. japonicum* from vast formerly endemic areas of The People's Republic of China.

3.3.1.2 Water resources development projects

Water resources management projects lead to environmental changes and can have negative or positive impacts on the transmission of schistosomiasis depending on their nature and technical specifications (He et al., 2006; Steinmann et al., 2006; Su et al., 2004). Digging and dredging canals, water saving and irrigation schemes, provision of drinking water, river boundary modifications, concrete lining of riversides and canal banks, and construction of facilities to catch snails were all tried and tested to decrease the habitat and snail density of (Wang and Xia, 2006; Zhang et al., 2009; Zhu et al., 2009).

3.3.1.3 Forestry projects

Forestry projects for snail control include the planting of suitable trees such as poplar and Chinese tallow tree in marshlands or mountainous regions in combination with ploughing land and planting crops between forests. These methods change the ecology of snail habitats by decreasing the water level and thus soil moisture, changing the light intensity, etc. (Peng, 2006; Sun et al., 2007; Zhang et al., 2006). Snail densities and survival decrease over several years and significant impacts on human and livestock schistosomiasis prevalence have been documented (Li et al., 2014; Liu et al., 2011; Zhang et al., 2012a,b).

3.3.2 Chemical methods

Mollusciciding is an important tool for the control of snail populations as it is much cheaper, quicker and can save manpower compared with environmental modification. In the early stage of the Chinese schistosomiasis control programmes, chemicals including copper sulphate, DDT, 666, Paris green, calcium arsenate and calcium cyanamide as well as extracts from native herbs were tested to kill *O. hupensis* snails. However, none of them were widely used due to their high cost, serious environmental pollution, or low efficacy (Maegraith, 1958). Sodium pentachlorophenate was found to have high activity against snails and was produced in large quantity since 1959 as it was applied widely in The People's Republic of China before the WBLP. Niclosamide is also widely used in The People's Republic of China since the country started to produce it in 1967 (WHO, 1983). Different formulations have been developed over the past decades, adapted to different environments (Chen, 2003; Dai et al., 2008; He et al., 2007; Xia et al., 2014). Meanwhile, considerable efforts to explore and develop plant molluscicides were not successful (Yang et al., 2014).

3.4 Control of reservoir hosts

The role of livestock, especially buffaloes, in the transmission of schistosomes particularly in lake and mountain regions was realized early. Parasitological methods to diagnose infections in livestock, such as nylon sieve washing and concentrating techniques, and the miracidium hatching technique, were developed. Immunological tests such as IHA and Dot-ELISA kits were developed by Chinese scientists and approved by the Ministry of Agriculture. They are widely implemented for screening. The formulation, dosage, toxicity and pharmacology of different drugs such as antimonials, dipterex, amoscanate and praziqutantel were studied over the past 60 years. Treating infected livestock with oral praziquantel simultaneously when chemotherapy for humans was conducted is a standard procedure since the WBLP. Animal vaccination was regarded as an effective tool to accelerate efforts to reach the final goal of schistosomiasis elimination, and vaccines such as irradiation-attenuated vaccine, paramyosin, and DNA-based vaccines were assessed since the 1980s in The People's Republic of China (Chen et al., 2000; Hsu et al., 1984; Liu et al., 1995, 1998, 2004; Shi et al., 1990, 2001). In the current phase of the national control program initiated in 2004, other methods to decrease or interrupt the contamination of water bodies with eggs from the faeces of infected livestock were implemented: reforming agricultural structures through encouraging the poultry industry instead of raising susceptible livestock, prohibiting the grazing of bovines on snail-infected beaches, raising livestock in stables, replacing bovines by machines, construction of methane tanks to capture manure and improve the living conditions of humans (Chen et al., 2014; Wang et al., 2009a,b; Xu et al., 2015).

4. EXPERIENCE AND LESSONS LEARNT FROM SCHISTOSOMIASIS CONTROL PROGRAMME

The achievements of the schistosomiasis control programmes in The People's Republic of China can be attributed to the strong and stable political commitment of the government, the uninterrupted execution of the national control program, the progressive introduction of newly developed technologies and tools as well as continuous surveillance activities.

4.1 Strong political will and multisectoral collaboration

Since the founding of The People's Republic of China, schistosomiasis control has been given high priority in the public health agenda. A schistosomiasis leading group at national level and a full-time office were established by the end of 1955 to enhance schistosomiasis control since Chairman Mao Zedong issued the slogan to eliminate schistosomiasis (Wang et al., 1989). President Jiang Zemin ordered to take necessary steps to control schistosomiasis after an outbreak with more than 1000 acute schistosomiasis cases happened in Wuchang district of Hubei province in 1989 (Chen, 1990). A schedule of conducting field investigations in spring and organizing a conference in autumn with participants from different sectors was established. With the resurgence of schistosomiasis at the beginning of the new millennium, schistosomiasis was listed as one of four major communicable diseases given high priority (the others being HIV/AIDS, tuberculosis and hepatitis B) in 2004 (Wang et al., 2008). The leading group on schistosomiasis at the State council level was re-established and a notice to further strengthening the schistosomiasis control was issued by the State council in 2004 to strengthen the collaboration between sectors. The promulgation of the Schistosomiasis Prevention and Control Regulations in 2006 accelerated the implementation of the integrated control strategy in endemic areas, making resource mobilization easier.

4.2 Scientific control strategies and effective intervention measures

Big difference exists between different endemic areas in terms of local epidemiology, environment and socioeconomic conditions. Strategies for schistosomiasis control had shifted from the initial elimination strategy before the mid-1980s, to morbidity control during the WBLP and to the current comprehensive strategy of blocking transmission. Research pertaining to schistosomiasis was listed as a key research program in the ministries of health, agriculture and water resources. The introduction of praziquantel, artemether and artesunate to kill schistosomula, transfer from bench to the field of sensitive and easy-to-use diagnostic tool, new chemicals for mollusciciding and livestock treatment were developed in the frame of research projects and promoted the progress of schistosomiasis control in The People's Republic of China (Xin and Dai, 2010; Yang et al., 2012; Zhang et al., 2013; Zhou et al., 2013a,b). Along with the shift of control strategies, criteria for schistosomiasis control and elimination were formulated and modified six times, providing guidance for control activities and to assess the effect of the interventions (Zhou et al., 2013a,b). Technical support to different endemic areas improved their capacity to implement and combine the appropriate interventions.

4.3 Vertical control program and sufficient workforce

The reliance on a professional workforce contributed to the success of schistosomiasis control in The People's Republic of China. The Ministry of Health played an important role in managing and monitoring the national control program. Antischistosomiasis institutions or stations were established at all levels (national, provincial, municipal, county and township) in the

1950s. They are well funded to take the main responsibility for disease control, treatment and prevention (Collins et al., 2012). By the end of 2011, except one national institute, 365 agencies for schistosomiasis control existed in seven provinces including Jiangsu, Anhui, Jiangxi, Hubei, Hunan, Sichuan and Yunnan. Among them 282 are responsible for schistosomiasis prevention and control and the others are in charge of prevention and clinical case management. Although many antischistosomiasis stations were integrated into general centre for disease control (CDC) institutions or other disease-specific facilities due to the decreased prevalence and scale down of programs, the workforce dedicated to schistosomiasis control full time has been maintained (Ross et al., 2013).

4.4 Epidemiological surveys and surveillance

National surveys conducted since the 1950s and three national sampling surveys conducted in the frame of the WBLP provided basic information on the epidemiological features and updated the endemic status of schistosomiasis in The People's Republic of China (Wu et al., 2007; Zhou et al., 2005). To monitor changes in the epidemiological status and assess the effectiveness of control strategies, systematic cohort monitoring and surveillance of schistosomiasis have been conducted since the 1990s (Zhou, 2009, Zhu et al., 2011). Other surveillance projects focussing on the impact of climate changes and large water conservancy projects on schistosomiasis transmission at the border of nonendemic and endemic areas, and sentinel mice-based surveillance in high risk water bodies are regularly conducted in The People's Republic of China (Dang et al., 2014; Zhang et al., 2012a,b; Zhu et al., 2011). New technologies such as remote sensing, geographical information system and predictive statistical modelling, and xeno-monitoring based on loop-mediated isothermal amplification technique are also implemented (Tong et al., 2015; Yang et al., 2006; Zhang et al., 2005). These activities provide basic information for decision-makers when they draft control programmes or design control activities and allow the assessment of the achievements obtained through decades of efforts (Tambo et al., 2014).

5. CHALLENGES

5.1 Extensive and complicated snail habitats

Over the past decade, the snail-infested areas nationwide remained at 3.6–3.8 billion m^2. In 2013, 96.5% of all snail habitats were located in the marshland and lake regions. Among these areas, 94.3% were distributed outside embankments where they are easily influenced by water level fluctuations (Lei et al., 2014). Big challenge exists to eliminate snails from such extensive areas with complicated ecological characteristics such as unstable water level or flourish vegetation. Furthermore, agricultural activities, flooding and water conservancy projects may spread snails to urban regions or previously uncolonized areas. Between 2002 and 2010, snails were found in areas previously free of snails measuring 125 million m^2 (Wang et al., 2015).

5.2 Management of different sources of infection

The schistosomiasis prevalence in bovines has been reduced to a very low level, but the number of livestock including bovines and goats in endemic areas is significant. Other species, especially rodents, which also play important roles in some lake and mountainous regions, make it difficult to completely eliminate schistosomiasis (Guo et al., 2013; Lu et al., 2010). Fishermen and boat people are currently at highest risk of schistosome infection, but control programs among such migrating populations are difficult to implement. They may also spread schistosomes to other places where intermediate host snails exist. Medical services also need to become aware of other forms of schistosomiasis, eg, in travellers and workers returning from African countries (Zhou et al., 2013a,b, Zhu and Xu, 2014).

5.3 Unbalanced implementation of integrated strategy

Despite the significant economic growth occurred in The People's Republic of China since the reform of the economic system in 1978, big differences exist between urban and rural areas, western and eastern regions, and lake and mountainous regions (Bian et al., 2004; Tang et al., 2008). Many of the proposed integrated measures such as improving safe water supply and sanitation, mechanization of agriculture, building methane tanks, environmental modification, etc. need large funds which are not available in poor areas. Particularly problematic is the Chinese system that programs and interventions are centrally planned but implementation and financing are largely up to local governments. Prohibiting grazing in snail habitats has also encountered resistance in some regions as it impacts farmers' benefits since such pastures are communal land requiring no or very limited investments for use (He, 2011).

5.4 Unavailability of sensitive diagnostic tools

As the prevalence in intermediate and end hosts decreases to a very low level, moving forward towards elimination requires sensitive diagnostic tools. The current strategy of conducting stool examination only for antibody-positive individual increases feasibility and compliance but risks missing infected individuals also increase due to the relative insensitivity of the Kato–Katz method and/or miracidium hatching technique in identifying light infections. Consequently, the current prevalence of schistosomiasis is probably underestimated and the undetected cases continue to serve as infection sources (Zhou et al., 2011). Snail surveys and dissection are labour intensive approaches and require trained technicians. Diagnostic tools and snails examination based on molecular techniques have a higher sensitivity and specificity than traditional approaches but they are expensive and their performance and applicability need further field assessment (Tong et al., 2015; Xia et al., 2009, 2014; Xu et al., 2010).

5.5 Weak surveillance and active response system

The biological and social factors promoting the transmission of schistosomiasis still exist in many areas where active transmission has ceased. Thus, a rebound or re-emergence of schistosomiasis can easily happen once infection sources or intermediate hosts are imported. Although systematic surveillance has been conducted since the 1990s and the current surveillance system covers all endemic counties, the tools did not change fundamentally and shortcomings such as simple monitored contents, insensitive indicators, obsolete technologies and insufficient use of collected data become ever more pressing with the decrease of the prevalence. In counties which had reached transmission control or interruption for many years, the diagnostic and epidemiological survey capacity and the ability to respond to outbreaks decreases due to staff turnover, weak infrastructure, sliding consciousness and low training levels. During 2011–13, most acute cases that were ultimately reported were initially misdiagnosed and new cases are regularly seen from areas where transmission was thought to have ceased (Lei et al., 2014; Li et al., 2013; Zheng et al., 2012). The surveillance and particularly the ability to actively respond need to be strengthened to ensure early detection and correct handling of schistosomiasis outbreaks and thus accelerate progress towards schistosomiasis elimination nationwide (Zhang et al., 2016).

6. PROSPECT

The raise in awareness for the importance of schistosomiasis control and in view of the achievements gained in several countries, resolution WHA65.21 on the elimination of schistosomiasis was adopted by World Health Assembly (WHA) in 2012. It calls for increased investment in schistosomiasis control using multiple approaches, support for countries to initiate elimination programs where appropriate and the creation of a process to verify interruption of transmission (WHO, 2013). The action plan drafted by the WHO Western Pacific Region (WPRO) in 2012 expects The People's Republic of China to eliminate schistosomiasis as a public health problem (prevalence in human beings and livestock $<1\%$) by 2016 (WPR/RC63/6, 2012). According to the current trends, the target could be reached in 2015 (the Chinese criteria for transmission control are equal to the criteria for eliminating schistosomiasis as a public health problem set by WHO).

As the current phase of the national schistosomiasis control program will be successfully completed by the end of 2015, elimination of schistosomiasis must be the next target. In November 2014, the national schistosomiasis control conference at state council level was organized in Hunan Province. Based on the current achievements, a new goal was put forward to eliminate schistosomiasis nationwide following the approaches laid out in another two consecutive five year plans (Lei and Zhou, 2015). Systematic assessments will be conducted to understand the endemic status of schistosomiasis in the country and evaluate the efficacy of the current integrated strategy in The People's Republic of China. As changes existed to achieve elimination in current situation, full integration of interventions including chemotherapy, snail control, safe water supply, improving sanitation, environmental modification through water conservancy, agriculture, and forestry projects is required. Intersectoral cooperation needs to be strengthened. More sensitive and effective diagnostic and surveillance tools and techniques need to be explored to monitor the declination or cessation of transmission and verify elimination of schistosomiasis transmission. Risk assessments should be conducted to identify hotspots of transmission and guide policy makers. Capacity building in surveillance should be strengthened to consolidate achievements and prevent re-emergence of schistosomiasis.

APPENDIX

Milestones of schistosomiasis japonica control process in The People's Republic of China

Year	Political will	National program or plan	Instructive materials	Endemicity	Drugs development
1950	Instruction of schistosomiasis control issued by Ministry of Health		First version of manual for schistosomiasis control	1335 people died in an outbreak of schistosomiasis in Gaoyou county	
1955	Set up national leading group for schistosomiasis control				
1956	Chairman Mao issued a slogan of eliminating schistosomiasis	National plan for agricultural development (1956–65)	Second version of manual for schistosomiasis control	Estimated 11.6 million people infected with schistosomes and 1.2 million bovines infected	
1958	Chairman Mao wrote the poem of 'Farewell to the god of plague'		First version of criteria for schistosomiasis elimination	Yujiang county first announced schistosomiasis elimination	
1959					Production of sodium pentachlorophenate
1962					First nonantimonial oral drug synthesized by The People's Republic of China
1967					Production of niclosamide

(*Continued*)

Milestones of schistosomiasis japonica control process in The People's Republic of China—cont'd

Year	Political will	National program or plan	Instructive materials	Endemicity	Drugs development
1970	Reset up of national leading group for schistosomiasis control				
1977			Second version of criteria for schistosomiasis elimination		Praziquantel synthesized by The People's Republic of China
1978		National plan of eliminating schistosomiasis in 13 provinces	Third version of criteria for schistosomiasis elimination		
1980					Found the antischistosomal properties of artemisinin
1984	Chairman Deng Xiaopeng issued the instruction of schistosomiasis prevention and control				
1986	Dismissed the national leading group and set up Bureau of Eendemic Diseases in Ministry of Health		Fourth version of criteria for schistosomiasis elimination		

1987		Seventh five year plan for schistosomiasis control		
1989	Chairman Jiang Zemin put forward that control and elimination of schistosomiasis is the responsibility of government			1604 cases attacked by acute schistosomiasis in Wuhan city in Hubei Province
1990	State council issued the notice of strengthening schistosomiasis control and prevention			
1991		Eighth five year plan for schistosomiasis control		
1992		Started WBLP		Acute cases and snails found in Guangdong Province again
1995			Fifth version of criteria for schistosomiasis elimination	Five provinces eliminated schistosomiasis
1997		Ninth five year plan for schistosomiasis control		

(Continued)

Milestones of schistosomiasis japonica control process in The People's Republic of China—cont'd

Year	Political will	National program or plan	Instructive materials	Endemicity	Drugs development
2001		Termination of WBLP tenth five year plan for schistosomiasis control	Third version of manual for schistosomiasis control		
2004	Schistosomiasis was listed as one of four priority disease and a strategic plan was issued Reset up of national leading group for schistosomiasis control	National key project for schistosomiasis comprehensive control (2004–08)			
2006	Promulgation of the schistosomiasis prevention and control regulations		Sixth version of criteria for schistosomiasis elimination		
2008				The whole country reached the criteria of infection control	
2009		National key project for schistosomiasis comprehensive control (2009–15)			

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